Disturbed Glucose Metabolism in Patients with a TIA or Ischemic Stroke: *Prognosis and Long-term Treatment*

Elizabeth Osei

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Disturbed Glucose Metabolism in Patients with a TIA or Ischemic Stroke:

Prognosis and Long-term Treatment

Gestoord glucose metabolisme bij patiënten met een TIA of herseninfarct:

Prognose en lange termijn behandeling

Thesis

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Elizabeth Osei

born in Amsterdam, the Netherlands

Erasmus University Rotterdam 

DOCTORAL COMMITTEE

Promotor:	Prof. dr. D.W.J. Dippel
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	Dr. A.A.M. Zandbergen

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CHAPTER 1
General introduction

STROKE AND TIA

Stroke is defined as rapidly developed sign of focal or global disturbance of cerebral function lasting longer than 24 hours, with no apparent nonvascular cause, according to the standard World Health Organization (WHO) clinical criteria. [1] Stroke can be classified as either ischemic or hemorrhagic. Ischemic stroke is more prevalent and comprises 73 to 90% of strokes, and is caused by an occlusion of a cerebral artery or arteriole. [2] In most national and international guidelines, the arbitrary time window of 24 hours has been abolished and instead imaging criteria have been added. The diagnosis of stroke requires appropriate imaging with non-contrast CT or MR. Transient ischemic attack (TIA) is then defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction on CT- or MRI-scan. [3] Stroke is one of the leading causes of morbidity and mortality in the developed world.[4,5] Identification and treatment of prevalent risk factors for stroke and TIA could have a significant positive impact on morbidity and mortality.

Disturbed glucose metabolism and association with outcome after stroke or TIA

Diabetes mellitus type 2 is a risk factor for stroke, and is clearly associated with poor functional outcome after stroke and stroke recurrence. [6,7] Glucose is the main source of energy for brain cells, and tight regulation of glucose metabolism is critical for brain physiology. [8] Prediabetes or impaired glucose metabolism is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus. Three detection methods are available to identify patients with (pre)diabetes: fasting glucose, glycosylated hemoglobin and 2-hour post-load glucose levels. The three tests combined identify the most patients with prediabetes accurately. Research by our group suggests that without the 2-hour post-load glucose and glycosylated hemoglobin levels, the majority of patients with prediabetes would have been missed.[9]

Prediabetes increases the risk of type 2 diabetes. [10] Up to 79% of patients with TIA or stroke and without a history of diabetes mellitus have either prediabetes or newly-diagnosed diabetes in the acute phase after TIA or stroke. [11]

Several studies have shown that prediabetes increases the risk of recurrent stroke and other cardiovascular diseases. [12] Hyperglycemia in the acute phase of an ischemic stroke in nondiabetic patients is associated with an increased risk of short-term poor functional outcome and mortality. [13] Only a few studies have investigated the influence of prediabetes on functional outcome after acute stroke and some suggested an association with unfavorable outcome. [14,15]

The underlying pathophysiology of the association of hyperglycemia with unfavorable outcome in stroke patients is due to several mechanisms. First, hyperglycemia can

cause impaired recanalization by increasing the production of thrombin–antithrombin complexes and stimulating the tissue factor pathway. It can decrease reperfusion by inhibition of vasodilation by reduction of nitric oxide. Furthermore, hyperglycemia can exacerbate tissue damage, edema and impaired blood-brain barrier by increasing oxidative stress and inflammation. Lastly, hyperglycemia can cause direct tissue injury through mitochondrial dysfunction.[16] The association of prediabetes with outcome in stroke patients is not fully known yet. We need confirmatory studies to establish this.

In addition, one might expect a beneficial effect on outcome of glucose lowering therapy in the acute phase of stroke. A few randomized controlled trials assessed the effect of glucose lowering therapy in the acute phase of hyperglycemic stroke patients. In the GIST-UK trial, 24-hour insulin infusion did not improve outcome in hyperglycemic stroke patients.[26] This trial possibly failed to show efficacy because the difference in blood glucose levels after 24 hours of treatment was only 0.6 mmol/L, and the trial was underpowered because it was stopped early due to slow enrolment. A randomized pilot trial reported that intensive glucose lowering therapy was safe and feasible; in the tight glycemic control group with insulin, there was a considerable lower glucose level of 6.2 mmol/L compared to the loose and usual care group of 8.4 mmol/L. However, in the tight glycemic control group, there were 30% of hypoglycemic cases vs 4% in the usual care and loose control group. Of these, there was one reported case of symptomatic hypoglycemia. [27] Another randomized pilot trial which assessed intensive glucose lowering therapy with insulin with usual care in diabetic acute stroke patients, reported that the glucose levels were significantly lower in the treatment group vs usual care (7.4 mmol/L vs 10.5 mmol). Hypoglycemia only occurred in the intensive treatment group (35% of the patients). [28] Intensive glucose lowering therapy has been shown to be challenging, probably because of the considerable risk of developing hypoglycemia, which also has a negative effect on recovery. [29]

So, glucose lowering therapy in the acute phase has not been proven to be beneficiary yet, and in some cases might even be harmful. Further research is needed to establish whether glucose lowering therapy in the acute phase is feasible and safe.

PREVALENCE AND PREDICTION OF PERSISTENT DISTURBED GLUCOSE METABOLISM

Approximately half of the patients with a TIA or ischemic stroke and impaired glucose metabolism in the acute phase have persistent disturbed glucose metabolism after 3 months. [17] It is important to identify patients with recent ischemic stroke or TIA and persistent impaired glucose metabolism as they might benefit from long-term lifestyle intervention and/or treatment with glucose-lowering agents.

A prediction model has been developed that accurately predicts persistent impaired glucose metabolism in these patients (bootstrapped AUC 0.777) based on age, current smoking, hypertension, previous ischemic cardiovascular disease, BMI, statin use, triglycerides, and fasting plasma glucose, clinical variables readily available on admission. [17] However, to test the accuracy of this model, an external validation in an independent group of stroke patients is needed.

DISTURBED GLUCOSE METABOLISM AFTER STROKE OR TIA AND ASSOCIATION WITH ACUTE TREATMENT

Acute treatment of ischemic stroke comprises intravenous thrombolysis, intra-arterial treatment (IAT) and stroke-unit care. Treatment with intravenous alteplase, aiming at early reperfusion, has been proven effective when given early and contra-indications are absent. [18,19] Recent studies have demonstrated that intra-arterial treatment (IAT) by means of thrombectomy with stent retrievers is both effective and safe in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion in the anterior circulation. [20,21] Several studies found that hyperglycemia on admission was associated with unfavorable outcome in patients receiving intravenous thrombolysis for acute ischemic stroke. [22,23] There is less evidence available for the association of hyperglycemia with outcome after intra-arterial thrombectomy. [24,25] Therefore, further research is warranted.

Whether glucose lowering therapy is beneficial in patients with acute stroke before administering intravenous alteplase has not been proven in humans yet. In an animal study, the effects of insulin combined with alteplase in diabetic rats with an embolic stroke was studied. Early insulin glycemic control combined with alteplase significantly reduced brain infarction and swelling, ameliorated alteplase-associated hemorrhagic transformation, and improved plasma perfusion at 24 hours after stroke.[30] Further research is needed to establish whether glucose lowering therapy before reperfusion therapy in acute stroke patients is beneficial.

DISTURBED GLUCOSE METABOLISM AFTER STROKE OR TIA AND SECONDARY PREVENTION

Previous studies have focused on whether glucose lowering therapy in patients with prediabetes is effective. In the DPP-trial, in nondiabetic patients with elevated fasting glucose and post-load glucose levels, lifestyle modification and metformin were both effective in reducing the incidence of diabetes type 2, with a better effectiveness of lifestyle modification than metformin. In addition, there was more weight loss in the group of patients with lifestyle modification than metformin. [35] However, in the 10-years follow-up, patients in the lifestyle modification group partly regained weight. The

incidence of diabetes was still more reduced in the lifestyle group than the metformin group. [36] So it seems that lifestyle modification is more effective in glucose lowering than anti-diabetic medication, and also might have a positive effect on other cardiovascular risk factors, but lifestyle modification is harder to sustain. Therefore, glucose lowering medication is often used as therapy in randomized controlled trials.

Recent studies have investigated whether tight glycemic control might reduce the risk of stroke and other cardiovascular diseases in patients with impaired glucose tolerance.[31–33] A randomized controlled trial showed that pioglitazone can prevent stroke and myocardial infarction among patients who have insulin resistance after ischemic stroke or TIA, but pioglitazone also gives a higher risk of weight gain, edema, and fracture. [31] A meta-analysis on glucose-lowering pharmacological interventions in patients with impaired glucose tolerance found possible beneficial effects on the risk of stroke and myocardial infarction. [32] A recent long-term study in patients with established type 2 diabetes however, showed no beneficial effect of intensive glucose lowering therapy on the glucose levels and incidence of cardiovascular events. [33] In the LIMIT-trial, we assessed the safety and feasibility of metformin in patients with minor ischemic stroke and TIA and impaired glucose tolerance (IGT). In this study, metformin treatment was safe and lead to improved glucose tolerance in the on-treatment analysis. [34] However, 50% of the patients experienced gastrointestinal side effects resulting in permanent discontinuation in 25% of the patients.

Previously mentioned studies have not conclusively established whether prediabetes is a treatable risk factor for cardiovascular diseases. Further research is needed to assess what the most effective and safe treatment option is for prediabetes in these patients.

AIMS AND OUTLINE FOR THIS THESIS

The aim of my thesis is to assess prognostic impact and to evaluate treatment options of disturbed glucose metabolism in nondiabetic stroke patients.

In chapter 2, I conduct a literature review of prediabetes and the association with outcome in patients with macrovascular diseases.

In chapter 3.1, the association of newly diagnosed disturbed glucose metabolism with outcome in patients with stroke derived from the Erasmus Stroke Study (ESS) database is assessed. In chapter 3.2, I report a prediction model for persistently impaired glucose tolerance after ischemic stroke or TIA.

Chapter 4 discusses the association of disturbed glucose metabolism with outcome in stroke patients treated with intravenous thrombolysis and/or thrombectomy. In chapter 4.1, I assess the association of fasting glucose levels with outcome in ischemic stroke

patients treated with intravenous thrombolysis derived from the ESS database. In chapter 4.2, the association of admission glucose and fasting glucose with short term outcome after intra-arterial treatment is studied in the Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN) pretrial cohort. Chapter 4.3 reports the effect of admission glucose on intra-arterial treatment effect in the MR-CLEAN trial.

In chapter 5, safety, I study the feasibility and efficacy of metformin and sitagliptin in patients with a TIA or minor stroke and impaired glucose tolerance in a randomized controlled trial, comparing these medical strategies to standard care. In chapter 6, the methodology and clinical implications of the studies in this thesis will be discussed.

Finally, I summarize the results of all studies in chapter 7.

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CHAPTER 2
Introduction

CHAPTER 2.1

Prediabetes and macrovascular disease: Review of the association, influence on outcome and effect of treatment

W. Kleinherenbrink
E. Osei
H.M. den Hertog
A.A.M. Zandbergen

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ABSTRACT

Prediabetes is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus. Patients with prediabetes have an increased risk (of up to 70%) of developing type 2 diabetes. Prediabetes is highly prevalent in patient with macrovascular disease including coronary artery disease, stroke and peripheral artery disease, persisting in the post-acute phase, which suggests true disturbance of glucose metabolism rather than a temporary reflection of stress. Moreover, the clinical and functional outcome in these patients is worse compared to patients with normal glucose metabolism. As the prevalence of prediabetes is growing rapidly, prediabetes might become an important modifiable therapeutic target in both primary and secondary prevention. Concerning primary prevention, lifestyle modification and to a lesser extend antidiabetic drugs decrease the risk of developing type 2 diabetes in patients with prediabetes. Furthermore, long-term follow-up studies showed that intensive lifestyle intervention, and/or medical treatment of cardiovascular risk factors reduced the incidence of macrovascular mortality and all-cause mortality in these patients as well.

As to secondary prevention, there is only little evidence that treatment of prediabetes in patients with macrovascular disease decreases the recurrence of macrovascular complications and improves outcome.

This review focuses on the association of prediabetes with outcome in patients with macrovascular disease, and the effect of treatment of prediabetes on the risk of developing macrovascular disease (in primary prevention) as well as on the outcome in patients with established macrovascular disease (secondary prevention).

INTRODUCTION

Prediabetes is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus. Following diabetes mellitus, the prevalence of prediabetes is growing worldwide (up to 30% when aged 60 years or more). It is well known that prediabetes increases the risk of type 2 diabetes to up to 70%. [1-3] In addition, prediabetes is highly prevalent in patients with macrovascular disease. As macrovascular diseases like coronary artery disease, heart failure, stroke and peripheral artery disease are the leading cause of morbidity and case fatality in developed countries, treatment of associated risk factors like prediabetes could significantly lower this burden. However, whether prediabetes leads to an adverse outcome in patients with macrovascular disease and whether treatment of prediabetes leads to prevention of macrovascular disease in primary prevention as well as in secondary prevention, is less known.

This review focuses on the association of prediabetes with outcome in patients with macrovascular disease, and the effect of treatment of prediabetes on the risk of developing macrovascular disease (in primary prevention) as well as on the outcome after macrovascular diseases (secondary prevention).

METHODS

A search of the literature was performed in the databases Medline, Embase, Cochrane Library and Web of Science.

Prediabetes was defined as an impaired fasting glucose of 5.6-6.9 mmol/L (100-125 mg/dl) and/or impaired glucose tolerance of 7.8-11.0 mmol/L (140-199 mg/dl) and/or HbA1C ranges of 38-46 mmol/mol (5.7%-6.4%). [4] Also, the higher threshold for IFG of 6.1 mmol/L used by the WHO-criteria was included. [5]

In Table 1 you will find the most important studies we used for this review, describing the prevalence of prediabetes, outcomes and limitations in different forms of macrovascular diseases.

PREVALENCE OF PREDIABETES AND ASSOCIATION WITH OUTCOME IN MACROVASCULAR DISEASE

The prevalence of prediabetes in patients with coronary artery disease varies between 19-36% in several studies, persisting in the post-acute phase. [1,3,6,7] This suggests a true disturbance of glucose metabolism rather than a temporary reflection of stress. [8] In patients with acute or stable coronary artery disease, impaired glucose tolerance (IGT) and diabetes mellitus are associated with unfavorable outcome, with a graded increase in the risk of mortality and nonfatal cardiovascular complications across the spectrum of glucose levels. [3, 9-11]

Table 1. Summary of most important included studies

Study	Population	Event	Intervention	Glucose assessment	Number of patients	Prediabetes, n (%)
Bartnik[7]	Europe	Coronary artery disease	-	OGTT or FPG	4196 (2107 acute and 2854 elective consultations)	332 (36%) of acute CAD without known diabetes
Norhammar[8]	Europe	Myocardial infarction	-	OGTT or FPG	181	58 at discharge (35%) and 58 after 3 months (40%)
Thrainsdottir[13]	Europe	Heart failure	-	OGTT or FPG	19.381	1977 (10%)
Berry[15]	Europe	Acute heart failure	-	Nonfasting plasma glucose levels (glucose at admission 8.0-10.99 mmol/L)	454	60 (13%)
Kernan[25]	USA	Ischemic stroke and TIA	-	FPG & OGTT	98	30 (31%)
Ivey[26]	USA	Ischemic stroke	-	FPG & OGTT	216	37 (46%)
Vermeer[32]	Europe	Ischemic stroke and TIA	-	Nonfasting plasma glucose levels	317	165 (5%)
Osei[34]	Europe	Ischemic and hemorrhagic stroke	-	FPG	1007	213 (21%)
Golledge[37]	Australia	Peripheral arterial disease	-	FPG	1637	460 (28.1%)
Liu[42]	Asia	Metabolic syndrome and cardiovascular diseases	-	FPG	30.378	6415 (21.1%)
Knowler[47]	USA	-	Metformin vs placebo vs lifestyle modification	OGTT and FPG	3234	All patients had prediabetes
Perreault [50]	USA	-	Metformin vs placebo vs lifestyle modification	OGTT or FPG	2775	All patients had prediabetes
Li[51:]	Asia	-	Lifestyle modification vs control group	OGTT	577	All patients had prediabetes

CAD: coronary artery disease. OGTT: oral glucose tolerance test. FPG: fasting plasma glucose. IGT: impaired glucose tolerance. TIA: transient ischemic attack. PAD: peripheral arterial disease. CVD: cardiovascular disease.

	Outcome	Limitations
	Majority of patients with CAD have abnormal glucose metabolism and OGTT is needed to disclose these patients	The OGTT was only performed in 56% of patients without known diabetes
	Prevalence of prediabetes (see column left)	Small sample size, no control group without myocardial infarction
	The incidence of heart failure in prediabetic patients is 6% versus 3.2% in normal glycemic patients and 11.8% in diabetic patients	Older study (includes inhabitants of Reykjavik in 1966) with other criteria for heart failure and prediabetes
	In hospital mortality and mortality and morbidity long term (median follow-up 812 days) were higher in patients with abnormal glucose tolerance and diabetes	No use of FPG or OGTT to determine IGT
	Prevalence of prediabetes (see column left)	Small sample size. No repetition of glucose tests
	Prevalence of prediabetes (see column left)	Small sample size. No repetition of glucose tests
	IGT was associated with higher risk of future stroke, not with myocardial infarction or cardiac death	No use of FPG or OGTT to determine IGT. No repetition of glucose tests
	Prediabetes was associated with poor functional outcome or death and with no discharge to home	Glucose levels measured in the acute phase after stroke, possibly reflecting an acute stress response. No repetition of glucose tests
	Patients with prediabetes had similar outcomes (mortality and PAD intervention) to patients without diabetes	No OGTT performed, relatively short follow-up of 2 years
	The risk of cardiovascular diseases in patients with prediabetes and diabetes was higher in patients who also had metabolic syndrome	No OGTT performed
	Incidence reduction of diabetes 58% with lifestyle intervention and 31% with metformin (compared to placebo)	No information about confounders like weight loss, dietary changes and increased physical activity
	Using the Framingham score for 10-year CVD risk, the mean scores were highest in prediabetes group during 10 year follow-up. Restoration to normal glucose regulation and medical treatment of CVD risk factor can reduce the CVD risk	No results on hard CVD outcome yet. Variability in glucose measures
	Lifestyle intervention in prediabetes can reduce incidence of cardiovascular diseases and all-cause mortality and diabetes	Different follow-up methods were used. Lack of information about changes in behavior and cardiovascular risk factors after lifestyle intervention (blood pressure, cholesterol etc.)

In a group of 244 patients who received Coronary Artery Bypass Grafting (CABG), 24% had prediabetes with a successive increase in all-cause mortality and cardiovascular complications in the spectrum from normoglycemia through prediabetes to diabetes.[11] Additionally, a study of Selvin et al. showed that prediabetes and diabetes were independently associated with the development of subclinical myocardial damage, using hs-cTnT as marker for subclinical myocardial injury. The patients with evidence of subclinical damage were at highest risk for clinical events, particularly heart failure and mortality. [12]

In patients with chronic heart failure, the prevalence of prediabetes is around 40% in patients without known diabetes mellitus. [13-17] However, the literature on the association of prediabetes with adverse outcome in these patients is conflicting. One study showed no significant association between glucose values on admission and short- and long-term mortality in a large cohort of more than 50.000 patients hospitalized with heart failure. [18] However, the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) study clearly showed that the glycosylated hemoglobin A1c (HbA1c) level is an independent risk factor for cardiovascular as well as all-cause mortality and hospitalization for heart failure in patients with symptomatic heart failure. This association persisted in patients with prediabetes as well as diabetes mellitus, with an increased risk of cardiovascular events by 25% for every 1% increase in HbA1c level.[19] This is consistent with other studies which reported that prediabetes and diabetes at admission predicted mortality and more major cardiac and cerebrovascular events in heart failure patients, compared with normal admission glucose concentrations. [15,16]

Diabetic cardiomyopathy is a clinical condition with ventricular dysfunction in the absence of coronary atherosclerosis and hypertension. Insulin resistance in combination with hyperglycemia contributes to cardiac and structural abnormalities via reactive oxygen species (ROS) accumulation among other pathways. This results in myocardial hypertrophy and fibrosis with ventricular stiffness and chamber dysfunction. [6] The prevalence of this type of cardiomyopathy in patients with prediabetes is unknown. Only one echocardiographic study of Demmer et al. (n=1818 Hispanic/Latino men and women above 45 years old) showed unfavorable cardiac structure and function (particularly worsened measures of diastolic function) in patients with prediabetes (42% of all participants), persisting after adjusting for confounders like hypertension and adiposity. [20]

The prevalence of prediabetes in patients with a recent ischemic stroke or TIA is on average 34% in the acute phase (within 3 months after the event) and persists on 32% in the post-acute phase (≥3 months after the event). [21-27] In stroke patients, several studies show that prediabetes increases the risk of recurrent strokes and other macrovascular diseases, but there could also be underlying confounding. [28-32] Only a few studies have

assessed the influence of prediabetes on outcome after stroke and there seems to be a tendency of an association with poor outcome. Several studies found an association with poor functional outcome 30 days after stroke [33,34] and 1-year mortality [33]. However, other studies did not find an association with dependency at 1 year [34], neurological deterioration, poor functional outcome and mortality at 3 months [35]. Also, in patients receiving endovascular treatment for acute ischemic stroke, impaired fasting glucose was associated with unfavorable short-term outcome. [36] Interestingly, some data show the association of prediabetes with stroke, but not with myocardial infarction. [32]

A few studies analyzed the prevalence of prediabetes in patients with peripheral artery disease, and prediabetes was also highly prevalent, with a prevalence between 26% and 28%. [37-39] Whether prediabetes is associated with poor outcome in patients with peripheral artery disease is unknown.

PATHOPHYSIOLOGY

In our review, the focus is on macrovascular complications, and not on microvascular complications. Prediabetes is associated with macrovascular disease, but this increased risk seems to be modest according to a recent meta-analysis, with a relative risk of 1-1.7 with impaired fasting glucose (IFG) and IGT combined. [40] Being part of the metabolic syndrome, prediabetes alone is insufficient to explain the entire increased risk of macrovascular disease; the other components of the metabolic syndrome such as obesity, dyslipidemia and hypertension take part in the progression of the macrovascular disease with patients with prediabetes as well. [41,42]

Insulin resistance and defect glucose sensing resulting in beta-cell dysfunction are the main determinants that cause and predict hyperglycemia. This is a glycemic continuum extending from normal glucose regulation to diabetes mellitus type 2 and the development of macrovascular complications is hereby also a progressive process. Early endothelial dysfunction and vascular inflammation lead to monocyte recruitment, foam cell formation and subsequent development of fatty streaks. Eventually, this leads to atherosclerotic plaques, rupture and occlusive thrombus formation. Genetic influences can affect the beta-cell function, but overweight is also a known cause of impaired insulin action. The release of free fatty acids and cytokines from adipose tissue directly impairs insulin sensitivity. Also, oxidative stress plays a major role in the development of micro- and macrovascular diseases together with reactive oxygen species- driven epigenetic changes. [6,43]

It is not entirely clear whether the different forms of macrovascular complications share the same pathophysiological background in patients with prediabetes. One of the underlying mechanism of a negative outcome of prediabetes in patients with coronary

artery disease is that hyperglycemia increases stress-induced catecholamine release, which has a negative impact on myocardial metabolism and function. [6,12] As patients with chronic heart failure already have damaged myocardial tissue, the heart may be particularly susceptible to any toxic effects of elevated glucose levels, which can lead to increase in heart failure and mortality. [12]

Possible underlying mechanisms of the association of prediabetes with unfavorable outcome after stroke is that hyperglycemia can exert direct toxic effects and inflammation in stroke patients, which can also lead to impairment of mitochondrial function. [44,45] Moreover, hyperglycemia promotes blood coagulation mechanisms, thereby inducing atherosclerosis and plaque vulnerability, in patients with coronary artery disease as well as ischemic stroke. [46]

TREATMENT OF PREDIABETES AND RISK OF MACROVASCULAR DISEASE (PRIMARY PREVENTION)

Lifestyle intervention and risk of type 2 diabetes

In the Diabetes Prevention Program (DPP) trial, 3234 patients with prediabetes were randomly assigned to intensive lifestyle intervention, metformin treatment (850 mg twice daily) plus standard diet and exercise advices, or placebo with standard diet and exercise advices. The goals of the intensive lifestyle interventions were attaining and maintaining a weight reduction of at least 7 percent through diet and at least 150 minutes of physical activity of moderate intensity per week; a 16-lesson program covering diet, exercise, and behavior modification, followed by individual and group sessions during the whole follow-up period, were designed to help the participants achieve the goals. Lifestyle intervention decreased the incidence of type 2 diabetes by 58% compared with 31% in the metformin-treated group (average follow-up 2.8 years). Patients benefited the most if they were aged 60 years or less, had a BMI >35, and/or were women with a history of gestational diabetes. [47] The long-term follow up study of the DPP cohort (Diabetes Prevention Progress Outcome Study (DPPOS)) showed that the benefit of the abovementioned intensive lifestyle intervention persisted over 10 years with a reduction in cumulative incidence of diabetes of 34% compared with a reduction of 18% in the metformin group. [48]

Moreover, a recent meta-analysis found that lifestyle interventions were associated with a relative risk reduction of 39% and insulin-lowering medications with a reduction of 36% in diabetes incidence, with a range of follow-up of 0.5-6.3 years. At the end of the follow-up periods, lifestyle interventions achieved a reduction in relative risk of 28% in diabetes incidence (mean follow-up of 7.2 years). However, medication did not show a sustained relative risk reduction (mean follow-up of 17 weeks).

These results show that both lifestyle interventions and insulin-lowering therapy reduce diabetes incidence, but lifestyle interventions have a more prolonged effect. [49]

Lifestyle intervention and risk of macrovascular diseases

In the DPP-trial, patients with prediabetes with regression to normal glucose regulation had a significant decreased risk of macrovascular complications (stroke, congestive heart failure and peripheral artery disease) compared to individuals with persistent prediabetes after 10 years (Framingham 10-year cardiovascular risk score 15.5% in normal glucose regulation vs. 16.2% in prediabetes). This decreased risk of macrovascular complications in the DPP- trial is partially due to medical treatment of dyslipidemia and hypertension. [50]

Also, a recent study randomized 577 patients with impaired glucose tolerance in an intervention group (lifestyle, exercise or both) and a control group, with a long-term follow-up of 23 years after an initial lifestyle intervention program of 6 years. This study reported that this intervention program not only reduced the incidence of new-onset diabetes, but also cardiovascular mortality and all-cause mortality (cumulative incidence of cardiovascular mortality 11.9% in intervention group vs 19.6% in control group and all-cause mortality 28.1% vs 38.4%).[51] However, other interventions which might decrease cardiovascular complications, like lifestyle interventions and medical treatment of hypertension and dyslipidemia, were not mentioned in this study, so whether the effect was solely based on glucose lowering treatment is unknown.

Pharmacologic agents and risk of type 2 diabetes

Because maintaining adherence to strict lifestyle interventions has shown to be exceptionally difficult, the use of pharmacologic agents to prevent or delay new-onset diabetes is becoming more important. In general, pharmacologic treatment of prediabetes includes inhibition hepatic gluconeogenesis and reducing insulin resistance. Therefore, one of the first choices is treatment with metformin in combination with lifestyle changes. Metformin, in a dosage of 850 mg twice daily, studied in the DPP study, not only reduces the risk of developing type 2 diabetes in patients with impaired glucose tolerance [7,12-14,52,53] but also has additional favorable outcomes such as body mass index reduction and improved lipid profile, and is generally well-tolerated and safe. [12,13] Also, other antidiabetic drugs like the thiazolidinediones (rosiglitazone and pioglitazone) and alpha-glucosidase inhibitors (acarbose and voglibose) reduced the risk of progression to type 2 diabetes in patients with prediabetes. [13,14,53,54] Other possibilities are DPP4-inhibitors (such as sitagliptin) and GLP analogues (such as liraglutid). [55,56]

Pharmacologic agents and risk of macrovascular diseases

The STOP-NIDDM trial, in which a total of 1429 patients with impaired glucose tolerance were randomized to acarbose (titrated gradually from 50 mg once a day to a maximum of 100 mg 3 times daily or to the maximum tolerated dose for the rest of the study) or

placebo with a mean follow-up of 3.3 years, showed that treatment with acarbose leads to a lower incidence of hypertension and cardiovascular diseases (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event and peripheral vascular disease), also after adjustment for other vascular risk factors. [57] Furthermore, in another randomized controlled trial (median follow-up year of 2.4 years), 602 patients with impaired glucose tolerance were randomized to treatment with pioglitazone 45 mg once daily or placebo. The results showed not only a reduced risk on conversion to type II diabetes, but also a slowed progression of carotid-intima-thickening in the pioglitazone-treated patients. [58] As carotid-intima-thickening correlates with cardiovascular events, changes in this measure over time might have predictive value. [59]

In conclusion, multiple studies show that treatment of prediabetes, either with lifestyle-intervention or anti-diabetic medication as well as treatment of other cardiovascular risk factors, lead to a lower risk of macrovascular diseases in primary prevention.

TREATMENT OF PREDIABETES AND THE INFLUENCE ON OUTCOME AFTER MACROVASCULAR DISEASE (SECONDARY PREVENTION)

Only a few studies investigated the effects of oral antidiabetic drugs in patients with impaired glucose tolerance and acute coronary syndrome. In one study, treatment with sitagliptin 100 mg once daily for 12 weeks improved beta-cell function and post-load glucose metabolism as compared to placebo, but no improvement of endothelial function. [60]

In patients with heart failure, it is still uncertain whether strict glycemic control alters the risk of future cardiovascular events. One small study of 30 patients with impaired glucose tolerance and chronic heart failure were treated with voglibose, an alpha-glucosidase inhibitor, and their results showed an improved cardiac function.[61] However, some studies also showed potential harm with glucose-lowering medications, like fluid retentions due to thiazolidinediones. [62,63]

In patients with TIA or minor ischemic stroke and impaired glucose tolerance, treatment with metformin, 1000 mg twice daily, leads to reduction of 2-hour postload glucose levels.[64] Recently, a multicenter randomized controlled trial showed that in non-diabetic stroke patients with insulin resistance, pioglitazone (target dose 45 mg once daily) decreased the risk of stroke, myocardial infarction and diabetes. However, pioglitazone was also associated with higher risk of weight gain, edema and fracture.[65] A current ongoing multicenter randomized trial in the Netherlands, the MAAS-trial, investigates the feasibility, safety, and effects on glucose metabolism of both metformin (in ascending dosage to a maximum of 1000 mg twice daily) and sitagliptin, 100 mg once daily, in patients with TIA or minor ischemic stroke and impaired glucose tolerance. [66]

It is not known yet whether glucose lowering treatment has an effect on functional outcome or mortality in patients with prediabetes and established macrovascular complications. Also, there is no evidence available about whether glucose lowering treatment has an additional effect on the risk of developing macrovascular complications in patients who also receive treatment for dyslipidemia and hypertension.

In summary, there is only little evidence that treatment of prediabetes in patients with macrovascular diseases decreases the recurrence of macrovascular diseases and improves outcome. More studies are needed to confirm this.

CONCLUSION

Prediabetes is highly prevalent in patients with macrovascular disease and increases the risk for type 2 diabetes and macrovascular events with adverse outcome. Prediabetes could therefore become an important therapeutic target in both primary and secondary prevention. Both lifestyle modification and antidiabetic drugs decrease the risk of developing type 2 diabetes, and also prevent developing macrovascular disease. Whether treatment of prediabetes in patients with established macrovascular disease is beneficial as part of secondary prevention needs further studies.

RECOMMENDATIONS

We recommend to try to restore normal glucose regulation or to prevent or delay the progression to type 2 diabetes by lifestyle interventions (a combination of weight reduction, diet and physical activity). In concordance with the American Diabetes Association, lifestyle interventions are recommended in patients with impaired glucose tolerance, impaired fasting glucose and/or elevated HbA1c. [4] Because lifestyle intervention is difficult to sustain, antidiabetic medication can also be considered, of which metformin is the most extensively studied. In those individuals at highest risk for developing diabetes and who benefited most in the DPP study (age 60 years or less, BMI >35, women with a history of gestational diabetes) metformin treatment should be considered in primary prevention.

CONFLICTS OF INTEREST

None.

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CHAPTER 3

Prognostic impact of disturbed glucose metabolism in patients with stroke

CHAPTER 3.1

Glucose in prediabetic and diabetic range and outcome after stroke

E. Osei
S. Fonville
A.A.M. Zandbergen
P.J. Koudstaal
D.W.J. Dippel
H.M. den Hertog

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ABSTRACT

Background

Newly diagnosed disturbed glucose metabolism is highly prevalent in patients with stroke. Limited data are available on their prognostic value on outcome after stroke. We aimed to assess the association of glucose in the prediabetic and diabetic range with unfavorable short-term outcome after stroke.

Methods

We included 839 consecutive patients with ischemic stroke and 168 patients with intracerebral hemorrhage. In all nondiabetic patients, fasting glucose levels were determined on day 2-4. Prediabetic range was defined as fasting glucose of 5.6-6.9 mmol/L, diabetic range as ≥ 7.0 mmol/L, pre-existent diabetes as the use of anti-diabetic medication prior to admission. Outcome measures were poor functional outcome or death defined as modified Rankin Scale (mRS) score >2 and discharge not to home. The association of prediabetic range, diabetic range and pre-existent diabetes (versus normal glucose) with unfavorable outcome was expressed as odds ratios, estimated with multiple logistic regression, with adjustment for prognostic factors.

Results

Compared with normal glucose, prediabetic range (aOR 1.8; 95%CI 1.1-2.8), diabetic range (aOR 2.5; 95%CI 1.3-4.9) and pre-existent diabetes (aOR 2.6; 95%CI 1.6-4.0) were associated with poor functional outcome or death. Patients in the prediabetic range (aOR 0.6; 95%CI 0.4-0.9), diabetic range (aOR 0.4; 95%CI 0.2-0.9) and pre-existent diabetes (aOR 0.6; 95%CI 0.4-0.9) were more likely not to be discharged to home.

Conclusions

Patients with glucose in the prediabetic and diabetic range have an increased risk of unfavorable short-term outcome after stroke. These findings illustrate the potential impact of early detection and treatment of these patients.

INTRODUCTION

Diabetes mellitus type 2 is an independent risk factor for stroke, and is clearly associated with poor functional outcome after stroke. [1-9]

Prediabetes is an intermediate metabolic state between normal glucose tolerance and diabetes mellitus, and is associated with an increased risk of developing type 2 diabetes. Prediabetes and newly diagnosed diabetes are highly prevalent in patients with stroke without known diabetes prior to the event, varying from 23% to 52% and 16% to 26%, respectively [10-15], and are associated with an increased risk of recurrent stroke and other cardiovascular diseases [16-19].

Little is known about the prognostic value of newly diagnosed disturbed glucose metabolism on outcome after stroke. Two recent studies found a trend towards an association between newly diagnosed disturbed glucose metabolism and unfavorable outcome or mortality after stroke. [20,21] The mechanisms underlying these associations are not fully understood, but may involve enhanced post-ischemic inflammatory responses, increased blood-brain barrier permeability and hypercoagulable state, which can induce vascular complications and result in worse outcome after stroke. [22-26]

In this study, we aimed to assess the association of patients with glucose in the prediabetic and diabetic range with unfavorable outcome after stroke, compared with patients with normal glucose metabolism.

METHODS

Study population

Patients were derived from the Erasmus Stroke Study, an ongoing registry of patients with cerebrovascular diseases treated at the Erasmus Medical Centre Rotterdam, the Netherlands. All consecutive patients with a clinical diagnosis of acute ischemic stroke or intracerebral hemorrhage between December 2005 and January 2011 were included. Baseline clinical information included stroke severity assessed by means of the National Institutes of Health Stroke Scale (NIHSS), ischemic stroke subtype according to the TOAST classification [27] and cardiovascular risk factors. Pre-existent hypertension was defined as the use of anti-hypertensive medication prior to admission. Written consent was obtained from all the patients as approved by the institutional ethics committee.

Glucose assessment

In all nondiabetic patients, fasting glucose levels were measured on day two to four of admission (median time on day 2, IQR 2-4). Glucose in the prediabetic range was defined as fasting glucose levels of 5.6 to 6.9 mmol/L, and glucose in the diabetic range as 7.0 mmol/L or over according to the American Diabetes Association criteria [28]. Pre-existent

diabetes was defined as the use of oral or parenteral anti-diabetic medication prior to admission. Acute hyperglycemia was defined as admission blood glucose level of > 7.8 mmol/L.

Outcome measures

Unfavorable outcome or death was defined as modified Rankin Scale (mRS) score >2 at the end of hospital stay or discharge. Secondary outcome measures included discharge not to home. The outcome measures were determined by neurologists who were not aware of which glucose groups applied to their patients.

Statistical analyses

Means with standard deviations were used for normally distributed continuous variables. For the nonnormally distributed continuous variables and the ordinal variables, medians with interquartile ranges were used.

We compared patient characteristics between glucose groups. The differences in patient characteristics were tested by one-way analysis of variance (ANOVA) for normally or log-normally continuous distributed variables, Kruskal-Wallis for nonnormally continuous distributed variables and $\chi^{2\ for}$ categorical variables. We also compared patient characteristics between patients with good and poor functional outcome and between discharge and no discharge to home. Categorical variables were tested by χ^2 and continuous variables by Students t-test. Nonnormally distributed variables were compared by Mann-Whitney's test. $p < 0.05$ was considered statistically significant.

The relationship between glucose groups or acute hyperglycemia on the one hand and unfavorable functional outcome or discharge not to home on the other were expressed as odds ratios (ORs) with a corresponding 95% confidence interval (CI). Estimates were calculated with multiple logistic regression models, which were adjusted for multiple confounders. These confounders where chosen from the patient characteristics which differed significantly between the glucose groups and also between the outcome measures. Furthermore, we tested the difference in the effect of glucose groups on outcome between hyperglycemic and nonhyperglycemic patients and between patients with and without statin use prior to the event with a test for interaction.

The analysis was carried out with STATA 12.1 statistical package (Statacorp, College Station, Texas).

RESULTS

Between December 2005 and January 2011, 1322 consecutive patients were included in the Erasmus Stroke study. Of these, 315 patients (23.8%) were excluded because of

missing fasting glucose values. The excluded patients had higher NIHSS scores on admission and were significantly older (data not shown).

Of the remaining 1007 patients, mean age was 63 years (SD 15), 542 (53.8%) were men, and 839 (83.3%) had ischemic stroke. Two-hundred and thirteen patients (21.2%) had glucose in the prediabetic range, 78 (7.7%) had glucose in the diabetic range, 218 (21.6%) were classified as pre-existent diabetes and 498 (49.5%) patients had normal glucose metabolism. Patients with glucose in the prediabetic range, diabetic range and with pre-existent diabetes were significantly older and more often had hypertension than patients with normal glucose metabolism. Patients with pre-existent diabetes more often used statins before admission compared to the other glucose groups. Patients with glucose in the diabetic range were more often diagnosed with intracerebral hemorrhage than patients in the other glucose groups. Normal glycemic patients had less severe strokes on admission and were more often treated with intravenous tissue plasminogen Recombinant Alteplase compared to the other glucose groups (Table 1).

Table 1: Patients characteristics per glucose group

	Normal glucose (n=498)	**Prediabetic range (n=213)**	**Diabetic range (n=78)**	**Pre-existent diabetes (n=218)**	**p**
Median fasting glucose levels (IQR), mmol/L	5.0 (4.7-5.3)	6.1 (5.9-6.4)	7.9 (7.3-9.2)	7.2 (5.8-9.8)	<0.01
Median acute glucose levels (IQR), mmol/L	5.9 (5.4-6.8)	6.8 (5.9-7.8)	8.5 (7.0-10.9)	9.9 (7.4-12.6)	<0.01
Mean age ± SD, years	61±16	65±14	66±15	66±12	<0.01
Male, n (%)	261 (52%)	110 (52%)	39 (50%)	132 (61%)	0.16
Vascular risk factors					
Previous and current smoking, n (%)	289 (58%)	126 (59%)	35 (45%)	92 (42%)	<0.01
Pre-existent use of anti-hypertensive medication, n (%)	226 (45%)	125 (59%)	42 (54%)	166 76%)	<0.01
Median acute systolic blood pressure (IQR), mmHg	160 (135-180)	170 (151-192)	176 (146-200)	170 (150-200)	<0.01
Median acute diastolic blood pressure (IQR), mmHg	86 (74-100)	90 (78-100)	86 (74-97)	86 (76-100)	0.34
Pre-existent use of statins, n (%)	113 (23%)	60 (28%)	15 (19%)	121 56%)	<0.01
Median total cholesterol (IQR), mmol/L	4.8 (4.1-5.6)	4.9 (4.1-5.9)	4.9 (3.9-5.8)	4.2 (3.5-5.2)	<0.01
Median HDL-cholesterol (IQR), mmol/L	1.3 (1.0-1.6)	1.3 (1.0-1.5)	1.3 (1.0-1.5)	1.1 (0.9-1.3)	<0.01
Median LDL-cholesterol (IQR), mmol/L	2.9 (2.4-3.8)	3.1 (2.4-4.0)	3.1 (2.3-3.7)	2.5 (2.0-3.2)	<0.01

Table 1: Patients characteristics per glucose group

	Normal glucose (n=498)	**Prediabetic range (n=213)**	**Diabetic range (n=78)**	**Pre-existent diabetes (n=218)**	**p**
Median triglycerides (IQR), mmol/L	1.3 (0.9-1.7)	1.3 (1.0-1.8)	1.2 (0.9-1.8)	1.5 (1.2-2.2)	<0.01
Previous and newly diagnosed paroxysmal atrial fibrillation, n (%)	42 (8%)	17 (8%)	10 (13%)	27 (12%)	0.23
Treatment ischemic stroke					
Treatment with rtPA, n (%)	70 (14%)	24 (11%)	6 (8%)	10 (5%)	<0.01
Endovascular treatment, n (%)	10 (2%)	3 (1%)	4 (5%)	1 (1%)	0.02
Stroke subtype					
Primary intracerebral hemorrhage, n (%)	59 (12%)	37 (17%)	28 (36%)	44 (20%)	<0.01
Stroke severity					
Median NIHSS score on admission, (IQR)	3 (1-7)	3 (1-9)	2 (6-14)	4 (2-8)	<0.01
Ischemic stroke etiology					
Large vessel infarction, n (%)	72 (16)	45 (26%)	17 (22%)	28 (13%)	0.04
Cardio embolism, n (%)	61 (14)	25 (12%)	8 (10%)	25 (11%)	0.96
Lacunar infarction, n (%)	105 (24)	31 (17%)	10 (13%)	47 (22%)	0.07
Other determined etiology, n (%)	26 (6)	10 (5%)	0	8 (4%)	0.19
Undetermined etiology, n (%)	175 (40)	65 (37%)	14 (29%)	66 (38%)	0.02

The p values are the results of comparisons among the glucose groups
rtPA: recombinant tissue Plasminogen Activator. NIHSS: National Institutes of Health Stroke Scale. Ischemic stroke etiology: According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria

A total of 362 (35.9%) patients had unfavorable functional outcome or died and 597 patients (59.8%) were discharged to home.

The logistic regression was adjusted for the following factors: age, sex, NIHSS score on admission, pre-existent hypertension, previous and newly diagnosed atrial fibrillation, treatment with recombinant tissue Plasminogen Activator (rtPA), lacunar infarction according to TOAST classification [24], previous and current smoking and intracerebral hemorrhage. (Table 2 and 3)

Table 2: Patient characteristics compared between patients with good and poor functional outcome

Patient characteristics	Good functional outcome (n=645)	Poor functional outcome or death (n=362)	p
Male, n (%)	359 (56)	183 (51)	0.10
Mean age (SD), years	61 (14)	68 (15)	<0.01
Median total NIHSS score on admission (IQR)	2 (1-4)	10 (5-16)	<0.01
Pre-existent use of antihypertensive medication, n (%)	342 (53)	217 (60)	0.03
Pre-existent use of statins, n (%)	210 (33)	99 (27)	0.09
Previous and newly diagnosed paroxysmal atrial fibrillation, n (%)	50 (8)	46 (13)	0.01
Previous and current smoking, n (%)	383 (59)	159 (44)	<0.01
Intracerebral hemorrhage, n (%)	62 (10)	106 (29)	<0.01
Large vessel infarction, n (%)	95 (15)	67 (19)	0.12
Lacunar infarction, n (%)	160 (25)	33 (9)	<0.01
Treatment with iv-rtPA, n (%)	60 (9)	50 (14)	<0.01
Prediabetic range, n (%)	127 (20)	86 (24)	0.13
Diabetic range, n (%)	31 (5)	47 (13)	<0.01
Pre-existent diabetes, n (%)	117 (18)	101 (28)	<0.01

NIHSS: National Institutes of Health Stroke Scale. rtPA: recombinant tissue Plasminogen Activator. Large vessel infarction and lacunar infarction are defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST)-criteria.

Table 3: Patient characteristics compared between patients who were discharged to home to patients who were not discharged to home

Patient characteristics	Discharge to home (n=597)	No discharge to home (n=410)	p
Male, n (%)	349 (58)	193 (47)	<0.01
Mean age (SD), years	60 (14)	68 (15)	<0.01
Median total NIHSS score on admission (IQR)	2 (1-4)	8 (4-15)	<0.01
Pre-existent use of antihypertensive medication, n (%)	313 (52)	246 (60)	0.02
Pre-existent use of statins, n (%)	115 (28)	194 (33)	0.13
Previous and newly diagnosed paroxysmal atrial fibrillation, n (%)	40 (7)	56 (14)	<0.01
Previous and current smoking, n (%)	369 (62)	173 (42)	<0.01
Intracerebral hemorrhage, n (%)	44 (7)	124 (30)	<0.01
Large vessel infarction, n (%)	84 (14)	78 (19)	0.04
Lacunar infarction, n (%)	155 (26)	38 (9)	<0.01
Treatment with iv-rtPA, n (%)	60 (10)	50 (12)	0.28
Prediabetic range, n (%)	113 (19)	100 (24)	0.04
Diabetic range, n (%)	27 (5)	51 (12)	<0.01
Pre-existent diabetes, n (%)	114 (19)	104 (25)	0.02

NIHSS: National Institutes of Health Stroke Scale. rtPA: recombinant tissue Plasminogen Activator. Large vessel infarction and lacunar infarction are defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST)-criteria.

There were 347 (34.6%) patients with acute hyperglycemia. Hyperglycemia was associated with poor functional outcome or death (aOR 1.5, 95%CI 1.0-2.1). Compared with normal glucose metabolism, patients with glucose in the prediabetic range (aOR 1.8; 95%CI 1.1-2.8), diabetic range (aOR 2.5; 95%CI 1.3-4.9) and with pre-existent diabetes (aOR 2.6; 95%CI 1.6-4.0) were associated with poor functional outcome or death. Furthermore, patients in the prediabetic range (aOR 0.6; 95%CI 0.4-0.9), diabetic range (aOR 0.4; 95%CI 0.2-0.9) and with pre-existent diabetes (aOR 0.6; 95%CI 0.4-0.9) were more likely not to be discharged to home. Also, see Table 4 and 5. The test for interaction showed no significant difference in the effect of glucose groups on outcome between hyperglycemic and nonhyperglycemic patients and between patients with and without statins use prior to the event (p-values >0.05, data not shown).

Table 4: The number of patients in the glucose groups with the different outcome measures, with corresponding p value (compared with normal glucose metabolism)

	Normal glucose metabolism (n=498)	**Prediabetic range (n=213)**	**Diabetic range (n=78)**	**Pre-existent diabetes (n=218)**
Poor functional outcome or death, n (%) p	128 (26)	86 (40) 0.13	47 (60) <0.01	101 (46) <0.01
No discharge to home, n (%) p	155 (31)	100 (47) 0.04	51 (65) <0.01	104 (48) 0.02

Table 5: Association of patients with glucose in the prediabetic range, diabetic range and pre-existent diabetes with different outcome measures, with normal glucose metabolism as reference group

	Prediabetic range	**Diabetic range**	**Pre-existent diabetes**
Poor functional outcome or death, aOR (95%CI)	1.8 (1.1-2.8)	2.5 (1.3-4.9)	2.6 (1.6-4.0)
Discharge to home, aOR (95%CI)	0.6 (0.4-0.9)	0.4 (0.2-0.9)	0.6 (0.4-0.9)

Adjusted factors: age, sex, NIHSS score on admission, pre-existent hypertension, previous paroxysmal atrial fibrillation, treatment with rtPA, lacunar infarction according to TOAST-criteria, previous and current smoking, intracerebral hemorrhage

DISCUSSION

We found that patients with glucose in the prediabetic and diabetic range have an increased risk of unfavorable short-term outcome, compared to patients with normal glucose metabolism. This association matched that of pre-existent diabetes mellitus.

A few studies assessed the association between newly diagnosed disturbed glucose metabolism and outcome after stroke. [20,21] One study showed that patients with

newly diagnosed disturbed glucose metabolism tended to have an increased risk of poor outcome. However, this study was small, and therefore the increased risk in the group of patients with prediabetes did not reach the level of significance. [20] Another study found that impaired glucose tolerance was an independent risk factor for 1-year mortality, but not for dependency or stroke recurrence. [21] Other previous studies have demonstrated that newly detected impaired glucose tolerance is a strong predictor of future cardiovascular events [16-18] and is associated with a higher case fatality after stroke [3].

Strengths of our study are its large sample size, detailed information on confounders, and robust outcome measures.

Our study also has some limitations. First, patients with missing fasting glucose levels were excluded. The patients with missing fasting glucose levels had more severe strokes and/or were in a poor medical condition or were referred to another hospital. This might affect generalizability. However, there were no significant differences in sex, medical history and vascular history between the in- and excluded patients. Furthermore, fasting glucose values were measured from day two to four of admission. Disturbed glucose metabolism in the acute phase can be transient, reflecting an acute stress response. [29-30] This could have caused an overestimation of patients with glucose in the prediabetic and diabetic range. However, adjustment for acute hyperglycemia did not attenuate the association between the patients in the prediabetic and diabetic range and unfavorable outcome. Also, as fasting glucose values were not repeated, laboratory error could not be ruled out. HbA1c values would have been more indicative for the prestroke glycemia status. Unfortunately, these data were not recorded. Furthermore, there was no data available on the exact number of days of admission per patient. Also, adjustments could not be made for possible rapid changes in the NIHSS-score in the first hours of stroke.

The prevalence of patients in the prediabetic range (21.2%) was similar to other studies. [10-14,31] However, the prevalence of patients in the diabetic range (7.7%) was relatively low. Recent studies showed that 2-hour post load glucose identifies more patients with prediabetes and newly diagnosed diabetes than fasting plasma glucose alone. [10] We only used fasting plasma glucose, this might have caused an underestimation of patients with glucose in the prediabetic and diabetic range.

The association of glucose in the prediabetic and diabetic range with unfavorable outcome could be explained by several pathophysiological disturbances. First, acute hyperglycemia can exacerbate ischemic damage through enhanced neutrophil infiltration and plasma corticosteroids, and formation of O-linked glycoproteins. [22] An earlier study showed that diabetic mice had bigger infarctions and worsened neurological status due to an accumulation of cerebral water, increased inflammation and curtailed induction

of heat shock chaperone gene expression compared to normal glycemic mice. [23] In hyperglycemic mice, an imbalance of matrix metalloprotease-9 and tissue inhibitors of metalloproteases lead to greater neutrophil invasion, a compromised blood-brain barrier and consequently more severe tissue damage. [24] Lastly, hyperglycemia can also contribute to worse outcome after stroke by acceleration of blood coagulation mechanisms, with an elevated plasma factor VIIa. [25]

Glucose in the diabetic range was more prevalent in patients with more severe strokes. One may argue that disturbed glucose metabolism does not accelerate the ischemic cascade, but merely reflects extensive cerebral damage and thereby unfavorable outcome. However, the relationship between glucose in the prediabetic and diabetic range and poor outcome was independent of initial stroke severity.

In conclusion, patients with glucose in the prediabetic and diabetic range have an increased risk of unfavorable short-term outcome after stroke. These findings illustrate the potential impact of early detection and treatment of these patients. In patients with prediabetes, lifestyle interventions and pharmacological treatment reduce the rate of progression to diabetes mellitus type 2. [32] Whether these interventions reduce the risk of cardiovascular complications and improve functional outcome deserves further study.

CONFLICTS OF INTEREST

None.

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CHAPTER 3.2

Prediction of persistent impaired glucose tolerance in patients with TIA or minor ischemic stroke

E. Osei
H.M. den Hertog
S. Fonville
P.J.A.M. Brouwers
L.J.M.M. Mulder
P.J. Koudstaal
D.W.J. Dippel
A.A.M. Zandbergen
H.F. Lingsma

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ABSTRACT

Background

Impaired glucose tolerance (IGT) in patients with ischemic stroke can return to normal, reflecting an acute stress response, or persist. Persistent IGT is associated with an increased risk of recurrent stroke, other cardiovascular diseases and unfavorable outcome after stroke. We aim to validate our previously developed model to identify patients at risk of persistent IGT in an independent data set, and, if necessary, update the model.

Methods

The validation data set consisted of 239 nondiabetic patients with a minor ischemic stroke or TIA and IGT in the acute phase (2-hour post-load glucose levels between 7.8 and 11.0 mmol/l). The outcome was persistent versus normalized IGT, based on repeated oral glucose tolerance test after a median of 46 days. The discriminative ability of the original model was assessed with the area under the ROC curve (AUC). The updated model was internally validated with bootstrap resampling and cross-validated in the development population of the original model.

Results

One-hundred eighteen of 239 (49%) patients had persistent IGT. The original model, with the predictors age, current smoking, statin use, triglyceride, hypertension, history of cardiovascular diseases, body mass index (BMI), fasting plasma glucose performed poorly (AUC 0.60). The newly developed model included only BMI, hypertension, statin use, atrial fibrillation, 2-hour post-load glucose levels, HbA1c, large artery atherosclerosis, and predicted persistent IGT more accurately (internally validated AUC 0.66, externally validated AUC 0.71).

Conclusions

This prediction model with simple clinical variables can be used to predict persistent IGT in patients with IGT directly after minor stroke or TIA, and may be useful to optimize secondary prevention by early identification of patients with disturbed glucose metabolism.

INTRODUCTION

Impaired glucose tolerance (IGT) is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus, with a growing prevalence worldwide. IGT is highly prevalent in patients with recent ischemic stroke or transient ischemic attack (TIA). This IGT can be transient, reflecting an acute stress response, or persistent, representing undiagnosed impaired glucose metabolism. [1] Of nondiabetic stroke patients with IGT in the acute phase after stroke and repeated glucose assessment after 3 months, 22–47% has persistent IGT after 3 months. [1–4]

IGT increases the risk of recurrent stroke and other cardiovascular events. [5,6] Moreover, IGT is also associated with poor functional outcome and mortality after stroke. [5,7,8] Glucose lowering medication or lifestyle interventions may be beneficial for these patients, in the acute phase as well as part of secondary prevention. In a previous study by our group, we developed a prediction model to identify patients with persistent impaired glucose tolerance at 3 months after TIA and ischemic stroke. This prediction model including age, current smoking, statin use, triglyceride, hypertension, previous ischemic cardiovascular disease, body mass index, and fasting plasma glucose accurately predicted persistent IGT. [4] However, this prediction model has not been externally validated in an independent population.

The aim of our study was to externally validate the original prediction model and, if necessary, to update the model to identify patients at risk of persistent IGT after TIA and minor stroke.

METHODS

Study population

Patients were included if they were 18 years or older and attended the TIA outpatient clinic, or were admitted to the stroke unit of Medical Spectrum Twente in Enschede and Ikazia Hospital in Rotterdam, the Netherlands between February 2014 and December 2017. These patients had a clinical diagnosis of TIA, amaurosis fugax or minor ischemic stroke (defined as a modified Rankin scale score of 3 or less) within the previous 6 months. Written informed consent was obtained from all patients or a first-degree relative, as approved by the Institutional Ethics Committee.

Patient characteristics

Demographic data, vascular history and risk factors, including statin use, hypertension (defined as previous use of antihypertensive medication or blood pressure higher than 140/90 mmHg), current smoking, atrial fibrillation, body mass index (BMI), laboratory assessments, including lipid profile and ischemic stroke subtype according to the TOAST classification [9] were collected.

Glucose assessment

In all nondiabetic patients (defined as no use of oral or parenteral antidiabetic medication), fasting plasma glucose and post-load glucose levels were assessed on the day of the TIA outpatient clinic visit or the second day of admission on the stroke unit as part of standard care. Post-load glucose levels were assessed by performing the oral glucose tolerance test (OGTT). The OGTT was performed after overnight fasting, and patients drank a solution of 75 g glucose in 150 mL water. Eligible patients were diagnosed with IGT, defined as 2-hour post-load glucose levels between 7.8 and 11.0 mmol/L. [10] The glycosylated hemoglobin A1c levels (HbA1c) were assessed at the follow-up visit, two to 12 weeks after admission and at 6 months.

Outcome measures

Two to 12 weeks after the initial OGTT, patients with IGT were asked to undergo a second OGTT. We previously stated in the study protocol that the OGTT should be repeated after 2-6 weeks. Due to logistic reasons, this time frame was extended to 2-12 weeks. Patients with fasting plasma glucose levels of 7.0 mmol/L or higher were diagnosed with diabetes and therefore did not undergo the repeated OGTT. Based on the results of the second OGTT, patients were classified in the following two groups: normalized post-load-glucose levels (2-hour post-load-glucose levels < 7.8 mmol/L) or persistent IGT (2-hour post-load glucose levels ≥ 7.8 mmol/L according to international guidelines ([10]).

Statistical analysis

We used means with standard deviations to describe normally distributed continuous variables, and medians and interquartile ranges to describe the non-normally distributed continuous variables. We compared patient characteristics between glucose groups, with normalized post-load-glucose levels as a reference. The differences between categorical variables were tested by chi-square and continuous variables by Student's t-test. Non-normally distributed variables were compared by Mann–Whitney U-test. $P < 0.05$ was considered to indicate statistical significance. Missing data were imputed with single imputation using baseline characteristics and the outcome variable, if the frequency was less than 5%. The analysis was carried out with STATA 12.1 statistical package (Statacorp, College Station, Texas) and R statistical software.

Model validation

First, we compared patient characteristics between the current study and the previous (development cohort). [4] Second, to assess the validity of the original prediction model, we assessed the effect of the predictors of the original model in the current development population. As the final validation step, overall model performance was assessed in terms of discrimination and calibration. Calibration refers to the agreement between observed and predicted outcomes. Calibration plots were used to visualize the observed

and predicted rates. The intercept shows whether predictions are systematically too low or too high, and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model, and was estimated in a logistic regression model. In a perfect model, the slope is 1. Discrimination refers to the ability to distinguish a patient with and without persistent IGT, with the use of the area under the ROC curve (AUC). The AUC ranges from 0.5 for noninformative to 1.0 for perfect models. [11]

Model development

The next, optional third step was to develop a new, updated model. Possible predictors of persistent IGT included known risk factors for developing diabetes and other vascular risk factors according to the previous literature: age, sex, current smoking, statin use, hypertension, previous ischemic cardiovascular disease, atrial fibrillation, BMI, TIA versus ischemic stroke, large artery atherosclerosis, fasting plasma glucose, 2-hour post-load glucose, and HbA1c levels. [1–3,12–15] Large artery atherosclerosis was defined as significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, due to atherosclerosis. [9]

All potential predictors were tested with a multivariable logistic regression model and tested for the final model with stepwise backward selection, with a p-value of ≤ 0.2. The internal validity of the model was assessed by means of bootstrapping techniques, resulting in an internally validated AUC. A bootstrap sample means that a random sample of the same size of the original population is drawn with replacement. The model is developed in the bootstrap sample and evaluated in the original sample. To obtain stable results, the procedure has to be repeated multiple times. For correction of too optimistic estimation of the predictive value, we performed shrinkage of the regression coefficients based on the difference between the apparent and internally validated AUC.

As a fourth step, we assessed the external validity of the new updated model by testing the performance of the new model in the population that was used to develop the original model. [4]

RESULTS

Study population

A total of 239 patients had IGT based on the first OGTT. Mean age was 68 years (SD 10 years), 134 (56%) patients were men, 136 (57%) had ischemic stroke, 158 (66%) had hypertension, and 195 (82%) used statins.

Of the total of 239 patients, 118 (49%) had persistent IGT based on the repeated OGTT performed after a median of 46 days (IQR 33). In patients with persistent IGT, mean BMI, HbA1c, triglycerides and LDL-levels were significantly higher than patients with

normalized IGT. Patients with persistent IGT more frequently had hypertension and atrial fibrillation than patients with normalized IGT. (Table 1)

A total of 105 patients were included within 6 weeks after TIA or ischemic stroke and 11 patients around 6 months after the event. The percentage of persistent IGT was quite similar in both groups: 52 of the 105 patients (50%) and 6 of the 11 patients (55%) respectively.

Table 1. Patient characteristics compared between transient impaired glucose tolerance and persistent impaired glucose tolerance

	Total population (n=239)	**Transient impaired glucose tolerance (n=121)**	**Persistent impaired glucose tolerance (n=118)**	**p-value**
Age, years (SD)	68 (10)	68 (10)	69 (11)	0.30
Sex (male), n (%)	134 (56%)	70 (58%)	64 (54%)	0.57
Vascular risk factors				
Current smoking, n (%)	35 (15%)	16 (13%)	19 (16%)	0.53
BMI in kg/m^2, mean (SD)	27 (4)	26 (4)	28 (4)	<0.01
Hypertension, n (%)	158 (66%)	71 (59%)	87 (74%)	0.01
Statin use, n (%)	195 (82%)	94 (78%)	101 (86)	0.12
Atrial fibrillation, n (%)	24 (10%)	6 (5%)	18 (15%)	<0.01
Vascular history				
Ischemic cardiovascular disease, n (%)	72 (30%)	37 (31%)	35 (30%)	0.88
Event				
Ischemic stroke, n (%)	136 (57%)	68 (56%)	68 (58%)	0.82
TOAST classification				*0.09*
Large artery atherosclerosis, n (%)	33 (14%)	14 (12%)	19 (16%)	
Cardioembolism, n (%)	26 (11%)	8 (7%)	18 (15%)	
Small vessel occlusion, n (%)	117 (49%)	61 (50%)	56 (48%)	
Other determined etiology, n (%)	2 (1%)	1 (1%)	1 (1%)	
Unknown, n (%)	60 (25%)	37 (31%)	23 (20%)	
Glucose assessment during admission/visiting TIA clinic				
Fasting glucose levels, mean (SD), mmol/L	5.5 (0.5)	5.5 (0.5)	5.5 (0.8)	0.35
2-hour postload glucose levels, mean (SD), mmol/L	9.1 (1)	8.9 (0.8)	9.4 (0.9)	<0.01
HbA1c, mean (SD), mmol/mol	38 (3)	37 (3.3)	38 (3.1)	<0.01
Days between event and first OGTT, median (IQR)	46 (33)	44 (30)	47 (36)	0.69

Table 1. Patient characteristics compared between transient impaired glucose tolerance and persistent impaired glucose tolerance

	Total population (n=239)	Transient impaired glucose tolerance (n=121)	Persistent impaired glucose tolerance (n=118)	p-value
Lipid profile				
Total cholesterol, mean (SD), mmol/L	5 (1.2)	5.0 (1.2)	4.9 (1.1)	0.35
Triglycerides, mean (SD), mmol/L	1.5 (0.7)	1.3 (0.7)	1.4 (0.7)	0.05
HDL-cholesterol, mean (SD), mmol/L	2.9 (1)	1.7 (0.8)	1.4 (0.6)	<0.01
LDL-cholesterol, mean (SD), mmol/L	1.3 (0.6)	2.9 (1)	3 (0.9)	0.58

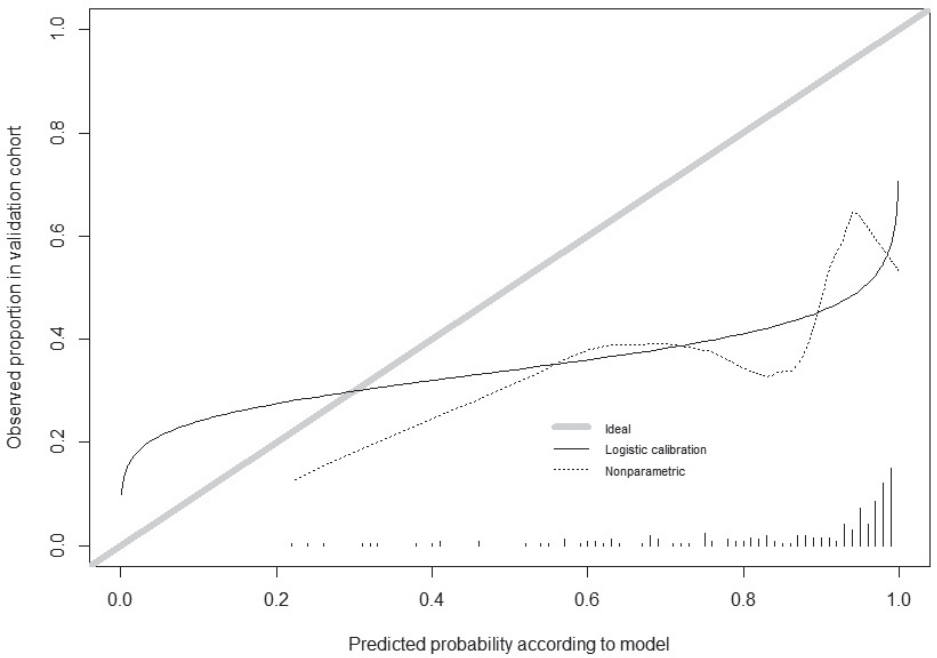
BMI: body mass index. TIA: transient ischemic attack. TOAST: Trial of Org 10172 in Acute Stroke Treatment. HbA1c: glycosylated Hemoglobin 1c. OGTT: oral glucose tolerance test.

External validation of original model

Compared to the patient characteristics of the previous original model [4], in our present study mean age was higher, current smoking was less frequent, whereas hypertension, statin use, TIA, large artery atherosclerosis, and small vessel disease were more frequent. Comparing the characteristics between patients with transient and those with persistent IGT, we found a significant difference in percentage of patients with atrial fibrillation, mean BMI and 2-hour post-load glucose levels, which was not the case in the previous study. [4] In addition, in our present study there was no significant difference in percentage of statin use and in mean age between patients with or without persistent IGT, contrary to the previous study.

Overall, the performance of the original model was poor with an AUC of 0.60, calibration slope of 0.22 and intercept of -2.97. [11] (Figure 1) Therefore, we developed a new, updated model.

Figure 1. Calibration plot of external validation of previous original model in current study population, with the predictors age, current smoking, statin use, triglyceride, hypertension, history of cardiovascular diseases, body mass index (BMI), fasting plasma glucose



Model development

The following predictors from the multivariable logistic regression were selected for the new prediction model after stepwise backward selection: BMI, hypertension, statin use, atrial fibrillation, large artery atherosclerosis, first 2-hour post-load glucose levels, and HbA1c levels. (Table 2) The AUC of the newly developed model was 0.72 and the internally validated bootstrapped AUC 0.66. For correction of too optimistic estimation of the predictive value, shrinkage of the regression coefficients was performed. (Table 3)

The risk of persistent IGT in patients with ischemic stroke or TIA can be calculated as follows: exp(linear predictor)/(1+exp[linear predictor]). Linear predictor= -7.4706 + 0.0529 x BMI + 0.3924 x hypertension + 0.3668 x statin use + 0.8444 x atrial fibrillation + 0.2598 x 2-hour post-load glucose levels + 0.0793 x Hba1c + 0,3579 x large artery atherosclerosis.

The model was externally validated in the population of the previous original model, which showed the discriminative ability (AUC) of 0.71, calibration slope of 1.15 and intercept of 0.3 (Figure 2).

Table 2. Possible predictors of persistent impaired glucose tolerance

	aOR (95%CI)	95% CI
Age	1.02	0.99-1.05
Male	1.42	0.79-2.57
Current smoking	1.61	0.69-3.79
BMI	1.08	0.99-1.18
Hypertension	1.70	0.92-3.13
Statin use	2.04	0.96-4.33
Atrial fibrillation	4.22	1.43-12.39
Previous ischemic cardiovascular disease	0.70	0.36-1.37
Ischemic stroke vs TIA	0.92	0.52-1.64
Large artery atherosclerosis vs other causes	2.10	0.91-4.84
Fasting glucose levels per mmol/L	1.14	0.66-1.95
2-hour post-load glucose levels per mmol/L	1.54	1.11-2.14
HbA1c per mmol/mol	1.11	1.00-1.23

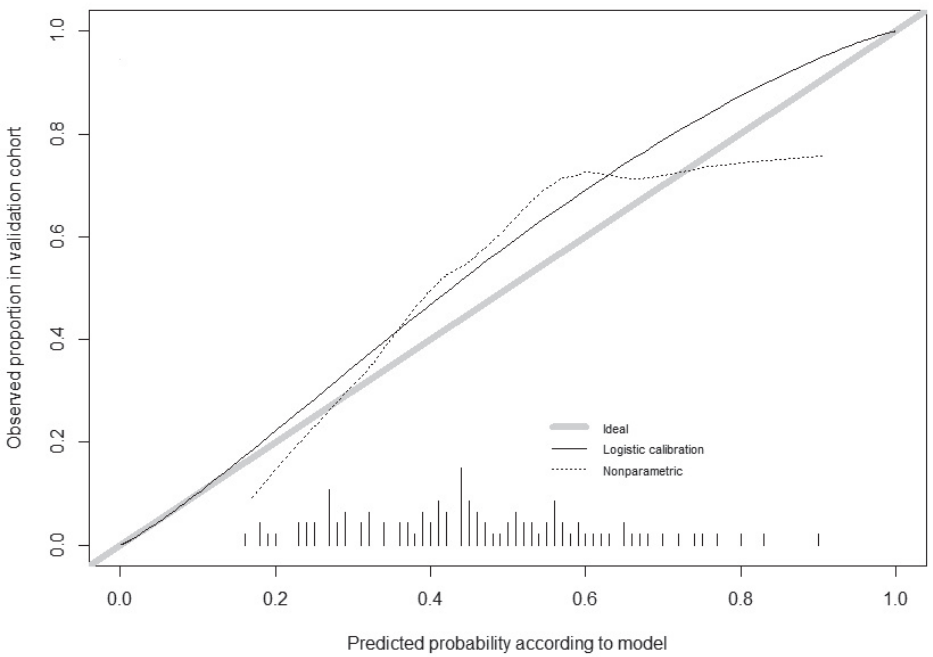
BMI: body mass index. TIA: transient ischemic attack. HbA1c: glycosylated Hemoglobin 1c.

Table 3. Predictors in the final model after correction for optimism

	aOR	95% CI
BMI (per kg/m^2)	1.05	0.99-1.12
Hypertension	1.48	0.93-2.37
Statin use	1.44	0.81-2.56
Atrial fibrillation	2.32	1.08-5.00
Large artery atherosclerosis	1.43	0.75-2.72
2-hour postload glucose levels	1.08	1.01-1.16
Hba1c	1.30	1.03-1.63

Formula prediction model:
exp(linear predictor)/(1+exp[linear predictor]).
Linear predictor= -7.4706 + 0.0529 x BMI + 0.3924 x hypertension + 0.3668 x statin use + 0.8444 x atrial fibrillation + 0.2598 x 2-hour postload glucose levels + 0.0793 x Hba1c + 0,3579 x large artery atherosclerosis

Figure 2. Calibration plot of external validation of newly developed prediction model in previous study population.



DISCUSSION

In our study, 118 of the 239 patients (49%) with IGT after a minor ischemic stroke or TIA had persistent IGT in the two to 12 weeks after initial assessment. Our original prediction model did not perform well in our new dataset. Therefore, we developed a new updated prediction model that more accurately predicts persistent IGT in patients with minor ischemic stroke or TIA. The predictors were BMI, hypertension, statin use, atrial fibrillation, large artery atherosclerosis, 2-hour post-load glucose levels and HbA1c levels. The prediction model still performed well when we externally validated it in the population of our previous study [4], which had a comparable proportion of patients with persistent IGT of 47%.

Age, current smoking, triglycerides and fasting plasma glucose were not predictors in our study, in contrast to our previous study. [4] Possible reasons are that increasing age and currently smoking are variables that are generally associated with cardiovascular diseases, but perhaps not specific enough to predict IGT. Also, triglycerides in this range are less associated with cardiovascular diseases than LDL-cholesterol. [16] In addition, 2-hour post-load glucose levels and HbA1c levels may be a better reflection of disturbed glucose metabolism than fasting glucose levels alone. [17] However, diabetes is less frequently identified with Hba1c levels compared with fasting glucose levels and 2-hour post-load glucose levels. [10] In addition, in our study population of stroke patients, 2-hour post-load glucose levels and HbA1c levels may be a better reflection of disturbed glucose metabolism than fasting glucose levels alone.

In concordance with previous studies that tried to predict persistent IGT, 2-hour post-load glucose levels were a significant predictor. [1–3] Also, the proportion of persistent IGT in these studies was comparable with our study and varied between 41%- 69%. A difference was that in our previous original study and the other previous mentioned studies, the OGTT was repeated at 3 months, which is later than the median of approximately 6 weeks in our current study. Also, the predictors of persistent IGT were different among the studies, which shows that persistent IGT is difficult to predict. Lifestyle modification after TIA or ischemic stroke could also improve glucose metabolism [18], which also influences the prediction of persistent IGT.

To date, we performed the only study which externally validated a prediction model to predict persistent IGT. Our study provides evidence that IGT in patients with ischemic stroke or TIA is not only due to a stress reaction, but in half of the patients can be due to underlying abnormal glucose metabolism. It is important to predict which patients have persistent IGT. IGT increases the risk of developing type 2 diabetes. [19,20] IGT can also increase the risk of recurrent stroke and other cardiovascular diseases [5,21] and is associated with poor outcome after stroke [8,22].

Patients with persistent IGT might benefit from glucose-lowering therapy. With our prediction model, one could consider treating patients with the highest risk of developing persistent IGT in the acute phase after TIA or stroke. In a recent trial with nondiabetic patients with ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone in the acute phase than among patients who received placebo, and pioglitazone was also associated with a lower risk of diabetes. [23] The Metformin and sitAgliptin in patients with IGT and a recent TIA or minor ischemic Stroke (MAAS) trial is recently completed and the results are expected soon, which is assessing the feasibility and safety of metformin and sitagliptin in patients with IGT and ischemic stroke or TIA. [24]

The strengths of our study are that it was prospectively designed and used easily accessible clinical variables in the prediction model. Also, we externally validated our prediction model, showing a good performance. However, we had missing variables which we tried to overcome with single imputation. Furthermore, we did not include patients with more severe ischemic strokes, so it is not certain whether the prediction model can also be used in this group of patients.

In conclusion, persistent IGT can accurately be predicted with our prediction model, using BMI, hypertension, statin use, atrial fibrillation, large artery atherosclerosis, 2-hour post-load glucose levels in the acute phase and HbA1c levels as clinical predictors. The model can be used to develop new strategies for secondary prevention in these patients.

CONFLICTS OF INTEREST

None.

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None.

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CHAPTER 4

Prognostic impact of disturbed glucose metabolism in stroke patients treated with thrombolysis or thrombectomy

CHAPTER 4.1

Impaired fasting glucose is associated with unfavorable outcome in ischemic stroke patients treated with intravenous thrombolysis

E. Osei
S. Fonville
A.A.M. Zandbergen
P.J. Koudstaal
D.W.J. Dippel
H.M. den Hertog

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ABSTRACT

Background

Hyperglycemia on admission and diabetes mellitus type II are associated with unfavorable outcome in stroke patients. We studied whether impaired fasting glucose (IFG) is associated with unfavorable outcome in ischemic stroke patients treated with intravenous alteplase as well and if IFG is a stronger prognostic factor than hyperglycemia on admission.

Methods

We studied 220 consecutive patients with ischemic stroke treated with intravenous alteplase. In all nondiabetic patients, fasting glucose was determined on day 2-5. IFG was defined as fasting glucose level of ≥ 5.6 mmol/L, hyperglycemia on admission as glucose levels ≥ 7.9 mmol/L. The primary effect measure was the adjusted common odds ratio (acOR) for a shift in the direction of worse outcome on the modified Rankin Scale at three months, estimated with ordinal logistic regression, and adjusted for common prognostic factors.

Results

The fasting glucose levels were available in 194 and admission glucose levels in 215 patients. Sixty-three (32.5%) had IFG, 58 (27%) hyperglycemia on admission and 32 (14.6%) pre-existent diabetes. Patients with IFG showed a shift towards worse functional outcome compared with patients with normal fasting glucose levels (acOR 2.77; 95%CI 1.54-4.97), which was stronger than hyperglycemia on admission (acOR 1.75; 95%CI 0.91-3.4).

Conclusions

IFG is associated with unfavorable outcome after treatment with intravenous alteplase for acute ischemic stroke. IFG predicts unfavorable outcome better than hyperglycemia on admission.

INTRODUCTION

Hyperglycemia on admission is associated with unfavorable outcome in patients receiving intravenous alteplase. Patients with hyperglycemia are more likely to have poor functional outcome, increased infarction volume and/or symptomatic hemorrhages. [1-6]

Diabetes mellitus type 2 is also associated with unfavorable outcome [7-9] and less recanalization after treatment with intravenous alteplase. [10] Impaired fasting glucose (IFG) is highly prevalent in patients with stroke without known diabetes prior to the event. IFG is associated with an increased risk of recurrent stroke and other cardiovascular events. [11-13] Since IFG is a more reliable screening tool for diabetes mellitus than random glucose levels, it could also be a stronger predictor of outcome than random glucose levels. [14] Few data are available on the association of IFG and outcome in ischemic stroke patients who received intravenous alteplase. One study showed that increased fasting glucose levels on the day after treatment with intravenous alteplase was associated with unfavorable outcome, but admission glucose levels and diabetes were not. [15]

The possible underlying mechanisms of the association between hyperglycemia and poor outcome after intravenous alteplase in stroke patients are reduction of the fibrinolytic activity of alteplase, impairment of cerebrovascular reactivity in the microvasculature and altered blood-barrier permeability. [16-18]

These associations of increased glucose with poor outcome could be of importance of determining the prognosis and possible treatment options in patients treated with intravenous alteplase who have disturbed glucose metabolism.

Therefore, our aim is to assess the association between IFG and unfavorable outcome in patients with ischemic stroke treated with intravenous alteplase, and assess whether IFG has a stronger association with outcome than admission glucose levels and pre-existent diabetes.

METHODS

Study population

Patients were derived from the Erasmus Stroke Study, a registry of patients with cerebrovascular diseases treated at the Erasmus Medical Center Rotterdam, the Netherlands. We included all consecutive patients with a clinical diagnosis of acute ischemic stroke who were treated with intravenous alteplase between October 2007 and January 2013. Intravenous alteplase was administered according to international guidelines within 4.5 hours of ischemic stroke onset. Baseline clinical information included demographic data, stroke severity assessed by means of the National Institutes of Health Stroke Scale (NIHSS), ischemic stroke subtype according to the TOAST

classification [19], cardiovascular history and risk factors and time from symptom onset to intravenous thrombolysis.

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written consent was obtained from all the patients as approved by the institutional ethics committee.

Glucose assessment

In all patients without known diabetes mellitus, fasting glucose levels were determined once on day two to five of admission. According to current American guidelines [14], impaired fasting glucose was defined as fasting glucose levels of ≥ 5.6 mmol/L. Hyperglycemia on admission was defined as serum glucose levels on admission of ≥ 7.9 mmol/L [14,20], patients with a history of diabetes mellitus included. Pre-existent diabetes mellitus was defined as the use of oral or parenteral anti-diabetic medication prior to admission.

Outcome measures

The primary outcome measure was the modified Rankin Scale (mRS) score at three months. Secondary outcome measures were poor functional outcome or death at three months defined as mRS score >2; neurological deterioration defined as an increase of the NIHSS scores of four points or more at discharge compared to the NIHSS scores on admission; mortality at 3 months and the occurrence of symptomatic intracerebral hemorrhages during admission. Symptomatic intracerebral hemorrhage was defined as parenchymal hemorrhage at any site in the brain shown on the CT-scan being compatible with neurological deterioration during admission. Assessment of the outcome measures were blinded for the glucose groups.

Statistical analysis

The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in the direction of a worse outcome on the mRS at three months, estimated by means of multivariable ordinal logistic regression. The binary secondary outcome measures were analyzed using multivariable logistic regression, expressed as adjusted odds ratio (aOR). Adjustments were made for age, sex, NIHSS score on admission, time from stroke onset to treatment with intravenous alteplase, pre-existent hypertension and atrial fibrillation.

The difference in occurrence of symptomatic intracerebral hemorrhage in the patients with impaired fasting glucose, hyperglycemia or pre-existent diabetes on admission on the one hand and normal glucose values at the other were tested by Fisher's exact test. $p < 0.05$ was considered as statistically significant.

Missing variables were imputed with multiple imputation using the baseline characteristics and outcome variables.

The analysis was carried out with STATA 12.1 statistical package (Statacorp, College Station, Texas).

RESULTS

A total of 220 patients were included in the study. Mean age was 64 years (SD 16), 105 (47.7%) were men and the median NIHSS score was 8 (IQR 3-14). Median time from stroke onset to treatment with intravenous alteplase was 135 minutes (IQR 97-190 minutes). (Table 1) Of these 220 analyzed patients, 100 patients (45.6%) had poor functional outcome or died, 18 (8.2%) neurologically deteriorated and 5 (2.2%) had symptomatic intracerebral hemorrhage.

Table 1: Patients characteristics (n=220)

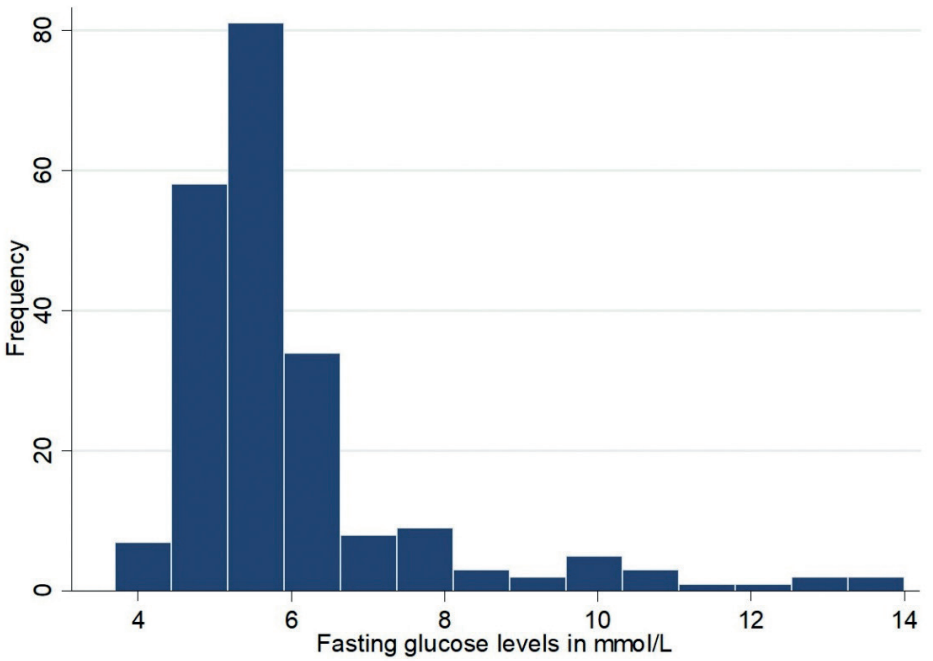
Mean age ± SD, years	64 (16)
Male, n (%)	105 (47.7)
Time from stroke onset to IV-rtPA treatment (minutes), median (IQR)	135 (97-190)
Intra-arterial therapy, n (%)	14 (6.4)
Vascular risk factors	
Smoking, n (%)	110 (50)
Hypertension, n (%)	104 (47.3)
Statin use, n (%)	64 (29.1)
Atrial fibrillation, n (%)	16 (7.3)
Stroke severity	
NIHSS score on admission, median (IQR)	8 (3-14)
Ischemic stroke etiology	
Large artery atherosclerosis, n (%)	55 (25)
Cardio embolism, n (%)	36 (16.4)
Small vessel occlusion, n (%)	36 (16.4)

rtPA: recombinant tissue Plasminogen Activator. NIHSS: National Institutes of Health Stroke Scale. Ischemic stroke etiology: according to Trial of Org 10172 in Acute Stroke Treatment (TOAST)-criteria.

Fasting glucose values were available in 194 of the 220 patients (88.2%), with median fasting glucose levels of 5.4 mmol/L (IQR 5.0-6.2). (Figure 1) Reasons for missing fasting glucose values were a moribund state or patients had died before assessment was possible. Patients with IFG or pre-existent diabetes were significantly older than patients with normal glucose values at admission at day two to five of admission (mean age of patients with IFG 66 years (SD 15) and patients with pre-existent diabetes 72 years

(SD 12), compared to patients with normal glucose with a mean age of 61 years (SD 16); p<0.01), the other patient characteristics were not significantly different (data not shown).

Figure 1. Histogram of fasting glucose levels



Sixty-three patients (32.5%) had IFG. Patients with IFG showed a shift towards worse functional outcome compared with patients with normal fasting glucose levels (acOR 2.77; 95%CI 1.54-4.97 for IFG and acOR 1.12; 95%CI 0.94-1.33 for the continuous fasting glucose). IFG was also associated with poor functional outcome or death (aOR 3.5; 95%CI 1.78-6.87) and with neurological deterioration (aOR 5.54; 95%CI 1.49-20.68). (Table 2 and 3, Figure 3)

Table 2. Association of impaired fasting glucose and hyperglycemia on admission with outcome

	Impaired fasting glucose (n=63)	Hyperglycemia on admission (n=58)	Pre-existent diabetes (n=32)
Primary outcome measure	acOR (95%CI)*	acOR (95%CI)*	acOR (95%CI)*
mRS score at 3 months	2.77 (1.54-4.97)	1.75 (0.91-3.4)	1.83 (0.83-4.03)
Secondary outcome measures	aOR (95%CI)*	aOR (95%CI)*	aOR (95%CI)*
Poor functional outcome or death at 3 months	3.5 (1.78-6.87)	2.13 (1.01-4.46)	1.95 (0.78-4.84)
Neurological deterioration during admission	5.54 (1.49-20.68)	1.20 (0.39-3.67)	2.9 (0.91-9.29)
Mortality at 3 months	1.63 (0.62-4.34)	2.49 (0.91-6.82)	4.45 (1.36-14.52)

*Adjusted for age, sex, NIHSS score on admission, atrial fibrillation, hypertension and time from stroke onset to treatment with intravenous alteplase

Table 3. Association of continuous fasting and admission glucose levels with outcome

	Continuous fasting glucose levels	Continuous admission glucose levels
Primary outcome measure	acOR (95%CI)*	acOR (95%CI)*
mRS score at 3 months	1.12 (0.94-1.33)	1.07 (0.96-1.20)
Secondary outcome measures	aOR (95%CI)*	aOR (95%CI)*
Poor functional outcome or death at 3 months	1.29 (1.05-1.57)	1.12 (1-1.26)
Neurological deterioration during admission	1.32 (1.03-1.69)	1.05 (0.87-1.26)
Mortality at 3 months	1.18 (0.91-1.54)	1.15 (0.96-1.37)

*Adjusted for age, sex, NIHSS score on admission, atrial fibrillation, hypertension and time from stroke onset to treatment with intravenous alteplase

The serum glucose values on admission were available in 215 of the 220 patients (97.7%), with median glucose values of 6.7 (IQR 5.7-7.9). (Figure 2) Fifty-eight of the 215 patients (27%) had hyperglycemia on admission. Of these patients, 43 (74.1%) had IFG. Patients with hyperglycemia on admission showed a trend towards an association with worse functional outcome (acOR 1.75; 95%CI 0.91-3.4 for hyperglycemia on admission, acOR 1.07; 95%CI 0.96-1.20 for admission glucose). Hyperglycemic patients on admission more frequently had poor functional outcome or died (aOR 2.13; 95%CI 1.01-4.46). (Table 2 and 3)

Figure 2. Histogram of admission glucose levels

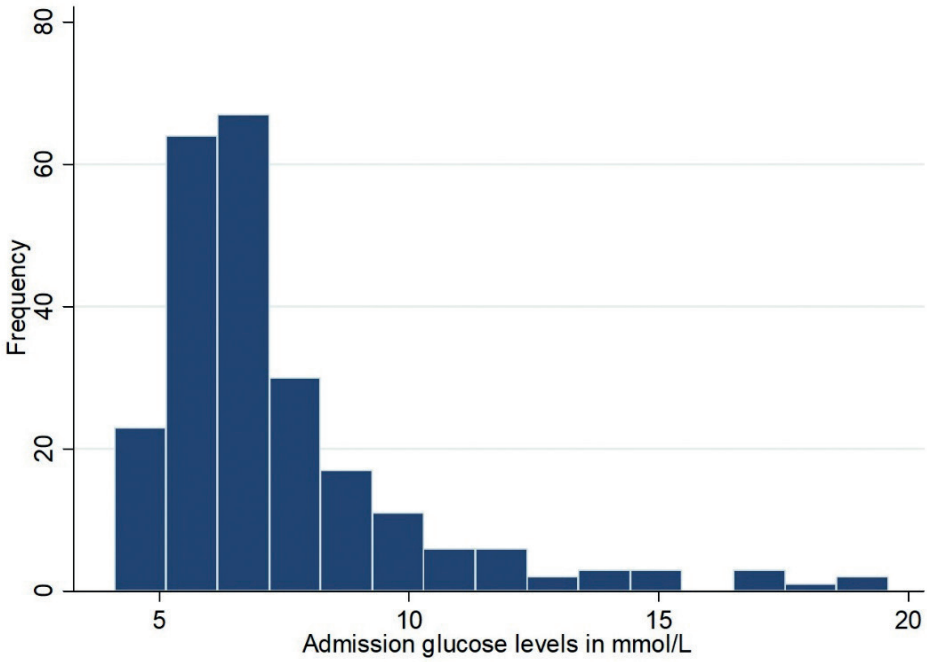
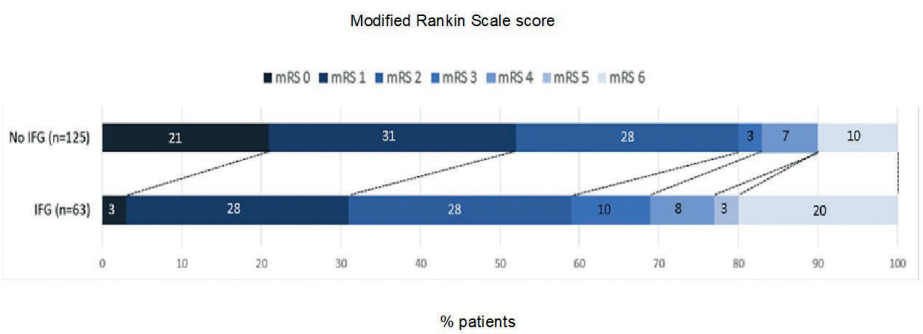


Figure 3. Proportion of mRS scores in patients with IFG vs normal glucose, numbers in bars are percentages



Thirty-two of the 220 patients (14.6%) had pre-existent diabetes. Patients with pre-existent diabetes also showed a trend towards an association with worse functional outcome (acOR 1.83; 95%CI 0.83-4.03 for pre-existent diabetes). Pre-existent diabetes was associated with mortality (aOR 4.45; 95%CI 1.36-14.52). (Table 2)

Compared to normal glucose metabolism, five of the 63 patients with impaired fasting glucose (7.9%, p <0.05), three of the 58 patients with hyperglycemia on admission (5.2%, p=0.1) and three of the 32 patients with pre-existent diabetes (9.4%, p<0.05) had symptomatic intracerebral hemorrhage. Symptomatic intracerebral hemorrhage did not occur in patients with normal fasting glucose levels, and occurred in two patients with normal admission glucose levels.

The test for interaction showed no significant difference in the effect of IFG or hyperglycemia on functional outcome between patients with and without statin use (p-values >0.05, data not shown).

DISCUSSION

We found that stroke patients with IFG have an increased risk of unfavorable outcome after treatment with intravenous alteplase, compared to patients with normal glucose metabolism. This association was stronger in patients with IFG than in patients with hyperglycemia on admission and pre-existent diabetes.

The association of hyperglycemia on admission and pre-existent diabetes with poor outcome in stroke patients is well established. [1,4,6-10] However, our study is one of the few that analyzed the association of IFG with outcome in stroke patients. A previous study also found that higher fasting glucose levels in the acute phase after treatment with intravenous alteplase for acute ischemic stroke predicted poor functional outcome or death better than admission glucose and pre-existent diabetes. [15] Compared to the study of Cao et al, we had a larger study population and we used more outcome measures besides the mRS scores to analyze the association of glucose with outcome.

The association of hyperglycemia with poor outcome after intravenous alteplase could be explained by several pathophysiological mechanisms. Hyperglycemia may have inhibitory effects on intravenous thrombolysis due to the reduction of the fibrinolytic activity of alteplase by inhibiting plasma fibrinolysis and increasing the production of plasminogen activator inhibitor-1. [16] Hyperglycemia can also impair cerebrovascular reactivity in the microvasculature, thereby disturbing reperfusion after recanalization. [17] Also, high glucose levels may alter blood-barrier permeability and induce blood-barrier disruption, which can aggravate brain edema formation and lead to hemorrhagic transformation. [18]

It is not entirely clear what the underlying mechanism is of the stronger association of IFG with outcome after intravenous thrombolysis compared to random glucose levels. IFG is a more reliable screening tool for diabetes mellitus than random glucose levels [14], and might be a better representation of disturbed glucose metabolism than random glucose levels.

Strengths of our study are the thorough definition of the glucose groups, detailed information on potential confounders and robust outcome measures. Our study also has some limitations. First, the study population was relatively small and symptomatic hemorrhages were rare, limiting the statistical power of our study. Second, the fasting glucose levels were measured days after the decision was made to treat the patients with acute ischemic stroke with intravenous alteplase, which can cause bias. Third, disturbed glucose metabolism in the acute phase can be transient, reflecting an acute stress response. [21,22] This could have caused an overestimation of patients with disturbed glucose metabolism in our study. One study performed a controlled comparison of 24-hours decline in glucose in patients treated with intravenous alteplase and control patients, and tested the interaction between intravenous alteplase and early improvement for 24-hours falls in glucose. The results showed that intravenous alteplase predicted significant 24-hour falls in glucose in stroke patients, but intravenous alteplase did not interact with early neurological improvement for 24-hour falls in blood glucose. So it seems that a stress response does not appear to be the principal cause of elevations in blood glucose. [23]

Our results might implicate that glucose lowering therapy could improve the functional outcome of stroke patients who receive intravenous alteplase. One study found that insulin therapy in mild non-diabetic hyperglycemic patients leads to better neurologic outcome after 30 days. [24] However, other studies found that insulin therapy had no clinical benefit. [25-27]

In conclusion, stroke patients with IFG have an increased risk of unfavorable outcome after treatment with intravenous alteplase. This might indicate that therapy with intravenous alteplase has less effect in patients with disturbed glucose metabolism compared with patients with normal glucose metabolism. Further studies are needed to confirm this.

CONFLICTS OF INTEREST

None.

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None.

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CHAPTER 4.2

Increased admission glucose and impaired fasting glucose are associated with unfavorable short-term outcome after intra-arterial treatment of ischemic stroke in the MR CLEAN Pretrial cohort

E. Osei
H.M. den Hertog
O.A. Berkhemer
P.S.S. Fransen
Y.B.W.E.M. Roos
D. Beumer
R.J. van Oostenbrugge
W.J. Schonewille
J. Boiten
A.A.M. Zandbergen
P.J. Koudstaal
D.W.J. Dippel
for the MR CLEAN pretrial investigators
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ABSTRACT

Background

Limited data are available on the impact of fasting glucose on outcome after intra-arterial treatment (IAT). We studied whether hyperglycemia on admission and impaired fasting glucose (IFG) are associated with unfavorable outcome after IAT in acute ischemic stroke.

Methods

Patients were derived from the pretrial registry of the MR CLEAN-trial. Hyperglycemia on admission was defined as glucose >7.8 mmol/L, IFG as fasting glucose > 5.5 mmol/L in the first week of admission. Primary effect measure was the adjusted common odds ratio (acOR) for a shift in the direction of worse outcome on the modified Rankin Scale at discharge, estimated with ordinal logistic regression, adjusted for common prognostic factors.

Results

Of the 335 patients in which glucose on admission was available, 86 (26%) were hyperglycemic, 148 of the 240 patients with available fasting glucose levels (62%) had IFG. Median admission glucose was 6.8 mmol/L (IQR 6-8). Increased admission glucose (acOR 1.2, 95%CI 1.1-1.3), hyperglycemia on admission (acOR 2.6, 95%CI 1.5-4.6) and IFG (acOR 2.8, 95%CI 1.4-5.6) were associated with worse functional outcome at discharge.

Conclusion

Increased glucose on admission and IFG in the first week after stroke onset are associated with unfavorable short-term outcome after IAT of acute ischemic stroke.

INTRODUCTION

Patients with disturbed glucose metabolism have an increased risk of unfavorable outcome after ischemic stroke. [1,2] Furthermore, in patients with acute ischemic stroke receiving intravenous recombinant tissue Plasminogen Activator (iv-rtPA), hyperglycemia on admission and diabetes mellitus type II are associated with poor functional outcome, symptomatic intracranial hemorrhage and incomplete recanalization. [3-8]

Until recently, treatment with iv-rtPA was the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke. [9-11] However, new studies have shown that intra-arterial treatment (IAT) of acute ischemic stroke caused by a proximal intracranial arterial occlusion is safe and effective. [12-16]

Several studies found that hyperglycemia on admission was associated with unfavorable outcome in terms of functional outcome, death, neurological deterioration, symptomatic intracranial hemorrhage or hemorrhagic transformation in patients receiving intra-arterial thrombolysis for acute ischemic stroke. [17-21] One study found that diabetes mellitus is also associated with poor functional outcome after intra-arterial thrombolysis. [22] Less evidence is available for patients who have been treated with intra-arterial thrombectomy. Only a few studies indicate that hyperglycemia increases the risk of poor functional outcome after intra-arterial thrombectomy as well. [23-25]

The association of newly diagnosed disturbed glucose metabolism with outcome in patients with an acute ischemic stroke who receive endovascular treatment is not fully known yet. Therefore, the aim of our research was to assess the association of increased admission serum glucose and impaired fasting glucose (IFG) with unfavorable outcome after endovascular treatment of acute ischemic stroke.

METHODS

Study design

We conducted a retrospective cohort study in patients from the pretrial cohort of the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) registry, which consists of all consecutive patients with acute ischemic stroke treated with IAT in 16 stroke centers in The Netherlands. [12] Information concerning procedures and treated patients was gathered in order to assess pretrial experience in centers that were committed to participate in the MR CLEAN trial. The registry started in October 2002 and continued until a center started participation in the MR CLEAN trial (last center in March 2014). The institutional review board from the coordinating institution approved registration and use of the data. IAT consisted of an arterially given thrombolytic agent, thrombectomy using a dedicated clot retriever or

a retrievable stent, or both. The method of IAT was left to the discretion of the treating interventional radiologist. For the present study, we included only patients with an anterior circulation stroke of whom admission glucose values and/or fasting glucose values on day 1-7 of admission were available.

Procedures

All centers kept a prospective registry of patients who received IAT. Data collection itself was largely retrospective and included demographic variables, National Institutes of Health Stroke Scale (NIHSS) score at baseline, use of iv-rtPA, timing of baseline and treatment procedures, and treatment type (intra-arterial thrombolytics, mechanical treatment, or both). When necessary and possible, NIHSS at baseline was reconstructed from clinical data with a modified algorithm.[26] When missing, IAT time points were reconstructed from the digital subtraction angiography series. For start of IAT we took the time of first scan minus 5 minutes.

Glucose assessment

Hyperglycemia on admission was defined as admission serum glucose of > 7.8 mmol/L [27,28], these glucose levels were non fasting. Fasting glucose levels were determined from day 1 to 7 of admission. Impaired fasting glucose was defined as fasting glucose values of >5.5 mmol/L. [27] History of diabetes was defined as the use of oral or parenteral anti-diabetic medication prior to admission.

Outcome measures

The primary outcome measure was the modified Rankin Scale (mRS) score at discharge. Secondary outcome measures were poor functional outcome or death at discharge defined as mRS score >2, neurological deterioration, vessel recanalization and symptomatic hemorrhages. Neurological deterioration was defined as an increase of the NIHSS scores in the first week of admission of four points or more compared to the NIHSS scores on admission. Grade of recanalization was assessed with the modified Thrombolysis in Cerebral Infarction score (mTICI). Recanalization was defined as TICI score 2b or 3 on Digital Subtraction Angiography (DSA) imaging at the end of the procedure. [29] Three experienced observers from a center that was not involved in the treatment assessed all DSA runs. Observers were blinded for baseline data of the patient and for intervention center.

Symptomatic intracerebral hemorrhage consisted of hemorrhagic conversion of the infarction or primary intracerebral hemorrhage with a focus elsewhere in the brain, anytime during hospitalization. If patients showed neurological deterioration (defined as any increase in the NIHSS scores), and CT showed hemorrhagic transformation of the infarcted area or intracerebral hematoma, this was considered as symptomatic. If patients had hemorrhagic conversion of infarction without corresponding neurological

deterioration, this was considered as asymptomatic. Assessment of the outcome measures were blinded for the glucose groups.

Statistical analysis

Baseline characteristics were compared between patients with hyperglycemia on admission and normal serum glucose values. Categorical variables were tested by χ^2 and continuous variables by Students t-test. Nonnormally distributed variables were compared by Mann-Whitney's test.

The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in the direction of a worse outcome on the mRS at discharge, estimated by means of multivariable ordinal logistic regression. The binary secondary outcome measures were analyzed using multivariable logistic regression, expressed as adjusted odds ratio (aOR). Adjustments were made for age, sex, NIHSS score on admission, atrial fibrillation, hypertension, history of diabetes and time from stroke onset to IAT. The analysis was carried out with STATA 12.1 statistical package (Statacorp, College Station, Texas).

RESULTS

A total of 514 patients was enrolled in the pretrial of the MR CLEAN study. We excluded 160 patients with an occlusion in the posterior circulation, leaving 354 patients with an occlusion in the anterior circulation for inclusion. Admission blood glucose levels were available in 335 patients. Mean age was 61 years (SD 15) and 175 patients (52%) were male. Median NIHSS score before IAT was 15 (IQR 12-19) and the median time from stroke onset to IAT was 225 minutes (IQR 180-284).

A total of 256 patients (76%) had poor functional outcome at discharge, of whom 57 patients (22%) had died during hospital stay. Recanalization was present in 122 patients (42%). Fifty-five patients (16%) had symptomatic intracerebral hemorrhage. Neurological deterioration occurred in 86 patients (26%). In patients with neurological deterioration, 34 patients (40%) had intracerebral hemorrhage, two (2%) recurrent or progressive stroke, one patient had pneumonia (1%), one cardiac abnormalities (1%).

Median admission serum glucose was 6.8 mmol/L (IQR 6-8). In total, 86 patients (26%) were hyperglycemic on admission. The baseline characteristics were not significantly different between patients with hyperglycemia compared to no hyperglycemia, besides a medical history of diabetes. (Table 1) There was a shift towards worse functional outcome in patients with increased glucose levels at admission (acOR 1.2 per mmol, 95%CI 1.1-1.3 for continuous glucose levels) and in patients with hyperglycemia on admission (acOR 2.6; 95%CI 1.5-4.6 for hyperglycemia on admission) compared to normoglycemic patients. (Table 2, Figure 1). In addition, patients who were hyperglycemic on admission had a higher risk of poor functional outcome or death (aOR 3.1; 95%CI 1.2-

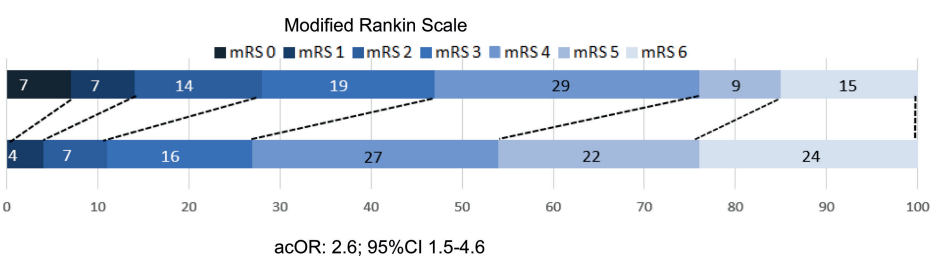
8.0) and symptomatic intracerebral hemorrhage (aOR 2.7; 95%CI 1.2-5.9) compared with normoglycemic patients. (Table 2)

Table 1. Baseline characteristics between patients with hyperglycemia on admission compared to no hyperglycemia

	Hyperglycemia on admission (n=86)	**No hyperglycemia (n=249)**	**p-value**
Mean age ± SD, years	64 (14)	60 (16)	0.07
Male, n (%)	50 (58)	125 (50)	0.2
Time from stroke onset to intra-arterial treatment, median (IQR)	218 (176-291)	234 (185-283)	0.32
Treatment with intravenous thrombolysis, n (%)	64 (74)	187 (75)	0.81
Vascular risk factors			
Smoking, n (%)	21 (24)	60 (24)	0.88
Hypertension, n (%)	45 (52)	126 (51)	0.56
Hypercholesterolemia, n (%)	35 (41)	118 (47)	0.34
Atrial fibrillation, n (%)	24 (28)	56 (22)	0.25
History of diabetes, n (%)	27 (31)	22 (9)	<0.01
Stroke severity			
NIHSS score on admission, median (IQR)	16 (13-20)	15 (12-18)	0.1

NIHSS: National Institutes of Health Stroke Scale.

Figure 1. Percentages of patients with corresponding mRS scores at hospital discharge, in patients with hyperglycemia on admission vs normal glucose



acOR: 2.6; 95%CI 1.5-4.6

Table 2. Association of glucose on admission and acute hyperglycemia with outcome measures, compared to normoglycemic patients

	Glucose on admission (continuous glucose levels[a])	**Hyperglycemia on admission (glucose >7.8 mmol/L, n=86)**	
Primary outcome measure	acOR[b] (95%CI)	acOR[b] (95%CI)	
mRS score at discharge	1.2 (1.1-1.3)	2.6 (1.5-4.6)	
Secondary outcome measures (n)	aOR[c] (95%CI)	n (% of outcome events)	aOR[c] (95%CI)
Poor functional outcome, mRS >2 (256)	1.3 (1.1-1.6)	77 (30)	3.1 (1.2-8.0)
Neurological deterioration (86)	1.1 (1.0-1.2)	31 (36)	1.7 (0.9-3.5)
Recanalization (122)	1.0 (0.8-1.1)	28 (23)	0.7 (0.4-1.4)
Symptomatic intracerebral hemorrhage (55)	1.0 (0.9-1.2)	22 (40)	2.7 (1.2-5.9)

mRS: modified Rankin Scale.
a. acOR corresponded to 1 mmol increase of glucose
b. Adjusted common odds ratio, adjusted for: age, sex, NIHSS score on admission, atrial fibrillation, hypertension, history of diabetes and time from stroke onset to intra-arterial treatment
c. Adjusted odds ratio, adjusted for the same factors as in b.

In the hyperglycemic patients, 27 of the 86 patients (31%) had history of diabetes, compared to 22 of the 249 patients (9%) who were not hyperglycemic on admission ($p<0.01$). We therefore added history of diabetes as a prognostic factor in the model. This did not significantly change the associations with the outcome measures.

In addition, we compared the association of admission glucose with functional outcome (mRS at discharge) in patients with history of diabetes and no history of diabetes, and these associations did not significantly differ (in patients with history of diabetes: acOR 1.3; 95%CI 1.0-1.5, in patients with no history of diabetes: acOR 1.2; 95%CI 1.0-1.4).

Fasting glucose was available in 240 patients, of which 148 patients (62%) had IFG in the first week after stroke onset. Of the 148 patients with IFG, 32 patients (22%) were also hyperglycemic on admission. There was a shift towards worse functional outcome in patients with increased fasting glucose levels (acOR 1.4; 95%CI 1.1-1.6 for continuous fasting glucose levels) and in patients with impaired fasting glucose levels (acOR 2.8, 95%CI 1.4-5.6 for impaired fasting glucose). (Table 3) IFG was also associated with poor functional outcome or death (aOR 2.8; 95%CI 1.2-6.7) and with symptomatic intracerebral hemorrhage (aOR 5.4; 95%CI 1.1-27). (Table 3)

In addition, patients with history of diabetes tended to have a worse functional outcome and increased risk of neurological deterioration. (Table 4)

Table 3. Association of impaired fasting glucose with outcome measures, compared to patients with normal fasting glucose levels

	Fasting glucose (continuous fasting glucose levels)[a]	**Impaired fasting glucose (fasting glucose > 5.5 mmol/L, n=148)**	
Primary outcome measure	acOR[b] (95%CI)	acOR[b] (95%CI)	
mRS score at discharge	1.4 (1.1-1.6)	2.8 (1.4-5.6)	
Secondary outcome measures (n)	aOR[c] (95%CI)	n (% of outcome events)	aOR[c] (95%CI)
Poor functional outcome, mRS >2 (170)	1.7 (1.2-2.4)	113 (66)	2.8 (1.2-6.7)
Neurological deterioration (53)	0.9 (0.7-1.2)	32 (60)	0.8 (0.3-2.3)
Recanalization (79)	0.9 (0.7-1.1)	39 (49)	0.5 (0.2-1.1)
Symptomatic intracerebral hemorrhage (32)	1.2(0.9-1.5)	24 (75)	5.4(1.1-27)

mRS: modified Rankin Scale
a. acOR corresponded to 1 mmol increase of glucose
b. Adjusted common odds ratio, adjusted for: age, sex, NIHSS score on admission, atrial fibrillation, hypertension, history of diabetes and time from stroke onset to intra-arterial treatment
c. Adjusted odds ratio, adjusted for the same factors as in b.

Table 4. Association of pre-existent diabetes with the outcome measures, compared to patients with no pre-existent diabetes

	History of diabetes (n=49)	
Primary outcome measure	acOR[a] (95%CI)	
mRS score at discharge	0.9 (0.5-1.8)	
Secondary outcome measures (n)	n (% of outcome events)	aOR[b] (95%CI)
Poor functional outcome, mRS >2 (256)	40 (16)	1.9 (0.7-5.2)
Neurological deterioration (86)	14 (16)	1.7 (0.5-5.8)
Recanalization (122)	23 (19)	0.9 (0.4-2.2)
Symptomatic intracerebral hemorrhage (55)	8 (15)	1.1 (0.4-3.0)

mRS: modified Rankin Scale
a. Adjusted common odds ratio, adjusted for: age, sex, NIHSS score on admission, atrial fibrillation, hypertension and time from stroke onset to intra-arterial treatment
b. Adjusted odds ratio, adjusted for the same factors as in a.

DISCUSSION

We found that hyperglycemia on admission and IFG in the first week after stroke onset are associated with unfavorable short-term outcome after IAT of acute ischemic stroke.

These results matched that of previous studies, the majority of which studied only patients who were treated with intra-arterial thrombolysis for ischemic stroke. Several of these studies showed that hyperglycemia on admission had significant poorer functional outcome and higher mortality rates after IAT. [17-19,22,23] Furthermore, elevated admission glucose level was associated with a higher rate of primary intracerebral hemorrhages. [20-22]

To the best of our knowledge, no studies have yet assessed the association of impaired fasting glucose with outcome in stroke patients who received mechanical thrombectomy.

Strengths of our study are its clinically relevant outcome measures and the detailed information on confounders. This study also has some limitations. First, the study design was retrospective and non-randomized. Second, we assessed the mRS score at discharge, which was not developed for use at discharge. However, secondary analysis with a dichotomized mRS showed similar results. Third, the glucose tests were done from day one to seven of admission. Disturbed glucose metabolism in the acute phase can be transient, reflecting an acute stress response. [30,31] Furthermore, 32% of the included patients had missing fasting glucose levels, which could affect generalizability. The patients with missing fasting glucose levels were significantly older, more often had hypertension and less often hypercholesterolemia. The other baseline characteristics were not significantly different. Furthermore, the patients with missing fasting glucose had a higher rate of poor functional outcome, neurological deterioration and primary intracerebral hemorrhages. Probable causes for the glucose values being missing is that these patients had more severe strokes and were in a moribund state. However, the patients with missing fasting glucose levels and available admission glucose levels showed the same patrons as described above.

The association of disturbed glucose metabolism with poor outcome after IAT could be explained by several pathophysiological mechanisms. Hyperglycemia affects mitochondrial function in the ischemic penumbra, which leads to cortical acidosis and cell death. [32] It impairs cerebrovascular reactivity in the microvasculature, which may disturb reperfusion after recanalization. [33] Also, hyperglycemia may alter blood-barrier permeability and induce blood-barrier disruption, which may aggravate brain edema formation and lead to hemorrhagic transformation. [34]

Our results might implicate that glucose lowering therapy could improve the functional outcome of stroke patients who receive IAT. This has not been studied yet. Furthermore,

there is no evidence that in the first hours of acute stroke, administration of intravenous insulin improves functional outcome. [35]

Patients with disturbed glucose metabolism have an increased risk of unfavorable short-term outcome after endovascular therapy for ischemic stroke. Our findings might indicate that endovascular therapy has less effect in hyperglycemic patients compared with patients with normal glucose metabolism.

CONFLICTS OF INTEREST

None.

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CHAPTER 4.3

Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke in the MR-CLEAN cohort

E. Osei
H.M. den Hertog
O.A. Berkhemer
P.S.S. Fransen
Y.B.W.E.M. Roos
D. Beumer
R.J. van Oostenbrugge
W.J. Schonewille
J. Boiten
A.A.M. Zandbergen
P.J. Koudstaal
D.W.J. Dippel

on behalf of the MR CLEAN investigators.
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ABSTRACT

Background

Hyperglycemia on admission is common after ischemic stroke. It is associated with unfavorable outcome after treatment with intravenous thrombolysis and after intra-arterial treatment. Whether hyperglycemia influences the effect of reperfusion treatment is unknown. We assessed whether increased admission serum glucose modifies the effect of intra-arterial treatment in patients with acute ischemic stroke.

Methods

We used data from the Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN). Hyperglycemia was defined as admission serum glucose >7.8 mmol/L. The primary outcome measure was the adjusted common odds ratio (acOR) for a shift in the direction of a better outcome on the modified Rankin scale (mRS) at 90 days, estimated with ordinal logistic regression. Secondary outcome variable was symptomatic intracranial hemorrhage. We assessed treatment effect modification of hyperglycemia and admission serum glucose levels with multiplicative interaction factors and adjusted for prognostic variables.

Results

Four hundred and eighty-seven patients were included. Mean admission serum glucose was 7.2 mmol/L (SD 2.2). Fifty-seven of 226 patients (25%) randomized to intra-arterial treatment were hyperglycemic, compared with 61 of 261 patients (23%) in the control group. The interaction of either hyperglycemia or admission serum glucose levels and treatment effect on mRS scores was not significant (p=0.67 and p=0.87, respectively). The same applied for occurrence of symptomatic hemorrhage (p=0.39 for hyperglycemia, p=0.39 for admission serum glucose).

Conclusions

We found no evidence for effect modification of intra-arterial treatment by admission serum glucose in patients with acute ischemic stroke.

Clinical Trial Registration-URL: www.isrctn.com. Unique identifier: ISRCTN10888758

INTRODUCTION

Recent studies have demonstrated that intra-arterial treatment (IAT) by means of thrombectomy with stent retrievers is both effective and safe in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion in the anterior circulation.[1-5]

Hyperglycemia on admission is associated with unfavorable outcome also after IAT. Patients with hyperglycemia are at increased risk of poor functional outcome, symptomatic intracranial hemorrhage, and less successful revascularization after intra-arterial thrombolysis.[6-11] Less evidence is available for patients who have been treated with intra-arterial thrombectomy. Only a few uncontrolled studies suggest that hyperglycemia increases the risk of poor functional outcome after intra-arterial thrombectomy as well, especially after incomplete reperfusion.[12-14]

Admission hyperglycemia is also associated with unfavorable outcome in ischemic stroke patients who have been treated with intravenous tissue Plasminogen Activator (IV-tPA). Hyperglycemia leads to an increased risk of symptomatic intracerebral hemorrhage, poor functional outcome, and less recanalization after treatment with IV-tPA.[15-17] No clinical trials have reported whether hyperglycemia alters the treatment effect of IV-tPA on functional outcome. One controlled trial study reported no interaction of iv-tPA and 24-hours fall in glucose on early neurological improvement.[18] Another controlled trial study reported that higher admission glucose levels are associated with higher odds for undesirable clinical outcome and symptomatic intracerebral hemorrhage, regardless of IV-tPA treatment.[15] Moreover, previous studies reported no significant interaction of diabetes with iv-tPA on functional outcome at 90 days, however none of these studies reported admission blood glucose levels reported.[19-22]

Possible underlying mechanisms of the association between hyperglycemia and poor outcome in stroke patients include impairment of cerebrovascular reactivity in the microvasculature, altered blood-barrier permeability, increased cortical acidosis and hypercoagulability.[23-27]

Considering the associations with poor outcome and underlying pathophysiological mechanisms, one might expect that IAT has less effect in patients with hyperglycemia compared to patients with normal glucose values. However, no studies have yet reported the influence of hyperglycemia on the treatment effect of IAT.

We aimed to assess whether increased admission serum glucose modifies the effect of IAT in patients with acute ischemic stroke and a proximal intracranial arterial occlusion in the anterior circulation in the MR CLEAN cohort.

METHODS

Study design

The study protocol of the MR CLEAN-trial was described previously.[1,28] In summary, MR CLEAN was a phase 3, multicenter clinical trial with randomized treatment-group assignments, open-label treatment, and blinded end-point evaluation. The study was conducted in 16 centers throughout the Netherlands. Patients were 18 years of age or older with acute ischemic stroke caused by an intracranial arterial occlusion of the anterior circulation. Initiation of IAT had to be possible within 6 hours after stroke onset. IAT consisted of intra-arterial thrombolysis, mechanical thrombectomy, or both. Patients were randomized to IAT plus usual care or usual care alone.[28] The study protocol[28] was approved by the central medical ethics committee and the research board of each participating center. All patients or their legal representatives gave written informed consent before randomization.

Clinical definitions

All patients with available admission serum glucose levels were included. The serum glucose values were measured prior to IAT. As usual care also consisted of administration of IV-tPA when possible, patients with serum glucose levels of >22.2 mmol/L were excluded from the MR CLEAN-trial. Hyperglycemia was defined as blood glucose levels on admission of > 7.8 mmol/L.[29-30]

Outcome measures

The primary outcome measure was the modified Rankin Scale (mRS) score at 90 days. Secondary outcome measures were good functional outcome, defined as mRS score 0-2 at 90 days; NIHSS score at 24 hours; NIHSS score at 5 to 7 days or discharge if earlier; intracranial occlusion on follow-up CT-angiography at 24 hours; symptomatic intracranial hemorrhage, defined as parenchymal hemorrhage at any site in the brain shown on the CT-scan being compatible with neurological deterioration during admission; recanalization, defined as modified Thrombolysis in Cerebral Infarction (mTICI) score 2b or 3 on Digital Subtraction Angiography (DSA) imaging at the end of the procedure in the intervention group; and mortality. Observers were blinded for the baseline data of the patient and for the outcome.

Statistical analysis

All analyses were based on the intention-to-treat principle. Baseline characteristics were compared between patients with hyperglycemia on admission and normal serum glucose values. Categorical variables were tested by χ^2 and continuous variables by Students t-test. Non-normally distributed variables were compared by Mann-Whitney's test. $p < 0.05$ was considered to indicate statistical significance.

The primary effect parameter was the adjusted common odds ratio (acOR) for a shift in the direction of an improved outcome on the modified Rankin scale (mRS) at 90 days, estimated by means of multivariable ordinal logistic regression. The binary outcome measures were analyzed using multivariable logistic regression, expressed as adjusted odds ratio (aOR). Adjustments were made for age, sex, NIHSS score on admission, atrial fibrillation, Alberta Stroke Program Early CT Score (ASPECTS) and history of hypertension. Treatment effect modification by admission serum glucose values or hyperglycemia with IAT were assessed by means of a multiplicative interaction variable.

The prediction scores of the HIAT2 were used to predict poor outcome after IAT.[31] The scores ranges from 0-10: age (≤59 years=0, 60–79 years=2, ≥80 years=4), glucose (≤8.3 mmol/L=0, >8.3 mmol/L = 3), NIHSS (≤10=0, 11–20=1, ≥21=2), and ASPECTS (8–10=0, ≤7=3). A cutoff point of 5 was used to predict poor functional outcome, with the use of logistic regression. The analysis was carried out using STATA 12.1 statistical package (Statacorp, College Station, Texas).

Role of the funding source

The study sponsors were not involved in the study design, study conduct, protocol review, manuscript preparation or review.

RESULTS

Admission serum glucose values were available for 487 of the 500 patients included in the MR CLEAN trial. In total, 226 patients were randomized to IAT (46%), and 261 patients (54%) to the control group. Mechanical treatment was performed in 189 of the 226 patients (84%). No intervention was given in 36 patients (16%).

Mean admission serum glucose was 7.2 mmol/L (SD 2.2) (Figure 1). Fifty-seven of 226 patients (25%) assigned to IAT were hyperglycemic, compared with 61 of 261 patients (23%) in the control group. Hyperglycemic patients were older, and more often had a medical history of diabetes, hypertension, and hypercholesterolemia than patients with normal serum glucose values (Table 1). Hyperglycemic patients in the intervention group had higher NIHSS scores after 24 hours and at 5-7 days, compared to patients with normal serum glucose values. In addition, hyperglycemic patients in the intervention group less often experienced a good functional outcome, more often had symptomatic intracerebral hemorrhages, and had died more often than patients with normal serum glucose values (Table 2).

Table 1. Clinical baseline characteristics

Characteristics	Hyperglycemia on admission (n=118)	No hyperglycemia (n=369)	p
Age in years, mean (SD)	70 (11.5)	63 (14.1)	<0.01
Male, n (%)	68 (57.6)	213 (57.7)	0.99
Glucose at admission in mmol/L, mean (SD)	10.1 (2.6)	6.2 (0.8)	<0.01
History of diabetes mellitus, n (%)	41 (34.8)	26 (7.1)	<0.01
History of hypertension, n (%)	63 (53.4)	158 (42.8)	0.05
History of hypercholesterolemia, n (%)	40 (33.9)	87 (23.6)	0.03
History of atrial fibrillation, n (%)	35 (29.7)	95 (25.8)	0.40
History of ischemic stroke, n (%)	15 (12.7)	36 (9.8)	0.36
History of myocardial infarction, n (%)	20 (17.0)	52 (14.1)	0.45
History of peripheral arterial disease n (%)	6 (5.1)	18 (4.9)	0.93
Current smoking, n (%)	27 (22.9)	116 (31.4)	0.08
Current statin use, n (%)	41 (34.8)	100 (27.1)	0.11
Current anti-hypertensive medication use, n (%)	69 (58.5)	169 (45.8)	0.02
NIHSS at admission, median (IQR)	18 (15-21)	18 (14-22)	0.98
Pre-stroke mRS scores, n (%)			
0	89 (75.4)	308 (83.5)	0.05
1	13 (11.0)	32 (8.7)	0.44
2	8 (6.8)	17 (4.6)	0.35
>2	8 (6.8)	12 (3.3)	0.09
Treatment with IV-tPA, n (%)	100 (84.8)	333 (90.2)	0.10
Time of stroke onset to IAT in minutes, median (IQR)	255 (223-329)	260 (210-300)	0.42
ASPECTS, median (IQR)	9 (8-10)	9 (8-10)	0.63

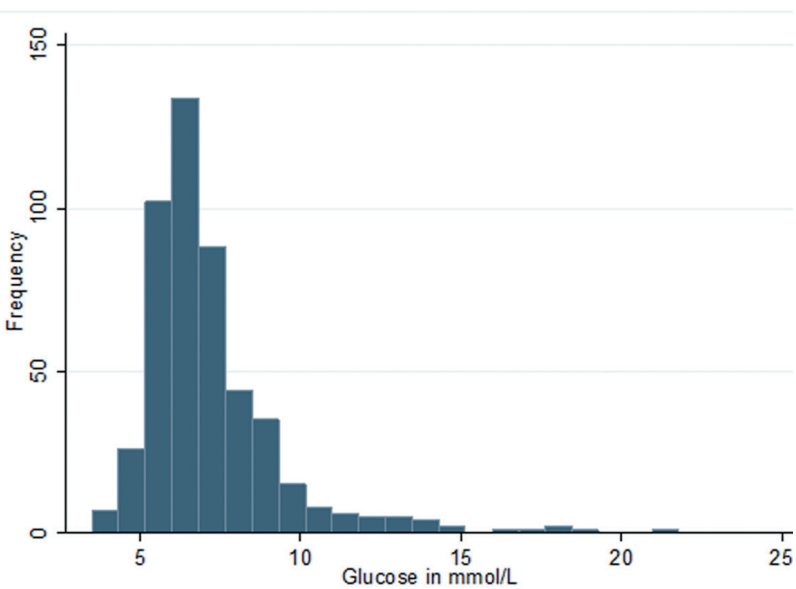
NIHSS: National Institute Health Stroke Scale. mRS: modified Rankin Scale. IV-tPA: intravenous tissue Plasminogen Alteplase. IAT: intra-arterial treatment. ASPECTS: Alberta Stroke Program Early CT score.

Table 2. The frequency of the primary and secondary outcome measures in the control group compared to the intra-arterial treatment group, within each group hyperglycemia on admission is compared to no hyperglycemia.

	Control group (n=261)		**Intra-arterial treatment (n=226)**	
Outcome	Hyperglycemia on admission (n=61)	No hyperglycemia (n=200)	Hyperglycemia on admission (n=57)	No hyperglycemia (n=169)
mRS score at 90 days, median (IQR)	2 (0-2)	2 (1-3)	2 (0-3)	3 (2-4)
NIHSS score after 24 hours, median (IQR)	18 (14-23)	16 (12-21)	15 (7-21)	13 (6-19)
NIHSS score at 5-7 days, median (IQR)	17 (8-19)	14 (7-18)	12 (2-18)	7 (2-16)
Good functional outcome, n (%)	6 (9.8)	44 (22.0)	13 (22.8)	60 (35.5)
Absence of intracranial occlusion, n (%)	7 (17.5)	60 (37.0)	30 (71.4)	106 (76.3)
Safety measures				
Symptomatic intracranial hemorrhage, n (%)	6 (9.8)	11 (5.5)	10 (17.5)	7 (4.1)
Mortality, n (%)	20 (32.8)	38 (19)	19 (33.3)	29 (17.2)

mRS: modified Rankin Scale. NIHSS: National Institute Health Stroke Scale

Figure 1. Distribution of admission serum glucose levels in 487 patients from the MR CLEAN cohort



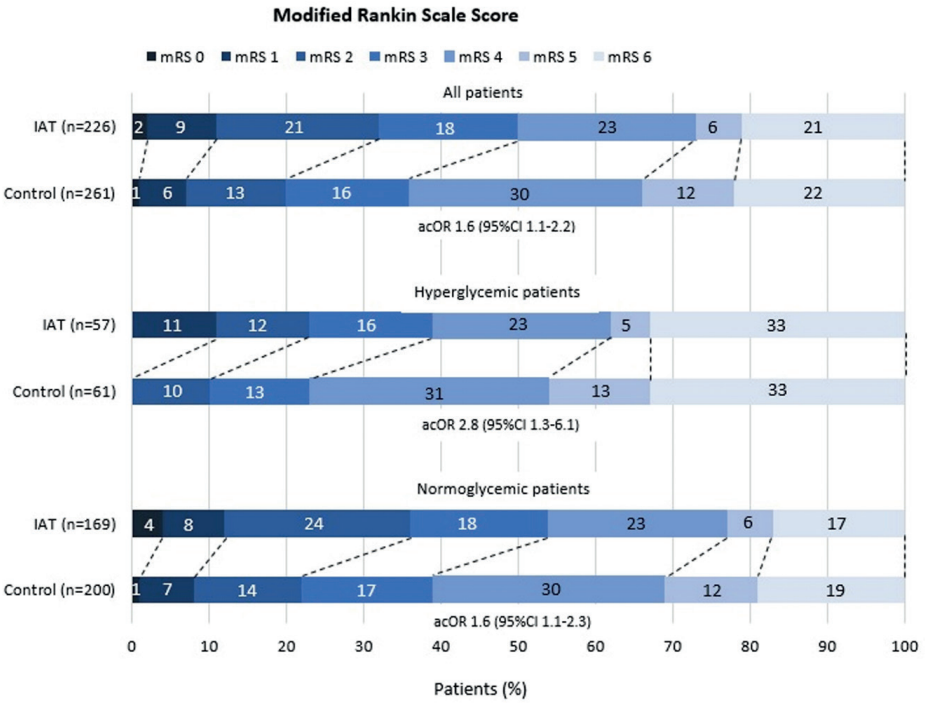
Overall, there was a shift towards an improved outcome in favor of the intervention in the distribution of mRS scores (acOR 1.6; 95%CI 1.1-2.2). Hyperglycemia on admission did not modify this shift towards improved outcome (Figure 2). The interaction of admission serum glucose levels and IAT effect for all outcome measures was not significant for the mRS score (p=0.87), nor for the other outcome measures. (Table 3)

Table 3. Interaction of admission serum glucose levels or hyperglycemia with IAT effect on several outcome measures

	Admission glucose		**Hyperglycemia**	
Outcome	Unadjusted interaction, p	Adjusted interaction[b], p	Unadjusted interaction, p	Adjusted interaction[b], p
mRS score at 90 days	0.88	0.87	0.90	0.67
NIHSS score after 24 hours	0.18	0.10	0.68	0.89
NIHSS score at 5-7 days	0.18	0.16	0.81	0.83
Good functional outcome (mRS 0-2)	0.60	0.57	0.57	0.47
Absence of intracranial occlusion[a]	0.16	0.14	0.20	0.29
Safety measures				
Symptomatic intracranial hemorrhage	0.22	0.39	0.19	0.39
Mortality	0.71	0.53	0.76	0.66

mRS: modified Rankin Scale. NIHSS: National Institute Health Stroke Scale
a. Absence of intracranial occlusion on follow-up CT-angiography at 24 hours
b. Adjusted for age, sex, atrial fibrillation, use of anti-hypertensive medication, NIHSS at admission, Alberta Stroke Program Early CT score

Figure 2. Effect of treatment on the distribution of the modified Rankin Scale scores at 90 days in hyperglycemia on admission vs no hyperglycemia. Numbers in the horizontal bars are percentages. Corresponding adjusted common odds ratios* (acOR) are reported below the bars.



*Adjusted for age, sex, atrial fibrillation, history of hypertension, National Institute Health Stroke Scale at admission, and Alberta Stroke Program Early CT score (ASPECTS).

In addition, the interaction of hyperglycemia on admission with effect of IAT was not significant (p=0.67) for mRS, nor for the other outcome measures (Table 3, Supplementary Table 1). Moreover, there was no significant effect modification of increasing admission glucose levels and IAT on the mRS scores when the admission glucose levels were divided into quintiles (p=0.21, p=0.31, p=0.49, p=0.99, respectively).

Hundred ninety-seven patients (46%) assigned to IAT received IV-tPA, compared to 236 patients (55%) assigned to the control group. Of the 226 patients who received IAT, 111 patients (49%) reached recanalization. Twenty-eight patients (25%) who had recanalization were hyperglycemic, compared to 29 patients (25%) who had no recanalization. The interaction of admission serum glucose levels and recanalization was not significant for the mRS score (p=0.55), the interaction of hyperglycemia and recanalization was also not significant (p=0.55). (Table 4, Supplementary Table 2 and 3)

Of the patients who received IAT, 136 patients (75%) had no intracranial occlusion on follow-up CT-angiography at 24 hours, compared to 67 patients (26%) in the control

group. In the intervention group, the interaction of admission serum glucose levels and no intracranial occlusion on follow-up CT-angiography at 24 hours for the mRS score was not significant (p=0.60), nor was the interaction of hyperglycemia and intracranial occlusion (p=0.67). The same applied for the control group (p =0.99 for admission serum glucose and p=0.06 for hyperglycemia).

Furthermore, the prediction scores of the HIAT2 were used.[31] Of all the patients with HIAT2 score ≥ 5 (n=152), 20 patients (13%) had good functional outcome, compared to 103 of the 335 patients (31%) with HIAT2 score <5 (p <0.01). Patients with HIAT2 score ≥ 5 were less likely to have good functional outcome than patients with HIAT2 score < 5 (odds ratio 0.4, CI 0.2-0.6).

Table 4. Interaction of admission serum glucose levels or hyperglycemia on recanalization and the outcome measures

	Admission glucose		**Hyperglycemia**	
Outcome	Unadjusted interaction, p	Adjusted interaction[b], p	Unadjusted interaction, p	Adjusted interaction[b] , p
mRS score at 90 days	0.33	0.55	0.55	0.55
NIHSS score after 24 hours	0.46	0.43	0.89	0.62
NIHSS score at 5-7 days	0.70	0.97	0.68	0.90
Good functional outcome (mRS 0-2)	0.63	0.92	0.96	0.99
Absence of intracranial occlusion[a]	0.94	0.99	0.66	0.68
Safety measures				
Symptomatic intracranial hemorrhage	0.67	0.73	0.22	0.30
Mortality	0.26	0.14	0.31	0.60

mRS: modified Rankin Scale. NIHSS: National Institute Health Stroke Scale
a. Absence of intracranial occlusion on follow-up CT-angiography at 24 hours
b. Adjusted for age, sex, atrial fibrillation, use of anti-hypertensive medication, NIHSS at admission, Alberta Stroke Program Early CT score

DISCUSSION

We found no evidence for effect modification of IAT by increased admission serum glucose in patients with acute ischemic stroke caused by an intracranial occlusion in an artery of the anterior circulation. Although poor functional outcome, symptomatic intracerebral hemorrhage, and mortality occurred more often in hyperglycemic patients, there was no significant interaction between increased serum glucose and IAT on these outcome measures.

To our knowledge, no clinical studies have yet investigated possible modification of IAT effect by hyperglycemia. Only a few studies indicate that increased serum glucose

leads to a higher risk of poor functional outcome after intra-arterial thrombectomy.[12-14] In addition, other studies report associations between hyperglycemia and poor functional outcome, symptomatic intracerebral hemorrhage, and less recanalization after intra-arterial thrombolysis.[6-11] Only one animal study found that interaction between hyperglycemia and IV-tPA increases hemorrhagic transformation, edema and neurological deficits.[32]

When taking these previous studies into consideration, it is surprising that we found no effect modification of IAT by hyperglycemia. Several reasons might explain our findings. First, hyperglycemia may have inhibitory effects on IV-thrombolysis by reduction of the fibrinolytic activity of tPA by inhibiting plasma fibrinolysis and increasing the production of plasminogen activator inhibitor-1.[33] These negative effects of hyperglycemia could be less in patients who receive intra-arterial thrombectomy, and could partially explain why we found no modification of the treatment effect of IAT by hyperglycemia. Second, one could hypothesize that hyperglycemia is a transient stress response after stroke and therefore mainly reflects the severity of the stroke itself rather than a pre-existent state of abnormal glucose metabolism in this study population.[34,35] Patients with more severe strokes might benefit more from IAT, and this could compensate for possible negative effects of hyperglycemia on IAT.

Strengths of our study are that admission glucose was a pre-specified baseline characteristic of the MR CLEAN-trial and that the hypothesis of possible modification of treatment effect by hyperglycemia was also pre-specified. However, our study had a few limitations. Firstly, patients with an admission serum glucose higher than 22.2 mmol/L were excluded from the MR CLEAN-trial. Therefore, the possible effect modification of serum glucose levels higher than 22.2 mmol/L could not be analyzed. Secondly, most patients in our study were normoglycemic, with an IQR of 5.8-7.8 mmol/L. This could have affected the precision of our estimates.

In conclusion, we demonstrated that increased glucose on admission does not modify the effect of IAT in patients with acute ischemic stroke due to intracranial proximal arterial occlusion of the anterior circulation. This study provides no arguments for withholding IAT from patients with glucose levels up to 22.2 mmol/l. Further studies are needed to confirm our findings and to study the effects of higher glucose levels on the treatment effect of IAT in patients with acute ischemic stroke.

CONFLICTS OF INTEREST

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Supplementary Table. 1 Effect of IAT on outcome by hyperglycemic status on admission and p (interaction) of IAT with hyperglycemia.

	Unadjusted effect estimate			**Adjusted effect estimate[b]**		
Outcome	Hyperglycemia on admission (n=118) cOR (95%CI)	No hyperglycemia (n=369) cOR (95%CI)	Unadjusted interaction, p	Hyperglycemia on admission (n=118) acOR (95%CI)	No hyperglycemia (n=369) acOR (95%CI)	Adjusted interaction[b], p
mRS score at 90 days	1.6 (0.8-3.0)	1.6 (1.1-2.4)	0.90	2.8 (1.3-6.1)	1.6 (1.1-2.3)	0.67
NIHSS score after 24 hours	0.6 (0.3-1.3)	0.5 (0.4-0.8)	0.68	0.5 (0.3-1.1)	0.5 (0.4-0.8)	0.89
NIHSS score at 5-7 days	0.5 (0.3-1.1)	0.5 (0.3-0.7)	0.81	0.5 (0.2-1.1)	0.5 (0.3-0.7)	0.83
	OR (95%CI)	OR (95%CI)		aOR (95%CI)	aOR (95%CI)	
Good functional outcome (mRS 0-2)	2.7 (1.0-7.7)	2.0 (1.2-3.1)	0.57	5.1 (1.4-18.2)	2.1 (1.2-3.4)	0.47
Absence of intracranial occlusion[a]	11.8 (4.1-33.9)	5.5 (3.3-9.0)	0.20	26.5 (5.9-119.2)	5.8 (3.4-9.7)	0.29
Safety measures						
Symptomatic intracranial hemorrhage	2.0 (0.7-5.8)	0.7 (0.3-2.0)	0.19	1.7 (0.5-5.5)	1.0 (0.3-2.6)	0.39
Mortality	1.0 (0.5-2.2)	0.9 (0.5-1.5)	0.76	0.7 (0.3-1.9)	1.0 (0.6-1.9)	0.66

mRS: modified Rankin Scale. NIHHS: National Institute Health Stroke Scale
a. Absence of intracranial occlusion on follow-up CT-angiography at 24 hours
b. Adjusted for age, sex, atrial fibrillation, use of anti-hypertensive medication, NIHSS at admission, Alberta Stroke Program Early CT score

Supplementary Table 2. Interaction of admission serum glucose levels on recanalization and the outcome measures

Outcome	Effect estimate, cOR (95%CI)	Unadjusted interaction term, p	Effect estimate[b], acOR (95%CI)	Adjusted interaction[b], p
mRS score at 90 days	0.9 (0.7-1.1)	0.33	0.9 (0.7-1.2)	0.55
NIHSS score after 24 hours	1.1 (0.9-1.4)	0.46	1.1 (0.9-1.4)	0.43
NIHSS score at 5-7 days	1.1 (0.8-1.4)	0.70	1.0 (0.8-1.3)	0.97
	OR (95%CI)		aOR (95%CI)	
Good functional outcome (mRS 0-2)	0.9 (0.7-1.3)	0.63	1.0 (0.7-1.4)	0.92
Absence of intracranial occlusion[a]	1.0 (0.6-1.9)	0.94	1.0 (0.5-1.8)	0.99
Safety measures				
Symptomatic intracranial hemorrhage	0.9 (0.6-1.4)	0.67	0.9 (0.6-1.4)	0.73
Mortality	1.2 (0.9-1.6)	0.26	1.3 (0.9-1.9)	0.14

mRS: modified Rankin Scale. NIHSS: National Institute Health Stroke Scale
a. Absence of intracranial occlusion on follow-up CT-angiography at 24 hours
b. Adjusted for age, sex, atrial fibrillation, use of anti-hypertensive medication, NIHSS at admission, Alberta Stroke Program Early CT score

Supplementary Table 3. Effect estimates in hyperglycemia on admission vs no hyperglycemia and interaction of hyperglycemia on admission with recanalization and outcome measures

	Unadjusted effect estimate			Adjusted effect estimate[b]		
Outcome	Hyperglycemia on admission (n=57) cOR (95%CI)	No hyper-glycemia (n=169) cOR (95%CI)	Unadjusted interaction, p	Hyperglycemia on admission (n=57) acOR (95%CI)	No hyperglycemia (n=169) acOR (95%CI)	Adjusted interaction[b], p
mRS score at 90 days	2.8 (1.1-7.5)	2.1 (1.2-3.5)	0.55	6.1 (1.9-19.7)	2.5 (1.4-4.5)	0.55
NIHSS score after 24 hours	0.4 (0.1-1.0)	0.3 (0.2-0.6)	0.89	0.2 (0.1-0.5)	0.3 (0.2-0.5)	0.62
NIHSS score at 5-7 days	0.5 (0.2-1.4)	0.3 (0.2-0.6)	0.68	0.1 (0.04-0.6)	0.2 (0.1-0.4)	0.90
	OR (95%CI)	OR (95%CI)		aOR (95%CI)	aOR (95%CI)	
Good functional outcome (mRS 0-2)	3.0 (0.8-11.1)	2.9 (1.5-5.5)	0.96	11.3 (1.4-91.5)	3.7 (1.8-7.7)	0.99
Absence of intracranial occlusion[a]	25.7 (2.9-(229.6)	14.7 (4.8-45.1)	0.66	N/A	17.3 (5.3-56.2)	0.68
Safety measures						
Symptomatic intracranial hemorrhage	0.4 (0.1-1.6)	1.4 (0.3-6.6)	0.22	0.2 (0.03-1.6)	1.5 (0.3-7.6)	0.30
Mortality	0.2 (0.1-0.8)	0.5 (0.2-1.1)	0.31	0.1 (0.01-1.0)	0.4 (0.2-1.1)	0.60

mRS: modified Rankin Scale. NIHSS: National Institute Health Stroke Scale
a. Absence of intracranial occlusion on follow-up CT-angiography at 24 hours.
b. Adjusted for age, sex, atrial fibrillation, use of anti-hypertensive medication, NIHSS at admission, Alberta Stroke Program Early CT score

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CHAPTER 5

Treatment of prediabetes in patients with TIA or minor ischemic stroke

CHAPTER 5.1

Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial

E. Osei
S. Fonville
A.A.M. Zandbergen
P.J.A.M. Brouwers
L.J.M.M. Mulder
H.F. Lingsma
D.W.J. Dippel
P.J. Koudstaal
H.M. den Hertog

Trials 2015

ABSTRACT

Background

Impaired glucose tolerance is present in one third of patients with a TIA or ischemic stroke and is associated with a two-fold risk of recurrent stroke. Metformin improves glucose tolerance, but often leads to side effects. The aim of this study is to explore the feasibility, safety, and effects on glucose metabolism of metformin and sitagliptin in patients with TIA or minor ischemic stroke and impaired glucose tolerance. We will also assess whether a slow increase in dose of metformin and better support and information on this treatment will reduce the incidence of side effects in these patients.

Methods

The Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke trial (MAAS trial) is a phase II, multicenter, randomized, controlled, open-label trial with blinded outcome assessment. Non-diabetic patients (n=100) with a recent (< 6 months) TIA, amaurosis fugax or minor ischemic stroke (modified Rankin scale ≤ 3) and impaired glucose tolerance, defined as 2-hour post-load glucose levels between 7.8 and 11.0 mmol/L after repeated standard oral glucose tolerance test, will be included. Patients with renal or liver impairment, heart failure, chronic hypoxic lung disease stage III-IV, history of lactate acidosis or diabetic keto-acidosis, pregnancy or breastfeeding, pancreatitis and use of digoxin will be excluded. The patients will be randomly assigned in a 1:1:2 ratio to metformin, sitagliptin or 'no treatment'. Patients allocated to metformin will start with 500 mg twice daily, which will be slowly increased during a 6 weeks period to a daily dose of two times 1000 mg. Patients allocated to sitagliptin will be treated with a daily fixed dose of 100 mg. The study has been registered as NTR 3196 in The Netherlands Trial Register. Primary outcomes include percentage still on treatment, percentage of (serious) adverse events, and the baseline adjusted difference in 2-hour post-load glucose levels at 6 months.

Discussion

This study will give more information about the feasibility and safety of metformin and sitagliptin as well as the effect on 2-hour post-load glucose levels at 6 months in patients with TIA or ischemic stroke and impaired glucose tolerance.

Trial registration number: NTR3196, Date of registration: 15 December 2011.

INTRODUCTION

Impaired glucose tolerance, an intermediate metabolic state between normal glucose tolerance and diabetes mellitus, is present in about a third of patients with transient ischemic attack (TIA) or ischemic stroke[1-4], and is associated with a two-fold risk of recurrent stroke[5]. The mechanisms underlying this association are not fully understood, but include insulin resistance, endothelial dysfunction, dyslipidemia, chronic inflammation, procoagulability, and impaired fibrinolysis.[6-8]

Pharmacological interventions reduce the rate of progression to type 2 diabetes by 10-60% in people with impaired glucose tolerance.[9-12] Lifestyle interventions are likely to be at least as effective as drug treatment [9-12], but often difficult to carry out successfully, and lifestyle advice needs to be reinforced on a regular basis.

There is no clear evidence that tight glycemic control reduces the risk of stroke in patients with diabetes or impaired glucose tolerance. A recent meta-analysis on glucose-lowering pharmacological interventions in patients with impaired glucose tolerance found no beneficial effects on all-cause mortality or death due to major cardiovascular events, with the possible exception of stroke.[13] In the UK Prospective Diabetes Study, however, metformin therapy or intensive treatment with sulphonylurea or insulin seems to be associated with less cardiovascular events in newly-diagnosed type 2 diabetics.[14] Furthermore, a large randomized placebo-controlled trial found that metformin reduces macrovascular complications when added to insulin treatment in type 2 diabetes.[15] However, metformin had no effect on the carotid intima media-thickness or carotid plaque in stroke patients.[16] Also, metformin was not more effective in preventing myocard infarction than other intensive therapy. Furthermore, metformin added to sulphonylurea therapy was associated with an increased risk of diabetes-related deaths and all-cause mortality.[14] Metformin is regarded as one of the most effective drugs for treating type 2 diabetes. Recent basic research reveals that suppression of hepatic gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase is the main underlying mechanism of metformin's blood glucose lowering effect.[17] It is recommended as first-line treatment in type 2 diabetes mellitus, and is cheap as compared to the newer antidiabetic drugs. Our recent findings suggest that metformin treatment is safe in patients with TIA or ischemic stroke and impaired glucose tolerance, and probably leads to improved glucose tolerance.[18] However, 50% of the patients experienced gastrointestinal side effects resulting in permanent discontinuation in 25%. Slower increase in dose of metformin and better information and support on the temporarily nature of the side effects might prevent the high incidence of side effects and discontinuation of treatment respectively.

Novel drugs, like selective dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes, might have fewer side effects than metformin and other anti-diabetic medication. They target primarily postprandial glucose, which is more closely associated with carotid intimal thickness and atherosclerosis risk factors than fasting plasma glucose or glycosylated hemoglobin A1 (HbA1c) levels.[19] Sitagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, improves glycemic control and β-cell function and has a safety profile similar to placebo, with low risk of gastrointestinal side effects.[20,21] Also, it is associated with weight loss and a lower risk on hypoglycemia.[20,21] However, some recent trials have shown that DPP-4 inhibitors had no effect on adverse cardiovascular outcomes in patients with type 2 diabetes.[19]

The aim of the study is to explore the feasibility, safety, and effect on glucose metabolism of both metformin and sitagliptin in patients with TIA or minor ischemic stroke and impaired glucose tolerance. Also, we will assess whether a slow increase in dose of metformin and better support and information on this treatment will reduce the incidence of side effects in these patients.

METHODS

Design

We conduct a phase II, multicenter prospective, randomized, open-label trial, blinded end point (PROBE) trial of standard care plus metformin or sitagliptin, as compared with standard care without antidiabetic treatment.

Patient population – inclusion and exclusion criteria

All adult patients attending the TIA outpatient clinic or admitted to the stroke unit in 3 hospitals in the Netherlands with TIA, amaurosis fugax or minor ischemic stroke (defined as a modified Rankin scale (mRS) (22) score of 3 or less) within the previous 6 months, and impaired glucose tolerance, defined as 2-hour post-load glucose levels between 7.8 and 11.0 mmol/L[23] after standard oral glucose tolerance test (OGTT)[24], will be invited to participate in the trial by their neurologist.

The diagnosis TIA (symptoms <24 hours) or ischemic stroke will be made by a neurologist by standard guidelines. An ischemic stroke or TIA will be defined as an episode of neurological dysfunction caused by focal cerebral or retinal infarction.[25] All patients will undergo a computed tomography (CT) scan of the brain, electrocardiogram, carotid ultrasound imaging and blood investigations which also includes the lipid profile.

The OGTT will be repeated after 2-6 weeks to rule out laboratory error and the acute phase effect. If the second OGTT confirms the diagnosis of impaired glucose tolerance, and all the selection criteria are fulfilled, the patient will be asked for written informed

consent by the investigators. So, written informed consent will be obtained by all participants. Inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and exclusion criteria

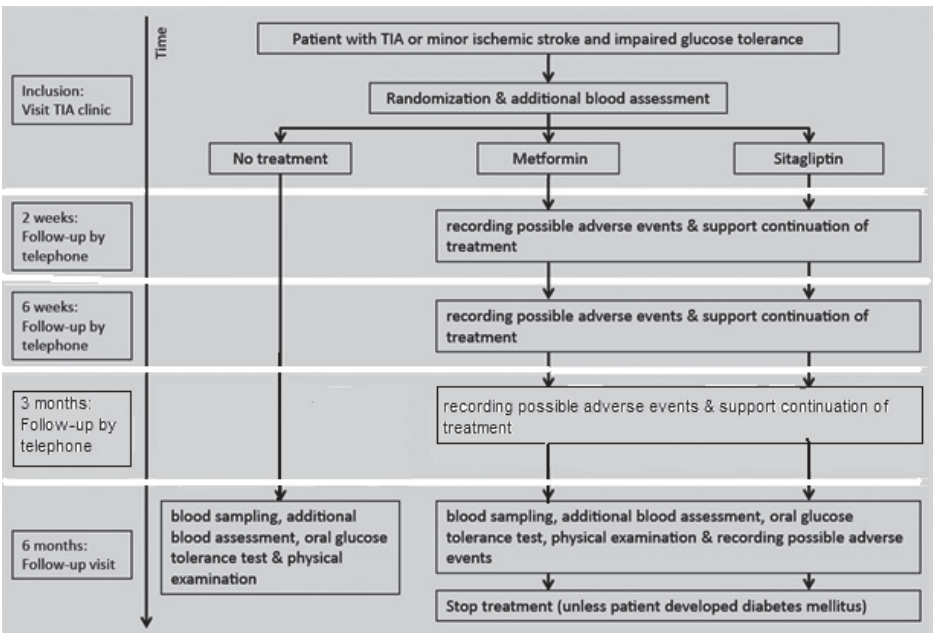
Inclusion criteria:
Age ≥18-years
TIA, amaurosis fugax or minor ischemic stroke (mRS ≤3)
Symptom onset <6 months
Impaired glucose tolerance (2-hour post-load glucose level between 7.8 and 11.0 mmol/L) in 2 consecutive measurements
Exclusion criteria:
Diabetes mellitus
History of diabetic ketoacidosis
Symptoms of type 1 diabetes
Signs of renal impairment (creatinin of 135 μmol/L or higher for men, and 110 μmol/L or higher for women)
Known liver disease or disturbed liver function tests (alanine amino transferase, aspartate amino transferas, alkaline phosphastase, or γ glutamyl transferase increased to more than twice the upper limit of typical values)
History of lactic acidosis
Heart failure requiring pharmacological therapy
Pancreatitis
Chronic hypoxic lung disease stage III-IV
Digoxin use
Pregnancy or breast feeding

Randomization, blinding and treatment allocation

Patients will be randomized by the investigators to receive either open-label metformin or sitagliptin or “no treatment” in a 1:1:2 ratio for 6 months. The randomization process will be available online by means of a list generated by computer before the start of the trial. Treatment allocation will be only possible after registration in the database. From this moment, it will not be possible to remove a patient from the database. The list with information regarding the treatment allocation will be kept separate from the study database. An independent statistician, who otherwise will not be involved in the study, will provide the list. The statistician will report unblinded data to the Data Safety and Monitoring Board (DSMB) for evaluation and interim analysis, for monitoring the safety and progression of the trial. The steering committee will be kept unaware of these results unless necessary (as judged by the DSMB), and the code will not be broken until the last patients have completed the six-months of follow-up.

Irrespective of treatment allocation, patients will receive optimal standard care from the neurologist, including antithrombotic and antihypertensive agents as well as cholesterol lowering drugs, where appropriate.[26] In addition, a stroke nurse specialist will provide general lifestyle advice including healthy diet, stop smoking, and regular physical exercise. These interventions will also be monitored by the investigators through the follow-up contacts.

Figure 1: Flowchart study design



Intervention

Patients will be randomly allocated to open-label metformin or sitagliptin or "no treatment" for a 6 months period. The treatment assignment is concealed. Patients allocated to metformin will start with 500 mg twice daily, which will be slowly increased in a 6-week period to 1000 mg twice daily (week 1: 2 times 500 mg, week 3: 2 times 850 mg, week 7: 2 times 1000 mg). If there are unmanageable side effects at an increased dose, the lower dose will be resumed and the increase will be tried again the next week. Patients allocated to sitagliptin will be treated with a daily fixed dose of 100 mg.

Study procedures

All patients will be assessed at baseline, and at 6 months. At baseline, data on clinical features of TIA or ischemic stroke, demographic data, medical history, vascular risk factors, and medication use will be obtained.

At the follow-up visit, patients will be asked to complete a single questionnaire to determine compliance and nature of any of the side effects of the study medication. Patients will also be contacted by telephone for recording of possible adverse events and to support continuation of treatment at 2 weeks, 6 weeks, and 3 months after inclusion. If necessary (e.g. in case of unmanageable side effects), the number of telephone contacts and or follow up visits will be intensified. Before randomization and at 6 months, all patients will undergo an oral glucose tolerance tests (OGTT) with 75-gram of glucose. Fasting glucose levels, body mass index, waist circumference, blood pressure and lipid profile will be assessed at baseline, and at 6 months. Patients will be excluded from other trials which involve any secondary prevention treatment of stroke like new medication or lifestyle adjustments. The final raters who will assess the outcome measures will be blinded for treatment allocation.

Primary outcomes

The primary outcomes are tolerability of metformin and sitagliptin, assessed as the number of patients still on treatment after 6 months, the number of adverse events and serious adverse events, and the baseline adjusted difference in 2-hour post-load glucose levels.

Secondary outcomes

Secondary outcomes are the effect of metformin and sitagliptin on fasting plasma glucose levels at 6 months, the percentage of patients with normal glucose tolerance at 6 months and on the body mass index (BMI) and waist circumference at 6 months.

Data Safety Monitoring Board

The DSMB is composed of independent experts in the field of statistics, neurology, and vascular internal medicine. It monitors the progress and safety of the trial, and performs an interim analysis. Based on this information, they advise the steering committee on pre-specified grounds, as formulated by the DSMB.

Sample size

We expect that 50% of patients on metformin will experience side effects during follow up. Assuming a difference of 40% in side effects between patients on metformin and patients in the control group, and a difference of 30% between patients on metformin and patients on sitagliptin, 100 patients will have a power of 80% to detect a significant (alpha=0.05) difference in side effects. A sample size of 100 patients, calculated by a statistician, (25 on metformin, 25 on sitagliptin, and 50 in the control group) will provide a power of 80%, to detect a difference of 8% in 2-hour post-load glucose level after 6 months between treatment groups, assuming a significance level of $\alpha = 0.05$ and a mean glucose level of 9.0 mmol/l in the control group, with a standard deviation of 1.0 mmol/l.

Statistical analyses

Analyses will be done by intention-to-treat and all patients who are randomly assigned to treatment will be included in the pre-specified analyses. The effect in each of the two treatment groups will be compared to the control group separately. We will estimate the baseline adjusted differences in mean 2-hour post-load glucose levels and fasting glucose levels between treatment groups with 95% confidence intervals (CI) with univariable linear regression. Adjustments will be made with a multivariable linear regression model that will include the following factors: age, sex, time to treatment, and baseline waist. Similar analyses will be performed to study the effect of treatment with metformin or sitagliptin on body mass index and waist circumference. We will compare the percentage of patients still on treatment after 6 months, the incidence of (serious) adverse events and percentage of patients with a normal glucose tolerance at 6 months between treatment groups with chi-square test. No adjustment for multiplicity will be done due to the explanatory nature of a phase II trial.

Ethical approval

The Medical Ethical Trial Commissions (METC) of both the Erasmus Medisch Centrum in Rotterdam and Medisch Spectrum Twente in Enschede gave approval for this trial.

DISCUSSION

Impaired glucose tolerance is present in up to one third of patients with TIA or stroke and is associated with a two-fold increased risk of recurrent stroke. The increased risk of impaired glucose tolerance could be due to the impaired lipid profile of these patients. However, there is an independent association of impaired glucose tolerance on cardiovascular diseases. Intensive glucose control with oral antidiabetic drugs reduces the rate of progression to type 2 diabetes in patients with impaired glucose tolerance.[9-12] Whether pharmacotherapeutical intervention reduces the risk of cardiovascular events in patients with TIA or minor ischemic stroke (who are often older with more co-medication) and impaired glucose tolerance is unknown. Our recent study (LIMIT) has shown that metformin treatment is safe and improves glucose tolerance in these patients, but often leads to gastrointestinal side effects.[18] The rationale for choosing metformin and sitagliptin is as follows: metformin is recommended as first-line treatment in type 2 diabetes, is cheap, and widely used in The Netherlands. However, in the LIMIT trial metformin caused frequent gastrointestinal side effects and consequently discontinuation of drug adherence in a large percentage of the patients.[18] When slow increase in dose of metformin and better support and information on this treatment proves to reduce the incidence of side effects in these patients, metformin will be a cheap, easy and widely used drug to improve glucose tolerance in a large proportion of stroke patients. Sitagliptin has proven to be equally effective and safe as metformin,

with improvement of glycemic control by lowering HbA1c levels, and a lower risk of gastrointestinal side effects and hypoglycemia.[20,21] This combined with the once daily, fixed dose makes it a patient friendly drug and is more prone to good adherence. However, the costs of sitagliptin are more than 16 times higher compared to metformin. To compare the effect in both treatment groups with the control group separately, a randomization ratio of 1:1:2 was chosen.

Although a double-blind, placebo-controlled designed trial would have been superior, the current trial has a PROBE design. The main reason is that the former comes with greater costs. Potential limitations are therefore the lack of a placebo group and its open design, which can give an increased risk on performance bias. However, outcome assessment will be blinded for treatment allocation. The final raters who will assess the outcome will be blinded for treatment allocation. And the design will resemble the effect in clinical practice after implementation.

Although lifestyle intervention is equally effective in lowering glucose levels as glucose lowering drugs, it is hard to sustain.[9,12] If we can prove with the MAAS trial that metformin and/or sitagliptin are safe and feasible in lowering glucose levels, a phase III trial is necessary to investigate the effect on the incidence of recurrent stroke and other cardiovascular complications, to improve secondary prevention in these patients. In this phase III trial, patients with a TIA or minor ischemic stroke and impaired glucose tolerance will receive standard care and be allocated to metformin or sitagliptin, depending on the results of this phase II-trial, and one of these will be compared to placebo.

TRIAL STATUS

MAAS-trial has started in January of 2014.

CONFLICTS OF INTEREST

None.

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None.

MAAS STUDY GROUP

Principal investigators:

Heleen M. den Hertog, neurologist, PhD, Medisch Spectrum Twente, Enschede

Adrienne A.M. Zandbergen, PhD, Ikazia Hospital, Rotterdam

Other study group members:

Elizabeth Osei, resident in neurology, Medisch Spectrum Twente, Enschede

Diederik W.J. Dippel, neurologist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Peter J. Koudstaal, neurologist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Hester F. Lingsma, clinical epidemiologist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Laus J.M.M. Mulder, neurologist, Ikazia Hospital, Rotterdam

Paul J.A.M. Brouwers, neurologist, PhD, Medisch Spectrum Twente, Enschede

Trial statistician:

Hester F. Lingsma, clinical epidemiologist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Data monitoring and safety committee:

Ale Algra, MD, clinical epidemiologist, PhD, Julius Center, University Medical Center Utrecht, Utrecht (chair)

Hester F. Lingsma, clinical epidemiologist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Paul J. Nederkoorn, neurologist, PhD, Amsterdam Medical Center, Amsterdam

Behiye Özcan, vascular internist, PhD, Erasmus Medical Center University Hospital, Rotterdam

Study coordinator:

Elizabeth Osei, resident in neurology, Medisch Spectrum Twente, Enschede

Trial registration:

NTR-number: 3196.

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CHAPTER 5.2

Safety, feasibility and efficacy of metformin and sitagliptin in patients with a TIA or minor stroke and impaired glucose tolerance

E. Osei
A.A.M. Zandbergen
P.J.A.M. Brouwers
L.J.M.M. Mulder
P.J. Koudstaal
H.F. Lingsma
D.W.J. Dippel
H.M. den Hertog

Submitted

ABSTRACT

Background

Impaired glucose tolerance (IGT) is highly prevalent after stroke and is associated with recurrent stroke and unfavourable outcome. We aimed to assess the feasibility, safety, and effects on glucose metabolism of metformin or sitagliptin in patients with TIA or minor ischemic stroke and IGT.

Methods

We performed a multicenter, randomized, controlled, open-label phase II trial with blinded outcome assessment. Patients were randomized in a 2:1:1 ratio to 'no medication', sitagliptin or metformin. Outcome measures were baseline adjusted differences of 2-hour post-load glucose, fasting glucose, glycosylated hemoglobin 1c (HbA1c) levels, tolerability and safety of metformin and sitagliptin at 6 months.

Results

Fifty-three patients were randomized to the control group, 26 to metformin and 22 to sitagliptin. We found no significant differences in 2-hour post-load glucose between patients on antidiabetic drugs and controls ((-0.04 mmol/L (95%CI -0.53 to 0.45)). Patients in the treatment arms had reduced fasting glucose: ((-0.21 mmol/L (95%CI -0.36 to -0.06)) and HbA1c levels ((-1.16 mmol/mol (95%CI -1.84 to -0.49)). Thirteen patients (50%) on metformin and 7 (32%) on sitagliptin experienced side effects. Sixteen patients (61%) in the metformin and 13 (59%) in the sitagliptin group were still on treatment after 6 months.

Conclusions

Metformin and sitagliptin were both effective in reducing fasting glucose and HbA1c levels in patients with recent TIA or ischemic stroke and IGT. A phase III trial is needed to investigate whether medical treatment not only improves glucose metabolism in IGT, but also leads to reduction of recurrences in patients with TIA or ischemic stroke.

INTRODUCTION

Impaired glucose tolerance (IGT), an intermediate metabolic state between normal glucose tolerance and diabetes mellitus, is highly prevalent in patients with transient ischemic attack (TIA) or ischemic stroke. [1–4] IGT can be transient, reflecting an acute stress response, or persistent, representing undiagnosed impaired glucose metabolism. [1] In nondiabetic stroke patients with IGT in the acute phase after stroke and repeated glucose assessment after 3 months, 22%–47% had persistent IGT. [1,5–7] IGT increases the risk of recurrent stroke and other cardiovascular events. [8,9] Moreover, IGT is also associated with poor functional outcome and mortality in stroke patients. [8,10,11] The mechanisms underlying this association are not fully understood, but may include insulin resistance, endothelial dysfunction, dyslipidemia, chronic inflammation, hypercoagulability, and impaired fibrinolysis. [12–14]

Tight glycemic control might reduce the risk of stroke in patients with diabetes or impaired glucose tolerance. A recent randomized controlled trial showed that pioglitazone can prevent stroke and myocardial infarction among patients with insulin resistance after ischemic stroke or TIA, but pioglitazone also gave a higher risk of weight gain, edema, and fractures. [15] A meta-analysis of glucose-lowering pharmacological interventions in patients with impaired glucose tolerance found no beneficial effects on all-cause mortality or death due to major cardiovascular events, with the possible exception of stroke. [16]

Metformin is regarded as one of the most effective oral drugs in the management of type 2 diabetes. It is recommended as first-line treatment in type 2 diabetes mellitus, and is cheap compared to the newer antidiabetic drugs. Our recent findings suggest that metformin treatment is safe in patients with TIA or ischemic stroke and impaired glucose tolerance, and probably leads to improved glucose tolerance. [17] However, 50% of the patients experienced gastrointestinal side effects resulting in permanent discontinuation in 25%. More gradual increase in dose of metformin and better information and support on the temporary nature of the side effects might diminish the high incidence of side effects and discontinuation of treatment.

Newer antidiabetic drugs, like selective dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes, might have fewer side effects than metformin. Sitagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, improves glycemic control and β-cell function and has a safety profile similar to placebo, with low risk of gastrointestinal side effects. Also, it is associated with weight loss and a lower risk of hypoglycemia. [18,19]

The aim of the study was to explore the feasibility, safety, and effects on glucose metabolism of both metformin and sitagliptin in patients with TIA or minor ischemic

stroke and impaired glucose tolerance. Considering our previous study [17], we also assessed whether a more gradual increase in dose of metformin and better support and information on this treatment reduce the incidence of side effects in these patients.

METHODS

Study design

The design of the Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS) trial has been reported earlier. [20] In summary, the MAAS-trial is a phase II, multicenter, randomized, open-label, blinded end point (PROBE) trial of standard care plus metformin or sitagliptin, as compared with standard care without anti-diabetic treatment. The study was conducted in two stroke centers in the Netherlands from 2014 to 2019. The study protocol [20] was approved by the central medical ethics committee and the research board of the participating centers. All patients or their legal representatives gave written informed consent before randomization.

An independent data and safety monitoring board monitored the progress and safety of the trial, and performed an interim analysis. Based on this information, they advised the steering committee on pre-specified criteria.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Study population

Patients were eligible for inclusion if they were 18 years or older and had a clinical diagnosis of TIA, amaurosis fugax or minor ischemic stroke (defined as a modified Rankin scale (mRS) score of 3 or less) [21] within the previous 6 months. The diagnosis TIA (symptoms <24 hours) or ischemic stroke was made by a neurologist according to standard guidelines.

Eligible patients were required to have IGT, defined as 2-hour post-load glucose levels between 7.8 and 11.0 mmol/L after standard oral glucose tolerance test (OGTT), which was performed on the day of the visit to the TIA outpatient clinic or on the first day after admission on the stroke unit. [22,23] We previously stated in the study protocol that the OGTT should be repeated after 2-6 weeks to rule out laboratory error and the acute phase effect. Due to logistic reasons, this time frame was broadened to 2-12 weeks. If the second OGTT confirmed the diagnosis of IGT, and all the selection criteria were fulfilled, the patients were asked for written informed consent by the investigators. Patients were excluded if they had a history of diabetes mellitus, defined as the use of oral or parenteral anti-diabetic medication. Other exclusion criteria included a history of diabetic keto-

acidosis, symptoms of type 1 diabetes, signs of renal impairment, known liver disease or disturbed liver function tests, history of lactic acidosis, heart failure, pancreatitis, chronic hypoxic lung disease stage III-IV, digoxin use, pregnancy or breastfeeding (for detailed list of inclusion- and exclusion criteria, see study protocol [20].

Study procedures

Before randomization and at 6 months, all patients underwent oral glucose tolerance tests (OGTT) with 75-gram of glucose. At baseline, data on clinical features of TIA or ischemic stroke, demographic data, medical history, vascular risk factors, and medication use were obtained. Fasting glucose levels, glycosylated hemoglobin 1c (HbA1c) levels, body mass index, blood pressure, and lipid profile were also assessed at baseline and at 6 months.

Patients were randomized to receive either open-label metformin or sitagliptin or "no medication" in a 1:1:2 ratio for 6 months. The treatment assignment was concealed. Patients allocated to metformin started with 500 mg twice daily, which was gradually increased in a 6-week period to 1000 mg twice daily (week 1: 2 times 500 mg, week 3: 2 times 850 mg, week 7: 2 times 1000 mg). If intolerable side effects for the patients occurred after increasing the dose, the previous dose was resumed and a second challenge was performed in the next week. Patients allocated to sitagliptin were treated with a fixed daily dose of 100 mg.

Patients on metformin or sitagliptin were contacted by telephone for recording of possible adverse events and to support continuation of treatment at 2 weeks, 6 weeks and 3 months after inclusion. At the follow-up visit at 6 months, patients were asked to complete a single questionnaire to assess compliance and nature of any of the side effects of the study medication.

Irrespective of treatment allocation, patients received usual care from the neurologist, including antithrombotic and antihypertensive agents as well as cholesterol lowering drugs, where appropriate. [24] In addition, a stroke nurse specialist provided general lifestyle advice concerning diet, smoking and physical exercise.

Study outcomes

The primary efficacy outcome was the level of 2-hour post-load plasma glucose. Safety and acceptability outcomes were the number of adverse events and serious adverse events, and the number of patients still on treatment after 6 months.

Secondary outcomes were the fasting plasma glucose levels, the body mass index (BMI) at 6 months, presence of normal glucose tolerance at 6 months. Moreover, we studied HbA1c levels, low-density lipoprotein (LDL) levels, systolic and diastolic blood pressure at 6 months. Also, the percentage of patients with normalized fasting glucose (defined

as fasting plasma glucose levels <5.6 mmol/L) and normalized HbA1c levels (defined as HbA1c levels < 39 mmol/mol) at 6 months was assessed. Outcome assessment was blinded for treatment allocation.

Statistical analyses

We estimated that a sample size of 100 patients, (25 on metformin, 25 on sitagliptin, and 50 in the control group) would provide a power of 80%, to detect a statistically significant (alpha<0.05) effect, based on an assumed difference of 8% in 2-hour post-load glucose level after 6 months between treatment and controls, assuming a mean glucose level of 9.0 mmol/l in the control group, with a standard deviation of 1.0 mmol/l.

The primary effect analysis estimated the difference in 2-hour post-load glucose levels at 6 months between the three groups, adjusted for baseline glucose level. Analyses were done by intention-to-treat and all patients who were randomized to a study arm were included in the pre-specified analyses.

We estimated the baseline adjusted differences of 2-hour post-load glucose levels, fasting glucose levels, HbA1c levels, BMI, LDL levels, and systolic and diastolic blood pressure between treatment groups with 95% confidence intervals (CI) with multivariable linear regression, but report unadjusted analyses as well. We previously stated in our protocol that adjustments were made with a multivariable linear regression model that included the following factors: age, sex, time to treatment and baseline waist circumference. We later, but before closure of the database, decided to add baseline glucose levels to the adjustments and replace baseline waist circumference by baseline BMI.[25]

We compared the percentage of patients still on treatment after 6 months, the incidence of (serious) adverse events and percentage of patients with a normal glucose tolerance, normal fasting glucose and normal HbA1c levels at 6 months between treatment groups with chi-square test. Furthermore, we expressed the association of the treatment groups with normalized glucose tolerance, fasting glucose and HbA1c levels with odds ratios and corresponding CI. These estimates were also made with multivariable logistic regression and adjusted for age, sex, time to treatment, BMI and baseline glucose levels.

In addition, subgroup analyses were performed in patients who used metformin 1000 mg twice a day, and patients with a combination of impaired glucose tolerance, impaired fasting glucose and impaired HbA1c levels at randomization. We also performed an “on treatment analysis”.

RESULTS

A total of 263 patients with IGT based on the first OGTT underwent a repeated OGTT. Of these patients, 162 (62%) had normalized IGT. The remaining 101 patients were included in our study. Fifty-three patients were allocated to the control group, 26 patients to metformin and 22 patients to sitagliptin.

The baseline characteristics of the enrolled patients are described in Table 1.

Table 1. Baseline characteristics

	Control (n=53)	**Metformin (n=26)**	**Sitagliptin (n=22)**
Age in years, mean (SD)	68 (11)	70 (10)	66 (11)
Men, n (%)	30 (57%)	15 (58%)	9 (41%)
Days between event and second OGTT, median (IQR)	53 (56)	46 (31)	56 (38)
Vascular risk factors			
Current smoking, n (%)	9 (17%)	4 (15%)	4 (18%)
BMI in kg/m^2, mean (SD)	28 (4)	27 (3)	28 (4)
Hypertension, n (%)	41 (77%)	18 (69%)	17 (77%)
Hypercholesterolemia, n (%)	47 (89%)	22 (85%)	20 (91%)
Atrial fibrillation, n (%)	7 (13%)	3 (12%)	3 (14%)
Systolic blood pressure in mmHg, mean (SD)	149 (21)	139 (20)	142 (21)
Diastolic blood pressure in mmHg, mean (SD)	82 (12)	76 (9)	79 (14)
Vascular history			
Ischemic cardiovascular disease, n (%)	11 (21%)	11 (43%)	4 (18%)
Event			
Ischemic stroke, n (%)	28 (53%)	10 (38%)	8 (36%)
TOAST classification			
Large artery atherosclerosis, n (%)	10 (19%)	2 (8%)	5 (23%)
Cardioembolism, n (%)	5 (9%)	4 (15%)	3 (14%)
Small vessel occlusion, n (%)	25 (47%)	15 (58%)	7 (32%)
Other determined etiology, n (%)	1 (2%)	0	1 (4%)
Unknown, n (%)	12 (23%)	5 (19%)	6 (27%)
Medication use			
Platelet aggregate inhibitors, n (%)	46 (87%)	22 (85%)	17 (77%)
Oral anticoagulant, n (%)	7 (13%)	4 (15%)	5 (21%)
Statin use, n (%)	47 (89%)	24 (92%)	20 (91%)
Beta-blockers, n (%)	16 (30%)	7 (27%)	5 (23%)
Renin-angiotensin-aldosterone system inhibitors, n (%)	19 (36%)	12 (46%)	9 (41%)
Diuretics, n (%)	16 (30%)	9 (35%)	8 (36%)

Table 1. Baseline characteristics

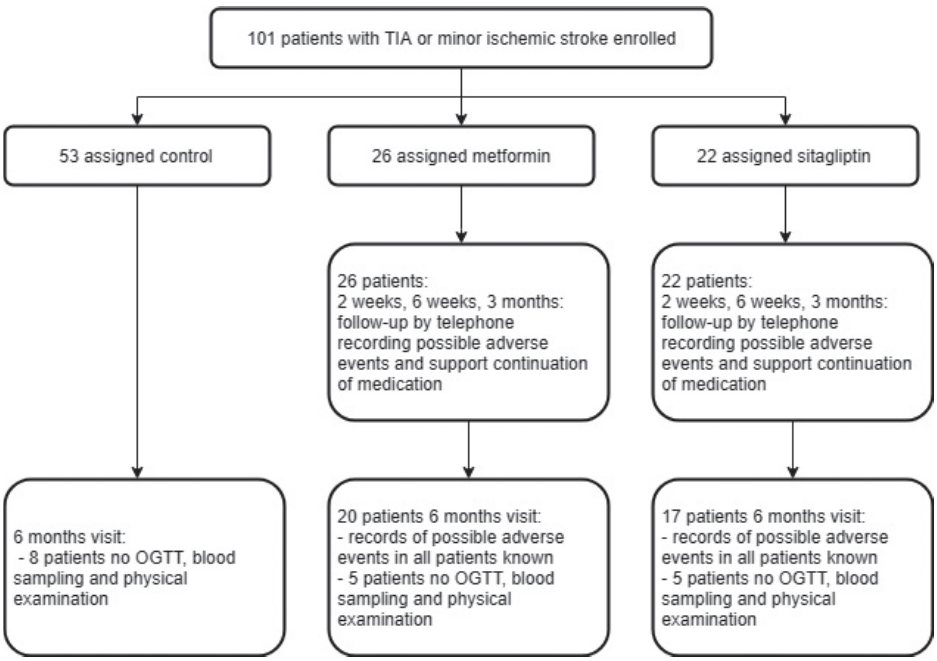
	Control (n=53)	Metformin (n=26)	Sitagliptin (n=22)
Calcium antagonists, n (%)	13 (25%)	5 (19%)	4 (18%)
Laboratory assessment during admission/visiting TIA outpatient clinic			
Total cholesterol levels in mmol/L, mean (SD)	4.8 (1)	4.6 (1.2)	5.1 (1.2)
LDL levels in mmol/L, mean (SD)	2.9 (0.9)	2.9 (0.9)	3.1 (1.0)
HDL levels in mmol/L, mean (SD)	1.4 (0.7)	1.6 (0.8)	1.3 (0.3)
Triglyceride levels in mmol/L, mean (SD)	1.4 (0.6)	1.1 (0.4)	1.5 (0.6)
Glucose assessment during admission/visiting TIA clinic			
2-hour post-load glucose levels in mmol/L, mean (SD)	9 (0.9)	8.9 (0.9)	8.9 (0.8)
Fasting glucose levels in mmol/L, mean (SD)	5.6 (0.6)	5.5 (0.7)	5.6 (0.9)
HbA1c levels in mmol/L, mean (SD)	38 (2.3)	38 (3.5)	37 (2.9)
Impaired fasting glucose ≥ 5.6 mmol/L, n (%)	25 (47%)	12 (46%)	10 (45%)
Impaired HbA1c levels ≥ 39 mmol/L, n (%)	21(40%)	13 (52%)	10 (45%)

BMI: body mass index.TIA: transient ischemic attack. TOAST: Trial of Org 10172 in Acute Stroke Treatment. HbA1c: glycosylated Hemoglobin 1c. OGTT: oral glucose tolerance test.

Of the total study population, 54 patients (53%) were men, mean age was 68 years (SD 11), 55 patients (54%) had ischemic stroke, and 47 (46%) had small vessel disease according to the TOAST criteria. The median time between the ischemic event and randomization was 51 days (IQR 38). Forty-seven patients (47%) also had impaired fasting glucose levels and 38 patients (37%) impaired HbA1c levels. The treatments groups were well matched, except for diastolic blood pressure and triglycerides levels, which were both lower in the metformin group. (Table 1)

Of 18 patients (18%) the 6-months follow up was not completed, and they did not undergo an OGTT, blood analysis, and physical examination; 8 (15%) in the control group, 5 (19%) in the metformin group and 5 (23%) in the sitagliptin group (p=0.72). (Figure 1) Underlying reasons were lack of motivation to continue the study and logistic problems to visit the hospital again. The patients of whom the 6 month-follow up visit was not completed, were older (71 vs 67 years), more often female (56% vs 45%), more often had ischemic strokes instead of TIA (56% vs 43%), and ischemic cardiovascular diseases in their medical history (33% vs 24%). (Table 2, supplement)

Figure 1. Flowchart of enrolment and follow-up



OGTT: oral glucose tolerance test

Table 2. (supplement) Baseline characteristics of patients with 6 months visit and patients with no 6 months visit

	Visit at 6 months, n=83	**No visit at 6 months, n=18**
Age in years, mean (SD)	67 (10)	71 (13)
Men, n (%)	46 (55)	8 (44)
Days between event and OGTT, median (IQR)	53 (33)	62 (33)
Vascular risk factors		
Current smoking, n (%)	16 (19%)	1 (6%)
BMI in kg/m^2, mean (SD)	28 (4)	27 (3)
Hypertension, n (%)	63 (76%)	13 (72%)
Hypercholesterolemia, n (%)	73 (88%)	16 (89%)
Atrial fibrillation, n (%)	10 (12%)	3 (17%)
Systolic blood pressure in mmHg, mean (SD)	144 (19)	147 (29)
Diastolic blood pressure in mmHg, mean (SD)	81 (11)	75 (16)
Vascular history		
Ischemic cardiovascular disease, n (%)	20 (24%)	6 (33%)

Table 2. (supplement) Baseline characteristics of patients with 6 months visit and patients with no 6 months visit

	Visit at 6 months, n=83	**No visit at 6 months, n=18**
Event		
Ischemic stroke, n (%)	36 (43%)	10 (56%)
TOAST classification		
Large artery atherosclerosis, n (%)	4 (22%)	13 (16%)
Cardio embolism, n (%)	3 (17%)	9 (11%)
Small vessel occlusion, n (%)	7 (39%)	40 (48%)
Other determined etiology, n (%)	1 (6%)	1 (1%)
Unknown, n (%)	3 (17%)	20 (24%)
Laboratory assessment during admission/visiting TIA outpatient clinic		
Total cholesterol levels in mmol/L, mean (SD)	4.8 (1.1)	4.8 (1.2)
LDL levels in mmol/L, mean (SD)	3 (0.9)	2.9 (0.9)
HDL levels in mmol/L, mean (SD)	1.5 (0.7)	1.3 (0.4)
Triglyceride levels in mmol/L, mean (SD)	1.3 (0.6)	1.4 (0.5)
Glucose assessment during admission/visiting TIA clinic		
Fasting glucose levels in mmol/L, mean (SD)	5.6 (0.7)	5.4 (0.8)
2-hour post-load glucose levels in mmol/L, mean (SD)	8.9 (0.9)	8.9 (1)
HbA1c levels in mmol/L, mean (SD)	38 (2.7)	37 (3.3)
Impaired fasting glucose ≥ 5.6 mmol/L, n (%)	42 (51)	12 (67)
Impaired HbA1c levels ≥ 39 mmol/L, n (%)	45 (56)	10 (56)

BMI: body mass index.TIA: transient ischemic attack. TOAST: Trial of Org 10172 in Acute Stroke Treatment. HbA1c: glycosylated Hemoglobin 1c. OGTT: oral glucose tolerance test.

At 6 months follow-up, patients with metformin had a mean 2-hour post-load glucose level of 8 mmol/L, with sitagliptin 8.1 mmol/L and with no medication 8.1 mmol/L. The baseline adjusted difference in 2-hour post-load glucose levels between treatment groups compared with control was not significant: -0.04 mmol/L (95%CI -0.53 to 0.45) (Table 3, Figure 2). The difference with controls was not significant, either for metformin (-0.13 mmol/L; 95%CI -1.14 – 0.87), or for sitagliptin (-0.03 mmol/L; 95%CI -0.55 – 0.5). At 6 months, 17 patients (39%) in the control group, 7 (33%) in the metformin group, and 7 (41%) in the sitagliptin group (p 0.87) reverted to normal glucose tolerance. (Table 4)

Table 3. Baseline adjusted differences in primary and secondary outcome measures between treatment groups (metformin and sitagliptin combined compared to no medication)

	Unadjusted	Adjusted
Baseline adjusted differences in 2-hour post-load glucose in mmol/L (95% CI)	-0.06 (-0.56 to 0.44)	-0.04 (-0.53 to 0.45)
Baseline adjusted differences in fasting glucose levels in mmol/L (95% CI)	-0.22 (-0.37 to -0.06)	-0.21 (-0.36 to -0.06)
Baseline adjusted differences in HbA1c levels in mmol/mol (95% CI)	-1.14 (-1.8 to -0.47)	-1.16 (-1.84 to -0.49)
Baseline adjusted differences in LDL levels in mmol/L (95% CI)	-0.12 (-0.28 to 0.04)	-0.11 (-0.27 to 0.06)
Baseline adjusted differences in BMI in kg/m^2 (95% CI)	0.1 (-0.37 to 0.57)	0.06 (-0.41 to 0.52)
Baseline adjusted differences in systolic blood pressure levels in mmHg (95% CI)	-2.91 (-7.59 to 1.77)	-2.46 (-6.98 to 2.06)
Baseline adjusted differences in diastolic blood pressure levels in mmHg (95% CI)	-1.8 (-5.08 to 1.47)	-1.57 (-4.91 to 1.78)

Adjusted for age, sex, time to treatment, BMI and baseline glucose levels

Table 4. Percentage of patients with normalized 2-hour post-load glucose, fasting glucose and HbA1c levels after 6 months compared with baseline

	Control (n=53)	Metformin (n=26)	Sitagliptin (n=22)	p-value	Adjusted odds ratio (95%CI)
Normalized 2-hour post- load glucose (<7.8 mmol/l) at 6 months, n (%)	17 (39)	7 (33)	7 (41)	0.87	1.07 (0.59 to 1.95)
Normalized fasting glucose (<5.6 mmol/l) at 6 months, n (%)	22 (48)	16 (70)	16 (89)	<0.01	3.01 (1.49 to 6.11)
Difference in patients with normalized fasting glucose at 6 months compared with baseline, (%)	-5%	16%	34%		
Normalized HbA1c (<39 mmol/mol), n (%)	21 (47)	11 (55)	11 (65)	0.43	1.83 (0.8-4.16)
Difference in patients with normalized HbA1c at 6 months compared with baseline, (%)	-13%	7%	10%		

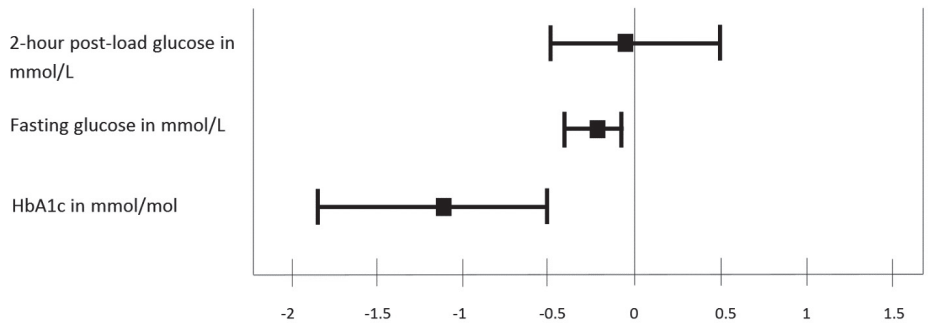
Adjusted for age, sex, time to treatment, BMI and baseline glucose levels

Patients on metformin or sitagliptin had lower fasting glucose levels (-0.21 mmol/L; 95%CI -0.36 to -0.06) and HbA1c levels (-1.16 mmol/mol; 95%CI -1.84 to -0.49) than the control group. (Table 3, Figure 2)

Also, both sitagliptin and metformin led to a higher rate of conversion to normalized fasting glucose and HbA1c levels at 6 months compared to no medication. (Table 4)

Overall, there was no significant reduction in BMI, LDL levels and blood pressure compared to control. (Table 3)

Figure 2. Mean change in glucose levels from baseline to 6 months with metformin or sitagliptin combined compared with no medication



Adjustments for age, sex, time event to randomization, baseline BMI, baseline glucose levels

PRESPECIFIED SUBGROUP ANALYSES

Patients who were on high dose metformin (1000 mg twice daily) did not have better outcomes on all relevant parameters than control patients. The same applied for patients with a combination of impaired glucose tolerance, impaired fasting glucose and impaired HbA1c levels at randomization. In addition, the on treatment analyses did not significantly differ from the intention to treat analyses. (Table 5, supplement)

ADVERSE EVENTS

The follow-up at 2 and 6 weeks, 3 months, and 6 months by telephone for recording of possible adverse events were completed in all patients on sitagliptin or metformin. Thirteen patients (50%) in the metformin group and 7 (32%) in the sitagliptin group experienced side effects. The most common side effects were gastro-intestinal complaints. (Table 6) There were no serious adverse events. Five patients (19% of the metformin group) lowered the metformin dose because of side effects.

A total of 24 patients discontinued the medication, of these 6 (25%) experienced side effects. Of the 10 patients with medication who did not come for the 6 months visit, 3 (30%) experienced side effects.

Sixteen patients (61%) in the metformin group and 13 patients (59%) in the sitagliptin group (p=0.86) were still on treatment after 6 months.

Table 5. (supplement) Subgroup analyses of primary and secondary outcome measures between treatment groups

	Patients who used metformin 2000 mg daily (n=11)	Patients with impaired glucose tolerance, fasting glucose and Hba1c (n=34)	On treatment analyses (n=82)
Baseline adjusted differences in 2-hour post-load glucose in mmol/L (95% CI)	-0.16 (1.47 to 1.14)	-0.29 (-1.19 to 0.63)	-0.26 (-0.8 to 0.29)
Baseline adjusted differences in fasting glucose levels in mmol/L (95% CI)	-0.44 (-0.87 to -0.02)	-0.03 (-0.35 to 0.28)	-0.22 (-0.4 to -0.04)
Baseline adjusted differences in HbA1c levels in mmol/mol (95% CI)	-2.49 (-4.46 to -0.52)	-0.93 (-2.38 to 0.51)	-1.1 (-1.87 to -0.33)
Baseline adjusted differences in LDL levels in mmol/L (95% CI)	0.36 (-0.08 to 0.79)	-0.06 (-0.35 to 0.23)	-0.04 (-0.23 to 0.14)
Baseline adjusted differences in BMI in kg/m^2 (95% CI)	-0.04 (-1.04 to 0.96)	-0.3 (-1.12 to 0.52)	-0.13 (-0.57 to 0.31)
Baseline adjusted differences in systolic blood pressure levels in mmHg (95% CI)	-0.6 (-14.22 to 13.02)	-0.99 (-9.26 to 7.28)	-1.41 (-6.6 to 3.78)
Baseline adjusted differences in diastolic blood pressure levels in mmHg (95% CI)	-4.29 (-15.15 to 6.56)	-1.16 (7.27 to 4.95)	-1.04 (-4.89 to 2.82)

Adjusted for age, sex, time to treatment, BMI and baseline glucose levels

Table 6. Side effects after 6 months in both treatment groups

	Metformin, n= 26	Sitagliptin, n=22
Patients with side effects, n (%)	13 (50%)	7 (32%)
Discontinuation of medication because of side effects, n (%)	4 (15%)	2 (9%)
Type of side effects		
Nausea, n	8	2
Diarrhea, n	8	0
Stomach ache, n	6	2
Loss of appetite, n	4	1
Dry mouth, n	1	2
Flu like symptoms, n	1	1
Muscle pain, n	-	2
Joint pain, n	-	1
Dizziness, n	-	1
Vomiting, n	1	-
Headache, n	1	-
Other, n	7	-

CONCLUSION

We found that metformin and sitagliptin had no significant effect on 2-hour post-load glucose levels in patients with minor ischemic stroke or TIA and impaired glucose tolerance, but both significantly reduced fasting glucose and HbA1c levels. Although metformin and sitagliptin were both safe, metformin more often caused side effects, but not a higher rate of treatment discontinuation than sitagliptin.

In contrast to our previous study [17], we did not find an effect of treatment on 2-hour post-load glucose levels. We chose this outcome measure because 2-hour post-load glucose levels detect more patients with impaired glucose metabolism than fasting glucose or Hba1c [22]. However, an OGTT is not easy to reproduce accurately, due to inter- and intra-individual variations, random variations of plasma glucose concentrations, and the effects of administration of hyperosmolar glucose concentration on gastric emptying.[26]

Interestingly, we did find a significant effect of metformin and sitagliptin on fasting glucose levels in a relative short period of 6 months and on Hba1c levels, which is a reflection of the average glucose levels of the past 2-3 months. In our previous study, we did not find a significant reduction in fasting glucose levels, maybe due to the shorter follow-up and smaller study population of our previous study. The HbA1c levels were not measured in our previous study.

Both studies reported a non-significant effect on BMI, lipid levels and blood pressure, whilst other studies report a decrease in weight, cholesterol levels and blood pressure with treatment with metformin or sitagliptin.[18,19,27–30] This might be explained by our relatively short follow-up period.

We found a similar percentage of patients who experienced side effects, but a higher proportion of patients who discontinued metformin (40% in the current study vs 22% in our previous study). The slow increase in dosage of metformin and better information and support in our study did not lead to a decrease in occurrence of side effects, compared to our previous study. [17]

We compared our results to a study which assessed the efficacy and safety of sitagliptin compared with metformin in patients with type 2 diabetes [19]. In our study, we found a higher incidence of side effects (32% vs 6%) and higher rates of discontinuation of sitagliptin (41% vs 12%). This might be explained by the fact that patients with TIA or ischemic stroke are on average older, and the majority uses other drugs such as statins, antihypertensives, and antithrombotic drugs, which may increase the risk of side-effects.

Importantly, in our study, the study-medication led to a higher rate of regression to normal glucose metabolism than no medication. Multiple studies have shown that regression to normal glucose tolerance is associated with reduction in cardiovascular risk during the time of intensive glucose lowering treatment, and that it possibly reduces mortality on the long term. [31,32]

Our study has limitations. First, our study had an open label design, and no placebo was used. However, outcome assessment was blinded for treatment allocation which decreased the risk of performance bias, and with this design, the study results are easier to relate to real life treatment strategies. Furthermore, a relatively large proportion of patients discontinued medication (40%), despite support with frequent telephone calls. The majority of these patients did not report side effects as cause of the discontinuation. This finding is in concordance with results of other studies of preventive medication in this patient group. [33] Also, we had a relatively large proportion of patients who did not attend the 6 months visit. This could have impaired the power of our results. However, in all patients the frequency and nature of side effects was known.

Our study is one of the few which assessed whether glucose lowering therapy is effective in stroke patients with impaired glucose metabolism. A recent trial reported that pioglitazone can prevent cardiovascular disease in stroke patients with insulin resistance. [15] A meta-analysis on glucose-lowering pharmacological interventions in patients with IGT found possible beneficial effects on the incidence of stroke. [16] However, a recent study showed no long term beneficial effect of intensive glucose lowering in patients with type 2 diabetes. [32] Furthermore, antidiabetic medication might not only have

positive effects on glucose, but also on weight, cholesterol levels and blood pressure. [18,19,27–30] So, although it is not known yet whether this will actually result in less (recurrent) cardiovascular morbidity and mortality, the results of our study could be important in optimizing the secondary prevention in stroke patients with IGT, who have a high risk of recurrent stroke and other cardiovascular diseases. [8,9]

A phase III study is needed to investigate whether glucose lowering therapy is effective in reducing the incidence of recurrent stroke or other cardiovascular diseases. We found a significant effect of metformin and sitagliptin on fasting glucose levels and HbA1c levels, but not on 2-hour post-load glucose levels. Fasting glucose levels and HbA1c levels are easy tests to perform. However, without the OGTT, more than half of patients with impaired glucose metabolism would be missed for inclusion. Therefore, we would recommend a repeated OGTT to screen patients, and fasting glucose and HbA1c levels for follow-up assessment.

Although there were more adverse events in the metformin group, the rate of discontinuation was the same in both treatment groups. Metformin is regarded as one of the most effective oral drugs in the management of type 2 diabetes. [22] A recent randomized trial reported that sitagliptin did not have a significant effect on the incidence of cardiovascular diseases in patient with type 2 diabetes, thereby making sitagliptin a less suitable drug to investigate the long-term effects in prediabetes. [30] Pioglitazone has also been proven effective as glucose lowering therapy in stroke patients, but pioglitazone gives a higher risk of weight gain, edema, and fracture. [15]

Therefore, for a next phase III study, one might consider to compare the effect of metformin against a background of lifestyle modification with one of the new promising drugs which actually reduce cardiovascular complications in patients with type 2 diabetes, like GLP1 analogues or SGLT2 inhibitors. [34,35]

In conclusion, metformin and sitagliptin are both effective and safe in reducing fasting glucose and HbA1c levels in patients with recent TIA or ischemic stroke and IGT. Antidiabetic medication as treatment of IGT as a target for secondary prevention should be further explored.

CONFLICTS OF INTEREST

None.

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SUPPLEMENT

Glucose modifies the effect of endovascular thrombectomy in patients with acute stroke. A pooled-data meta-analysis

Á. Chamorro
S. Brown
S. Amaro
M.D. Hill
K.W. Muir
D.W.J. Dippel
W. van Zwam
K. Butcher
G.A. Ford
H.M. den Hertog
P.J. Mitchel
A. M. Demchuk
C.B.L.M. Majoie
S. Bracard
I. Sibon
A.P. Jadhav
B. Luna- Rodriguez
A. van der Lugt
E. Osei
A. Renú
S. Richard
D. Rodriguez-Luna
G.A Donnan
A. Dixit
M. Almekhlafi
S. Deltour
J. Epstein
B. Guillon
S. Bakchine
M. Gomis
R. du Mesnil de Rochemont
D. Lope
V. Reddy
G. Rudel
Y.B.W.E.M. Roos
A. Bonafe
H.C Diener
O.A Berkhemer
G.C. Cloud
S.M. Davis
R. van Oostenbrugge
F. Guillemin
M. Goyal
B.C.V. Campbell
B.K. Menon

for the HERMES Collaborators

Stroke 2019

ABSTRACT

Background

Hyperglycemia is a negative prognostic factor after acute ischemic stroke but is not known whether glucose is associated with the effects of endovascular thrombectomy (EVT) in patients with large-vessel stroke. In a pooled-data meta-analysis, we analyzed whether serum glucose is a treatment modifier of the efficacy of EVT in acute stroke.

Methods

Seven randomized trials compared EVT with standard care between 2010 and 2017 (HERMES Collaboration [highly effective reperfusion using multiple endovascular devices]). One thousand seven hundred and sixty-four patients with large-vessel stroke were allocated to EVT (n=871) or standard care (n=893). Measurements included blood glucose on admission and functional outcome (modified Rankin Scale range, 0–6; lower scores indicating less disability) at 3 months. The primary analysis evaluated whether glucose modified the effect of EVT over standard care on functional outcome, using ordinal logistic regression to test the interaction between treatment and glucose level.

Results

Median (interquartile range) serum glucose on admission was 120 (104–140) mg/dL (6.6 mmol/L [5.7–7.7] mmol/L). EVT was better than standard care in the overall pooled-data analysis adjusted common odds ratio (acOR), 2.00 (95% CI, 1.69–2.38); however, lower glucose levels were associated with greater effects of EVT over standard care. The interaction was nonlinear such that significant interactions were found in subgroups of patients split at glucose < or >90 mg/dL (5.0 mmol/L; P=0.019 for interaction; acOR, 3.81; 95% CI, 1.73–8.41 for patients < 90 mg/dL versus 1.83; 95% CI, 1.53–2.19 for patients >90 mg/dL), and glucose < or >100 mg/dL (5.5 mmol/L; P=0.004 for interaction; acOR, 3.17; 95% CI, 2.04–4.93 versus acOR, 1.72; 95% CI, 1.42–2.08) but not between subgroups above these levels of glucose.

Conclusions

EVT improved stroke outcomes compared with standard treatment regardless of glucose levels, but the treatment effects were larger at lower glucose levels, with significant interaction effects persisting up to 90 to 100 mg/ dL (5.0–5.5 mmol/L). Whether tight control of glucose improves the efficacy of EVT after large-vessel stroke warrants appropriate testing.

INTRODUCTION

Glucose is essential for normal brain function but may also exacerbate ischemic brain injury through mechanisms occurring within the brain vasculature, microglia, neural cells, and infiltrating leukocytes.[1] Observational studies have shown that hyperglycemia is associated with poor stroke outcomes[2], whether the patients are treated with intravenous thrombolysis or not.[3-5] Hyperglycemia has also been associated with less favorable outcomes in patients with stroke treated with endovascular thrombectomy (EVT) in observational studies [6-8] and in 1 randomized controlled trial that compared the Merci and the Solitaire FR device.[9] However, a post hoc analysis of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) found no evidence for effect modification of intra-arterial treatment by glucose >140 mg/dL (7.8 mmol/L).[10] Hyperglycemia is frequent in the acute phase of ischemic stroke[11] but its definition varies widely across stroke studies, with cutoffs ranging from 109.8 mg/dL (6.1 mmol/L) to >180 mg/dL (9.9 mmol/L) random glucose levels.[12]

Hyperglycemia promotes tissue acidosis and the production of reactive oxygen and nitrogen species that increase infarct size, brain swelling, hemorrhagic transformation, blood-brain barrier disruption and results in more severe neurological deficits under experimental ischemic conditions.[13,14] Patients treated with EVT have the highest rate of recanalization of the occluded vessel and arguably have a greater exposure to redox-mediated mechanisms which are activated by the reoxygenation of the ischemic brain and also fueled by the levels of glucose.[15] It is uncertain whether in patients with large-vessel stroke treated with EVT, glucose could be not only a negative prognostic factor but also a treatment modifier of the efficacy of the procedure. Clarification of this important question is the main objective of the current analysis for it could provide evidence for or against strategies to maximize the benefits of EVT by optimization of glucose management in this population. To this end, we sought for modification of the effect of EVT by glucose level in the randomized phase 3 trials in which stent retrievers were used for acute treatment of ischemic stroke.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The HERMES collaboration (highly effective reperfusion using multiple endovascular devices)[15] pooled individual patient data from all randomized phase 3 trials in which stent retrievers or other second-generation devices were used in the majority of endovascular interventions for treatment of acute ischemic stroke and for which a peer-reviewed, complete primary results article was published by May 31,

2017. Comparative design features of the contributing trials have been described[15,16] and included MR CLEAN[17], ESCAPE (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times)[18], EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial)[19], SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment)[20], REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset)[21], PISTE (Pragmatic Ischemic Thrombectomy Evaluation)[22] and THRACE (Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke)[23] trials. The HERMES executive committee (comprising representatives of each trial) confirmed that all eligible trials were included and contributed their trial data. All participants provided informed consent according to each trial protocol, and each study was approved by the local ethics board. The current analysis was prospectively designed by one of the authors (Dr Chamorro), but not registered. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (See the online-only Data Supplement).

In the HERMES trials, glucose was collected as part of the prerandomization screening blood work, and patients with whole blood or plasma glucose levels between 48 mg/dL (2.7 mmol/L) and 400 mg/dL (22.2 mmol/L) fulfilled the entry criteria of the pooled trials. The reported management of glucose in the early phase of acute ischemic stroke was not identical among the different studies, as 2 trials (ESCAPE and MR CLEAN) referred to national standards and guidelines for glucose management, 1 trial (REVASCAT) recommended a target blood glucose level of >160 mg/dL (8.9 mmol/L) while advising against the correction of baseline glucose laboratory values to meet the inclusion criteria of the study, and 4 trials (EXTEND-IA, SWIFT PRIME, PISTE, THRACE) provided no specific recommendations for glucose management.

The primary outcome was defined as the degree of disability at 3 months, assessed across 6 levels of the modified Rankin Scale (mRS), with ranks 5 and 6 combined into a single worst outcome rank (primary outcome). Secondary outcomes included (1) functional independence at 3 months, defined as mRS scores of 0 through 2; (2) excellent outcome at 3 months, defined as mRS score of 0 through 1; (3) early neurological recovery at 24 hours, defined as a reduction in National Institutes of Health Stroke Scale score from baseline of at least 8 points or reaching mRS of 0 to 1; and (4) complete reperfusion, defined as a modified treatment in cerebral infarction score 2b or 3 at the end of EVT. Safety outcomes evaluated were 90-day mortality and symptomatic intracranial hemorrhage within 36 hours. Symptomatic intracranial hemorrhage was

classified according to the actual definitions used in each trial, whereas intracranial hemorrhage was defined as parenchymal hematoma type 2.[24]

Data were provided by the authors of all the trials meeting eligibility criteria and collected by independent statisticians. Dr Brown coordinated the creation of the unified database. We used a 1-stage approach, defined as the use of individual patient data with analysis including covariates and random study effects to appropriately incorporate any between-study differences.[25]

To account for between-study variance in relationships among predictors and outcomes, the statistical models incorporated random effects for study and study-by-treatment interaction (in those models assessing both treatment groups). Analyses were based on all randomized patients based on their original group of randomization, after excluding missing values for admission glucose and 90-mRS, and the relationship of glucose with clinical and radiological outcomes was evaluated principally through logistic regression models.

A detailed description of the analytic approach is provided in the statistical analysis plan (Appendix in the online-only Data Supplement). The primary analysis evaluated whether glucose modified the effect of treatment on mRS at 90 days, when adjusted for prespecified covariates using ordinal logistic regression adjusted for age, sex, National Institutes of Health Stroke Scale score at admission, prior use of intravenous alteplase, occlusion location (internal carotid artery/M1/M2), time from stroke onset to randomization, and history of diabetes mellitus. Treatment assignment was included as a variable with 2 levels: EVT and standard care. Baseline and procedural characteristics were compared between treatment groups and between glucose subgroups using t tests for continuous variables, Fisher exact test for binomial outcomes, and Pearson $\chi 2$ for multinomial outcomes. The interaction between glucose and treatment assignment on the primary outcome assessed glucose using subgroups defined by 10 mg/dL increments from 80 to 180 mg/dL (4.9–9.9 mmol/L); all subgroup results for the various cutoffs evaluated were then presented. Category-specific effects were reported (in text and using figures), and the presence of significant interactions were noted. For this purpose, P values are presented; adjustment for multiplicity of testing was applied in assessing the optimal cutoff for distinguishing treatment by glucose interaction. Secondary outcomes and safety outcomes were also adjusted for the same baseline prognostic factors. Statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cary, NC) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria). All P values presented are 2-sided, with values <0.05 defining statistical significance.

RESULTS

After pooling and screening data from all 7 trials in the HERMES collaboration, glucose was not available in 60 (3.4%) of 1764 patients, with 30 patients lacking glucose data in the endovascular group, and 30 patients lacking glucose data in the standard care group (Appendix Figure I in the online-only Data Supplement).

Across the entire study population, the median glucose on admission was 120 mg/dL (6.6 mmol/L; interquartile range 104–140 mg/dL; 5.7–7.7 mmol/L), and the distribution of glucose levels in the whole study group was well balanced between the 2 treatment arms (Appendix Figure II in the online-only Data Supplement). Results were consistent across the analysis methods and showed higher glucose levels to be significantly associated with worse outcomes, including reduced excellent outcome (mRS, 0–1), functional independence (mRS 0–2), and early neurological recovery and increased all-cause mortality and symptomatic hemorrhagic complications (Table 1). In contrast, blood glucose concentration was not associated with the occurrence of successful reperfusion at the end of EVT.

In the entire population, EVT improved the primary outcome compared with standard care (adjusted common odds ratio 2.00; 95% CI, 1.69–2.38). Notwithstanding, the treatment effect on the primary outcome was found to be nonlinearly dependent on the levels of glucose (Figure 1), and significant treatment interactions were found for subgroup cutoffs of 90 mg/dL (5.0 mmol/L), 6% of the study sample and 100 mg/dL (5.5 mmol/L), 17% of the study sample, but not for the subgroups of patients with glucose cutoffs above this level (Appendix Table I in the online-only Data Supplement). After Bonferroni correction, for the primary outcome only the difference in treatment effect between glucose <100 mg/dL and glucose ≥100 mg/dL remained significant. For the glucose cutoff of 90 mg/dL (5.0 mmol/L; Figure 2A), there were significant interactions for the rates of functional independence (mRS 0–2) and mortality; for the glucose cutoff of 100 mg/dL (5.5 mmol/L; Figure 2B), there were significant interactions for functional independence, early neurological recovery, and mortality. The interaction effect between treatment assignment and glucose level was also highly significant when comparing patients with glucose <100 mg/dL (5.5 mmol/L) with those >100 mg/dL (5.5 mmol/L; P=0.004) after Bonferroni adjustment for multiple comparisons against a threshold of 0.05/10=0.005; for the glucose cutoff of 110 mg/dL (6.6 mmol/L), there were significant interactions for functional independence (Appendix Table II in the online-only Data Supplement).

Table 1. Associations between continuous glucose levels and outcomes

	n	Glucose, mg/dL; Mean± SD [Median] (IQR)	P Value	Unadjusted (95% CI)[a]	P Value	Adjusted OR (95% CI)[b] P	P Value
Excellent outcome			<0.001	0.92 (0.88–0.95)	<0.0001	0.93 (0.89–0.96)	<0.0001
mRS 0–1	383	120.2± 33.5 [113.4] (100·0–130.0)					
mRS 2–6	1304	134.8± 74.6 [121.8] (106.2–145.0)					
Good outcome			<0.001	0.92 (0.90–0.95)	<0.0001	0.93 (0.90–0.96)	<0.0001
mRS 0–2	662	123.7± 54.8 [114.5] (101.8–133.2)					
mRS 3–6	1025	136.5± 74.6 [123.0] (107·3–147.0)					
Death			<0.0001	1.07 (1.04–1.10)	<0.0001	1.06 (1.03–1.09)	<0.0001
Yes	271	147.1± 111.3 [129.1] (107.3–157.0)					
No	1425	128.4± 55.1 [118.2] (104.4–138.2)					
ENR			<0.0001	0.92 (0.88–0.96)	<0.0001	0.93 (0.89–0.97	0.002
Yes	602	123.1± 34.6 [115.2] (102.6–134.0)					
No	1046	134.5± 63.6 [121.8] (106.0–145.5)					
sICH			<0.0001	1.07 (1.03–1.12)	<0.0001	1.06 (1.02–1.11)	0.006
Yes	62	172.9± 213.4 [127.5] (110.9–161.0)					

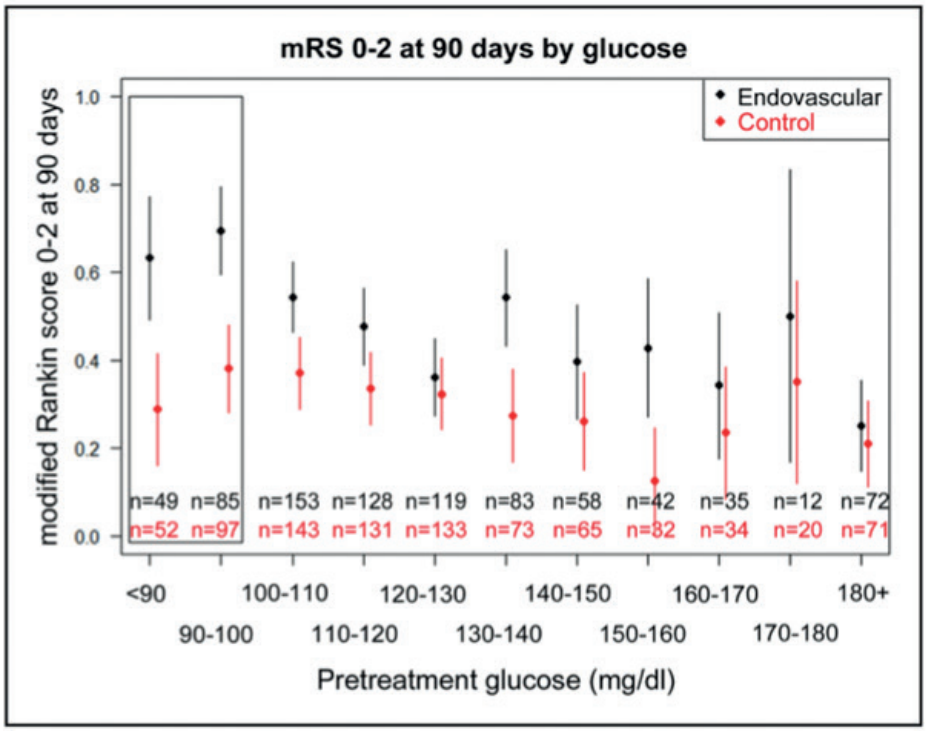
	n	Glucose, mg/dL; Mean± SD [Median] (IQR)	P Value	Unadjusted (95% CI)[a]	P Value	Adjusted OR (95% CI)[b] P	P Value
No	1612	129.6± 54.3 [119.0] (104.4–140.0)					
mTICI score			0.124	0.97 (0.93–1.01)	.175	0.97 (0.93–1.02	0.242
2b/3	535	129.5± 55.5 [119.0] (105.0–140.0)					
0-2	179	140.1± 127.2 [121.8] (107.3–143.0)					

ENR: early neurological recovery. mRS, modified Rankin Scale. mTICI: modified Thrombolysis in Cerebral Infarctions. NIHSS: National Institutes of Health Stroke Scale. sICH: symptomatic intracranial hemorrhage. tPA: tissue-type plasminogen activator.

a. OR for experiencing the first listed outcome; the incremental unit of glucose is 10 mg/dL.

b. Adjusted for age, sex, NIHSS, occlusion location, tPA administration, history of diabetes mellitus, and time from onset to randomization.

Figure 1. Modification of pretreatment glucose on treatment effect of endovascular thrombectomy over standard care on the rate of functional independence (modified Rankin Scale [mRS] 0–2)



ENR: early neurological recovery. LCL: lower confidence limits. mRS: modified Rankin Scale. sICH: symptomatic intracranial hemorrhage. UCL: upper confidence limits. The magnitude of these associations were clinically meaningful: for every 100 patients with glucose <100 mg/dL (5.5 mmol/L) treated with EVT, 45 will have a less disabled outcome than with best medical management, and 32 more will achieve functional independence (mRS, 0–2) as a result of treatment; for every 100 patients with glucose >100 mg/dL (5.5 mmol/L) treated with EVT, 23 will have a less disabled outcome than with best medical management, and 14 more will achieve functional independence (mRS 0–2) as a result of treatment. The rates of excellent outcome and symptomatic intracranial hemorrhage showed no significant interactions with the treatment effect at any glucose cutoff.

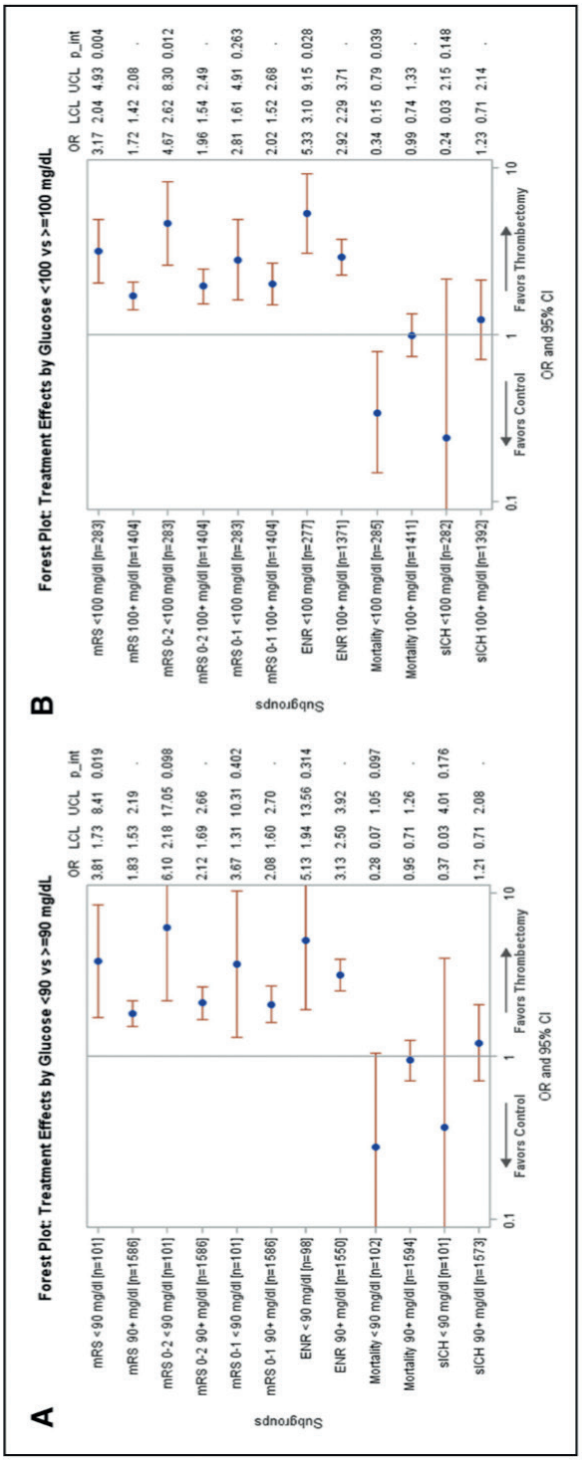


Figure 2. Forest plots of odds ratios for the model of main treatment effects of endovascular thrombectomy or standard care according to admission glucose concentration < or ≥90 mg/dL (5.0 mmol/L; A) and 100 mg/dL (5.5 mmol/L; B) in the HERMES (highly effective reperfusion using multiple endovascular devices) population.

Patients with glucose levels <100 mg/dL (5.5 mmol/L) were younger, had a lower rate of diabetes mellitus, were more likely to have a history of tobacco use, and had shorter time from stroke onset to randomization than patients without this range, but did not differ in baseline clinical stroke severity (according to National Institutes of Health Stroke Scale), occlusion location, affected hemisphere, or rates of hypertension, hyperlipidemia, and tPA (tissue-type plasminogen activator) use (Appendix Table III in the online-only Data Supplement).

The number needed to treat for benefit to improve outcome by 1 mRS category at 3 months was 2.2 in patients with glucose <100 mg/dL (5.5 mmol/L) versus 4.4 in patients with glucose ≥100 mg/dL (5.5 mmol/L).

DISCUSSION

This meta-analysis of individual patient data from 7 randomized trials provides post hoc evidence that EVT improved the primary outcome (mRS at 3 months) more effectively than standard care in patients with large-vessel ischemic stroke regardless of glucose levels at stroke onset. The analysis also identified that the patients with glucose ranging between 90 and 100 mg/dL (5.0–5.5 mmol/L) at stroke onset (17% of the study sample) had the largest treatment effect in favor of the intervention. Consistently, in subgroups with lower glucose levels, the larger benefits also extended to predefined secondary outcomes, including functional independence (dichotomized mRS 0–2), early neurological recovery at 24 hours, and all-cause mortality, whereas there were no significant differences in the rate of symptomatic or asymptomatic hemorrhagic complications.

The differences in efficacy between the randomly assigned treatments were significantly lower at glucose levels above 100 mg/dL (5.5 mmol/L).The study included a large cohort of patients with and without diabetes mellitus, and the findings were consistent with those of prior studies that did not include patients treated with EVT [1,9,26,27] showing that higher glucose levels were associated with worse functional outcomes at 3 months and were also associated with increased all-cause mortality and greater risks of symptomatic hemorrhagic complications. Hyperglycemia was deemed to impair the efficacy of intravenous thrombolysis in previous studies[5], whereas we found similar rates of successful reperfusion after EVT regardless of glucose levels, arguing that the worse outcomes found in patients with higher glucose levels were not the consequence of impaired brain reperfusion after the endovascular procedure.

The key question is whether lower glucose is a simply a marker for patients who have a better prognosis or if acutely lowering glucose could improve prognosis. The benefits of lowering glucose concentration in patients with acute ischemic stroke remain to be

demonstrated, but all the reported previous attempts have been unsuccessful.[28,29] In the GIST-UK trial (UK Glucose Insulin in Stroke Trial), 24-hour glucose potassium insulin infusion targeted to maintain glucose at 72 to 126 mg/ dL (4–7 mmol/L) did not improve outcome in patients with admission glucose concentration between 108-306 mg/dL (5.9–16.9 mmol/L).[28] However, this study was compromised by under-recruitment, late treatment initiation, and marginal reduction of blood glucose (10 mg/dL [0.5 mmol/L]) compared with control.[28] In the SELESTIAL trial (Spectroscopic Evaluation of Lesion Evolution in Stroke: Trial of Insulin for Acute Lactic Acidosis)[29], glucose potassium insulin infusion targeted to maintain blood glucose between 72 and 126 mg/ dL (4–7 mmol/L), did lower blood glucose from 6 to 12 hours after glucose potassium insulin initiation, and attenuated an increase in brain lactate, but the therapy did not affect cerebral infarct growth, and hypoglycemia (<72 mg/dL [4.0 mmol/L]) occurred in 76% of glucose potassium insulin–treated subjects, although it was predominantly asymptomatic.[29] The mean glucose levels obtained in these trials ranged between 105 and 112 mg/dL (5.8–6.2 mmol/L), and there was a low risk of symptomatic hypoglycemia. The SHINE trial (Stroke Hyperglycemia Insulin Network Effort Trial; https://www.clinicaltrials.gov. Unique identifier: NCT01369069) is currently determining the safety and efficacy of attaining a glucose range of 80 to 179 mg/dL (4.4–9.9 mmol/L) versus 80 to 130 mg/dL (4.4–7.2 mmol/L) for up to 72 hours, starting within 12 hours of stroke symptom onset, and the TEXAIS trial (Trial of Exenatide Versus Standard Care in Acute Ischemic Stroke; https:// www.clinicaltrials.gov. Unique identifier: NCT03287076) is comparing exenatide to standard of care in patients with acute ischemic stroke commencing treatment within 9 hours of symptom onset, although in this trial, there is not a target glucose level. However, in none of the ongoing trials, it is anticipated the inclusion of a sufficient number of patients that will receive EVT to detect a treatment effect in that subgroup. Altogether, it seems that moderate lowering of glucose levels in patients with acute ischemic stroke not treated with EVT prevents lactic acidosis, but this effect seems not to translate into clinical benefits. Indeed, extracellular lactate accumulation is not a crucial determinant of brain injury in experimental hyperglycemia[30], for prevention of tissue acidosis does not avoid brain tissue damage under hyperglycemic conditions.[31]

Endovascular thrombectomy achieves a high rate of successful reperfusion, facilitating the reentry of oxygen into the ischemic brain to a much larger extent than any other therapeutic options. Because oxygen boosts the formation of free radicals in parallel with the availability of glucose [2,3], it is possible that patients receiving EVT are more vulnerable to the redox-mediated effects of glucose. Classical experimental studies of focal cerebral ischemia support the significance of reperfusion in contributing to the detrimental effect of hyperglycemia.[32]

The results of this post hoc pooled-data meta-analysis need to be interpreted with caution and cannot be used to change clinical recommendations. These data do provide clinical justification for the study of tight glucose management in patients receiving EVT. Testing a glucose target of 90 to 100 mg/dL (5.0–5.5 mmol/L) seems justified, despite the risk that this approach might increase the occurrence of hypoglycemia, which has been predominantly asymptomatic in previous trials[28,29] Therapeutic alternatives without the risk of hypoglycemia could also be considered for further clinical testing, including the administration of the antioxidant uric acid. In the URICOICTUS trial[33], in addition to the antioxidant uric acid or placebo, all the patients received intravenous thrombolysis within 4.5 hours of stroke onset, and some also received rescue EVT.[34] In this trial, uric acid therapy reduced infarct growth and improved the functional outcome at 3 months more effectively than placebo even in patients with hyperglycemia [35], supporting the idea that the toxicity of hyperglycemia can be minimized by enhancing antioxidant exposure. Indeed, inactivation of the glucose-dependent nicotinamide adenine dinucleotide phosphate oxidase enzyme blocks neuronal reactive oxygen and nitrogen species production and negates the deleterious effects of hyperglycemia.[36]

Some limitations of this pooled-data analysis include the lack of information on the longitudinal course of glucose at follow-up, the undocumented use of lowering glucose drugs, or whether glucose concentration was measured in venous or capillary samples. Three of the trials analyzed patients that were treated following widely accepted guidelines recommending the administration of insulin in patients with glucose concentrations >140 mg/dL (7.8 mmol/L) to 185 mg/dL (10.3 mmol/L), although 4 trials provided no specific treatment recommendations. Low glucose at stroke onset could be associated with good prognostic variables not measured in this study, such as lower body mass index, better collaterals, or less need for general anesthesia. Given the exploratory analyses testing the effect modification of pretreatment glucose, concerns about type 1 error with multiple testing might arise, but the P value for interaction with glucose 100 mg/dL cutoff values remained significant after Bonferroni correction. Furthermore, the pooled patients were treated at many centers in multiple countries on 4 continents, suggesting wide applicability.

In conclusion, in this individual patient data meta-analysis of 7 randomized clinical trials of patients with large-vessel ischemic stroke, the effect of EVT on functional outcome at 3 months compared with standard treatment was severely diminished with increasing glucose levels.

CONFLICTS OF INTEREST

Dr Chamorro owns stock in FreeOx Biotech SL and has received consultancy fees from Boehringer Ingelheim. Dr Donnan reports grants from National Health and Medical Research Council, Astra Zeneca, Boehringer Ingelheim, Bristol Meyers Squibb, Pfizer, and Servier. Dr Campbell reports grants from National Health and Medical Research Council, Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, National Heart Foundation, National Stroke Foundation of Australia, and Covidien (Medtronic). Dr Ford reports personal fees or grants from Stryker, Pfizer, Bayer, AstraZeneca, Medtronic, and Cerevast. Dr Hill has received grant support from Medtronic LLC, Consultant fees from Boehringer Ingelheim, and speaker's fees from Amgen. Dr van der Lugt reports grants from Dutch Heart Foundation, AngioCare BV, Covidien/EV3, MEDAC Gmbh/ LAMEPRO, Stryker®, Penumbra Inc, and Medtronic. Dr Majoie is shareholder of Nico.lab and reports research support from the Netherlands CardioVascular Research Committee/ Dutch Heart Foundation, European Commission, and Stryker. Dr Muir reports grants from Medtronic, and Codman. Dr van Zwam reports personal fees from Cerenovus, and Stryker. Dr Roos reports other from Stock owner of Nico-Lab. Dr Diener received fees from Abbott, Achelios, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmol/lun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, JanssenCilag, Johnson & Johnson, Knoll, Lilly, MSD, Medscape, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Portola, Sanofi-Aventis, Schering-Plough, Servier, Solvay, St Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council, German Ministry of Education and Research, European Union, National Institutes of Health, Bertelsmann Foundation and Heinz-Nixdorf Foundation. Dr Demchuk reports personal fees from Medtronic. Dr Bonafé reports personal fees from Medtronic, Stryker, and Phenox. Dr Mitchell reports other or personal fees from Medtronic, Stryker, and Microvention. Dr Brown reports personal fees from University of Calgary and Medtronic. Dr Reimann reports personal fees from Bayer, Boehringer Ingelheim, Pfizer, and Daiichi Sankyo. Dr Goyal reports grants or personal fees from Medtronic, Stryker, Microvention, Cerenovus, and has a patent Systems of Acute Stroke Diagnosis issued to GE Healthcare. Dr Dippel reports grants from Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences & Health and unrestricted grants from AngioCare BV, Covidien/ EV3, MEDAC Gmbh/ LAMEPRO, Penumbra Inc, Top Medical/Concentric, Stryker, Stryker European Operations BV, Medtronic, Thrombolytic Science, LLC, all paid to institution.

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CHAPTER 6
General discussion

GENERAL DISCUSSION

The main subjects of this thesis are the prognostic value and treatment of disturbed glucose metabolism after stroke or TIA. I assessed the prognostic value of admission glucose and fasting glucose levels with outcome after stroke and in patients who were treated with intravenous alteplase and intra-arterial thrombectomy (IAT). Furthermore, I studied whether hyperglycemia modified the effect of IAT. I developed a prediction model to identify patients at risk of persisting impaired glucose tolerance (IGT). Also, I performed a first step in studying whether glucose lowering therapy reduces the risk of stroke and other cardiovascular diseases in patients with minor stroke or TIA and IGT, by performing a phase II trial with antidiabetic medication.

In this chapter, I summarize the main findings, review them in the context of existing literature, discuss the clinical implications and make recommendations for future research.

Review and interpretation of main findings

Prognostic value of disturbed glucose metabolism in the acute phase of stroke

Disturbed glucose metabolism is highly prevalent in stroke patients. Previous studies have shown an association of hyperglycemia on admission with unfavorable outcome after stroke. [1–3] The relationship of impaired fasting glucose (IFG) with outcome was previously less established. In chapter 3, I report that fasting plasma glucose values in the prediabetic and diabetic range were associated with unfavorable functional outcome at discharge. Possible underlying mechanisms of the association of disturbed glucose metabolism with unfavorable outcome after stroke is that hyperglycemia stimulates blood coagulation mechanisms and chronic inflammation.[4–6]

Treatment with intravenous alteplase and IAT have been proven safe and effective in eligible stroke patients. Hyperglycemia on admission is associated with unfavorable outcome in stroke patients who were treated with intravenous alteplase and IAT. [7,8] Whether IFG also is associated with outcome in these patients, is less well established. Described in chapter 4, I found that in patients who received intravenous thrombolytics, IFG and hyperglycemia on admission showed a shift towards worse functional outcome compared with patients with normal glucose levels. IFG had a stronger negative association with outcome than hyperglycemia on admission.

I also found that in patients with acute ischemic stroke and a proximal intracranial arterial occlusion who underwent IAT, IFG and hyperglycemia on admission were associated with unfavorable functional outcome. Possible underlying pathophysiological mechanisms of the previously mentioned associations with outcome are impairment of cerebrovascular reactivity in the microvasculature, which may disturb reperfusion

after recanalization. Hyperglycemia may aggravate brain edema formation and lead to hemorrhagic transformation by altering blood-barrier permeability. [9] Furthermore, hyperglycemia may also have inhibitory effects on intravenous thrombolysis due to the reduction of the fibrinolytic activity of alteplase by inhibiting plasma fibrinolysis and increasing the production of plasminogen activator inhibitor-1. [10]

I did not find that increased admission glucose modified the treatment effect of IAT in patients with an acute ischemic stroke and proximal intracranial occlusion. However, a recent meta-analysis of seven randomized controlled trials which compared IAT with standard care reported that lower glucose levels were associated with greater effects of IAT over standard care. [11] A possible explanation for these seemingly contradicting results, might be due to the smaller study population of my first mentioned study.

With before mentioned results, one might expect a beneficial effect of glucose lowering therapy in the acute phase of stroke. However, previous studies failed to show clinical benefit of glucose lowering therapy. Also, glucose lowering therapy could even have a negative effect on recovery because of the considerable risk of developing hypoglycemia.[12–15] In the randomized controlled SHINE trial, 72-hours insulin infusion did not have a clinical benefit compared to standard therapy, even with a considerably lower mean glucose level in the intensive treatment group of 3.4 mmol/L. Possible underlying reasons for not showing clinical benefit, is that in this trial a majority of patients had mild or moderate strokes, which have a higher chance of a favorable outcome than severe strokes. In addition, the target glucose levels for both interventions were not so different (4.4-7.2 mmol/L for the intensive treatment group and 4.4-9.9 for the standard treatment group). Also, severe hypoglycemia only occurred in the group with intensive glucose lowering therapy, and the intensive glucose lowering therapy had a higher rate of discontinuation than the control group. [16]

Also, whether glucose lowering therapy is beneficial in patients with acute stroke before administering intravenous alteplase has not been proven in humans yet. An animal study reported promising clinical benefits of early insulin glycemic control combined with alteplase, with reduction of brain infarction and swelling, ameliorated alteplase-associated hemorrhagic transformation, and improved plasma perfusion at 24 hours after stroke. [17] Whether these beneficiary effects also apply for humans, needs to be investigated.

Prediction of impaired glucose tolerance in stroke patients

IGT after stroke can be transient, reflecting an acute stress response [18], or reflect undiagnosed impaired glucose metabolism. Prediction of persistent IGT in stroke patients could be clinically relevant. IGT increases the risk of recurrent stroke and other cardiovascular events. [19,20] Moreover, IGT is also associated with poor functional

outcome and mortality in stroke patients. [19,21,22] It is important to identify patients with persistent IGT, as glucose lowering treatment could be beneficial for them as secondary prevention.

Therefore, in chapter 3, I externally validated our previous original prediction model in my cohort of 239 nondiabetic patients with minor ischemic stroke or TIA, to predict persistent IGT in the acute phase after stroke. The original prediction model used the predictors age, current smoking, statin use, triglyceride, hypertension, history of cardiovascular diseases, body mass index (BMI). [23] Because of its poor performance, I developed a new prediction model, in which we used the predictors BMI, hypertension, statin use, atrial fibrillation, 2-hour post-load glucose levels, HbA1c and large artery atherosclerosis. The new model predicted persistent IGT more accurately, and also performed well in the development study population of our original study.

Metformin and sitagliptin in patients with TIA or minor ischemic stroke and IGT
It is not conclusively established whether prediabetes is a treatable risk factor for cardiovascular diseases. Therefore, I conducted a phase II trial, the MAAS-trial, described in chapter 5, which investigated the feasibility, safety, and effects on glucose metabolism of metformin and sitagliptin in patients with impaired glucose tolerance after a TIA or minor ischemic stroke. Metformin and sitagliptin had no significant effect on 2-hour post-load glucose levels, but were both effective in reducing fasting glucose and HbA1c levels. Metformin caused side effects more frequently than sitagliptin, but this did not lead to more discontinuation of the medication. A relatively large proportion of patients discontinued medication (40%), despite support with frequent telephone calls. The majority of these patients did not stop the medication because of side effects. This is in concordance with other studies, which also reported that preventive medication is more difficult to sustain. [24] I did not find an effect of treatment on 2-hour post-load glucose levels. A possible explanation for this, is that an OGTT is not easy to reproduce accurately.

In a recent meta-analysis, multiple studies which reported the effect of glucose lowering treatment in patients with prediabetes were assessed. Lifestyle modification and antidiabetic medication both reduced the risk on developing diabetes type 2. However, antidiabetic medication showed no sustained risk reduction in the incidence of type 2 diabetes, but lifestyle modification did.[25]

GENERAL LIMITATIONS

In chapter 3 and 4, I report the association of impaired fasting glucose with outcome acute stroke patients. Impaired glucose metabolism in the acute phase can be transient, reflecting an acute stress response. [18] This could have caused an overestimation of

patients with glucose in the prediabetic and diabetic range. Also, the glycated hemoglobin A1c (HbA1c) levels, which are a better reflection of prestroke glycemic status, were not available in all studies.

Chapter 3 also describes the updated prediction model to predict persistent IGT in patients with TIA or minor ischemic stroke. Although I used readily clinical parameters to make the implementation in clinical practice more feasible, the prediction model could be perceived as challenging and not easy reproducible. Also, the question arises whether this prediction model is needed to identify this group of patients with persistent IGT. One could argue that all stroke and TIA patients should have a second glucose assessment in the acute phase after stroke. However, this could lead to patients being subjected to unnecessary and unpleasant investigations.

In chapter 5, I report our randomized controlled trial to assess the safety and feasibility of metformin or sitagliptin in patients with minor ischemic stroke or TIA. This study had an open label design, and no placebo was used. Also, a relatively large proportion of patients did not attend the 6 months visit. This could have impaired the power of the results.

CLINICAL IMPLICATIONS

In my thesis, I have reported evidence that IFG is negatively associated with outcome in stroke patients, and this association is stronger with IFG than hyperglycemia on admission. IFG is also a better representation of true disturbed glucose metabolism than random admission glucose levels, and not only of an acute stress reaction.

Therefore, for the assessment of prognosis in stroke patients, I would recommend to always measure fasting glucose levels. Also, my reported negative association of disturbed glucose metabolism in the acute phase of stroke could provide a rationale for glucose lowering therapy in these patients.

I developed a prediction model which can accurately predict persistent IGT in TIA and stroke patients. I also showed that glucose lowering therapy in patients with TIA or minor ischemic stroke and IGT is feasible and safe. Persistent IGT might be an indicator of development of diabetes mellitus type II, and increase the risk of cardiovascular diseases. Persistent IGT could therefore be a new target for secondary prevention in stroke patients. Also, with our prediction model, one could consider treating patients with the highest risk of developing IGT in the acute phase after TIA or stroke.

RECOMMENDATIONS FOR FURTHER RESEARCH

The question arises whether patients with normalized IGT in the acute phase only have an acute stress reaction, or if some of these patients also have a true disturbed glucose

metabolism in a later phase. If the latter is the case, than these patients also have an increased risk of cardiovascular diseases. Therefore, I would recommend to also follow the patients with normalized IGT.

Furthermore, a phase III trial is needed to investigate whether glucose lowering therapy is effective in reducing cardiovascular diseases in prediabetic stroke patients. Lifestyle modification and/or antidiabetic medication can be considered as treatment options. We used sitagliptin in the MAAS-trial, however a recent study reported that sitagliptin did not have a significant effect on the incidence of cardiovascular diseases in patients with type 2 diabetes. [26] Therefore, I would not recommend sitaglipin again as a treatment option. A recent meta-analysis found that glucagon-like peptide-1 (GLP) agonists have a beneficial effect on the incidence of cardiovascular diseases and mortality in patients with type 2 diabetes with and without established cardiovascular diseases. [27] Another recent meta-analysis reported that sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular events, with the most benefit in patients with established atherosclerotic cardiovascular disease. [28] Therefore, one could consider using lifestyle modification, and/or the newer antidiabetic medication GLP-agonists or SGLT2 inhibitors as treatment options. In the MAAS-trial, we found a significant effect of metformin and sitagliptin on fasting glucose levels and HbA1c levels, but not on 2-hour post-load glucose levels. Fasting glucose levels and HbA1c levels are more easy tests to perform. However, without the OGTT, more than half of patients with impaired glucose metabolism would not have been diagnosed. So, we would recommend a repeated OGTT to screen patients, and fasting glucose and HbA1c levels for the follow-up. This would also make the hospital visits for the patients more feasible and make patients more inclined to complete the follow-up.

Furthermore, more studies are needed to investigate the effect on outcome of glucose lowering therapy in the acute phase of stroke. Perhaps glucose lowering therapy is more beneficial in a subset of stroke patients. It would also be interesting to assess whether active glucose lowering would improve outcome in patients receiving intravenous thrombolysis and IAT.

CONCLUSION

Newly diagnosed disturbed glucose metabolism is associated with unfavorable outcome in patients with acute stroke, and in patients who receive intravenous thrombolysis and IAT. Whether glucose modifies the effect of IAT is still under debate. The association of disturbed glucose metabolism with unfavorable outcome could imply a beneficiary effect of glucose lowering therapy in the acute phase of stroke.

IGT can be accurately predicted using clinical variables, and IGT can be treated effectively and safely with metformin or sitagliptin. IGT could therefore be a new target for secondary prevention in stroke patients.

In my view, it would be interesting to investigate whether glucose lowering therapy before administrating intravenous alteplase or performing intra-arterial treatment would improve outcome in acute ischemic stroke patients. But more importantly, future research should address on the question whether antidiabetic medication and/or lifestyle modification is effective in reducing cardiovascular risk in stroke patients with persistent IGT.

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CHAPTER 7
Summary
Nederlandse samenvatting

Stroke is one of the leading causes of morbidity and mortality in the developed world. Hence, acute stroke treatment and prevention of recurrent stroke are important. Hyperglycemia at admission is highly prevalent in stroke patients. This may persist in the post-acute phase, then suggesting true disturbance of glucose metabolism rather than a temporary reflection of stress, and patients sometimes turn out to have diabetes mellitus or prediabetes. Prediabetes is highly prevalent in stroke patients, and reflects an intermediate state between normal glucose metabolism and diabetes mellitus. Prediabetes is associated with increased risk of recurrent stroke and other cardiovascular diseases. Therefore, prediabetes could be an important target for secondary prevention.

The aim of this thesis is to establish the prognostic value and treatment of newly diagnosed disturbed glucose metabolism in patients with stroke. I assess the association of newly diagnosed disturbed glucose metabolism with outcome at discharge and after acute stroke treatment, prediction of persistent impaired glucose tolerance, and the efficacy and safety of treating prediabetes in patients with acute stroke.

Chapter 1, the general introduction, outlines the background and rationale for the research reported in this thesis.

In Chapter 2, I review the literature on the association of prediabetes with outcome and effect of treatment in patients with cardiovascular disease including coronary artery disease, stroke and peripheral artery disease. Prediabetes increases the risk for type 2 diabetes and macrovascular events with adverse outcome. Both lifestyle modification and antidiabetic drugs decrease the risk of developing type 2 diabetes, and also prevent developing macrovascular disease (primary prevention). Whether treatment of prediabetes decreases the recurrence of macrovascular complications and improve outcome in patients with macrovascular disease (secondary prevention), is not fully established yet.

In chapter 3, I focus on the prognostic value of disturbed glucose metabolism in patients with stroke. In section 3.1, I report on the association of prediabetes and newly diagnosed diabetes with functional outcome in patients with ischemic stroke and intracerebral hemorrhage derived from the Erasmus Stroke (ESS) database, a registry of all neurovascular patients in the Erasmus Medical Center. Stroke patients with glucose in the prediabetic and diabetic range on admission have an increased risk of unfavorable short-term functional outcome or death, and not to be discharged home after stroke. These findings might illustrate the potential impact of early detection and treatment of these patients.

Previously, a prediction model was developed to identify patients at risk of persistent impaired glucose tolerance, using the following factors: age, current smoking, statin use,

triglyceride, hypertension, history of cardiovascular diseases, body mass index (BMI) and fasting plasma glucose. In section 3.2, I performed an external validation of this model and improved it because of poor performance of the previous existing model. The improved model includes BMI, hypertension, statin use, atrial fibrillation, 2-hour post-load glucose levels, HbA1c, large artery atherosclerosis, and predicts persistent impaired glucose tolerance more accurately. This prediction model can be used to predict persistent impaired glucose tolerance in patients with impaired glucose tolerance directly after minor stroke or TIA, to select which patients would have the most profit of secondary prevention.

Chapter 4 focuses on the prognostic value of disturbed glucose metabolism in stroke patients treated with intravenous thrombolytics or intra-arterial thrombectomy (IAT). In section 4.1, I assess the association of admission glucose and fasting glucose with outcome in stroke patients who received intravenous alteplase from the ESS database. Impaired fasting glucose (IFG) and hyperglycemia on admission are associated with unfavorable short term functional outcome. IFG predicts unfavorable outcome better than hyperglycemia on admission.

In section 4.2, I study the association of admission glucose and fasting glucose with outcome in acute stroke patients with an occlusion in the anterior circulation, who received IAT from the pretrial registry of the Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN) trial. Hyperglycemia on admission and IFG are associated with unfavorable functional outcome after IAT at discharge. These findings might indicate a possible influence of glucose on the effect of IAT in patients with acute ischemic stroke and an occlusion in the anterior circulation.

Therefore, in chapter 4.3, I assess the effect of admission glucose on IAT in the MR CLEAN trial, in which acute stroke patients with a proximal occlusion in the anterior circulation were randomized to IAT or standard care. The interaction of either hyperglycemia or (random) admission serum glucose levels and treatment effect on modified Rankin scale scores were not significant. The same applied for the occurrence of symptomatic hemorrhage. Hence, glucose seemed to have no effect on IAT in the MR CLEAN trial. However, a subsequent meta-analysis of seven randomized controlled trials which compared IAT with standard care shows that lower glucose levels were associated with greater effects of IAT over standard care.

Chapter 5 describes the treatment of prediabetes in patients with TIA or minor stroke. Patients were randomized to control group, metformin and sitagliptin. There was a significant mean change in fasting glucose and HbA1c levels, but not in 2-hour post-load glucose. Fifty percent in the metformin group and 32% in the sitagliptin group

experienced side effects. A total of 61% in the metformin group and 59% in the sitagliptin group were still on treatment after 6 months. Only a minority of patients who discontinued the medication reported side effects (25%). Eighteen percent of patients did not complete the 6 months visit. With these findings, I conclude that metformin and sitagliptin are both safe and effective in reducing fasting glucose and HbA1c levels in stroke patients with IGT.

In chapter 6, the clinical and scientific implications of the studies described in this thesis are discussed.

Newly diagnosed disturbed glucose metabolism after stroke or TIA is associated with unfavorable outcome. Prediabetes can be adequately treated with lifestyle changes and/or anti-diabetic medication. However, it is still uncertain whether this treatment will reduce the risk of recurrent cardiovascular diseases. Therefore, future research should focus on whether glucose lowering therapy in the acute phase improves outcome in patients who receive intravenous thrombolytics or intra-arterial treatment and whether treatment of prediabetes contributes to the secondary prevention after ischemic stroke or TIA.

NEDERLANDSE SAMENVATTING

Beroerte (herseninfarct en hersenbloeding) is één van de meest voorkomende oorzaken van morbiditeit en mortaliteit in de Westerse wereld. Daarom zijn de acute behandeling en het voorkomen van een recidief beroerte belangrijk. Hyperglycemie komt vaak voor in de eerste dagen na een beroerte. Dit kan na de acute fase persisteren, hetgeen wijst op onderliggende prediabetes of diabetes mellitus. Prediabetes is een voorstadium van diabetes mellitus type 2, en komt vaak voor bij patiënten met een beroerte. Patiënten met prediabetes hebben een hoger risico om opnieuw een beroerte te krijgen, maar ook andere cardiovasculaire aandoeningen. Prediabetes zou daarom een belangrijk aangrijppunt kunnen zijn voor secundaire preventie.

Het doel van dit proefschrift is om de prognostische waarde en de behandeling van nieuw-gediagnosticeerd gestoord glucosemetabolisme te bepalen bij patiënten met een beroerte. Ik heb de relatie tussen nieuw-gediagnosticeerd gestoord glucosemetabolisme en de uitkomst na ontslag en na de acute behandeling onderzocht. Ook heb ik een voorspellingsmodel gemaakt om onderscheid te maken tussen tijdelijk en blijvend gestoord glucosemetabolisme, en heb ik de effectiviteit en veiligheid van behandeling van prediabetes bij patiënten met een herseninfarct of TIA onderzocht.

Hoofdstuk 1, de algemene inleiding, beschrijft de achtergrond en motivatie van het onderzoek in dit proefschrift.

In hoofdstuk 2 wordt de literatuur beschreven over de relatie tussen prediabetes en de uitkomst en het effect van behandeling van prediabetes bij patiënten met macrovasculair lijden, zoals coronairlijden, beroerte en perifeer vaatlijden. Prediabetes geeft een hoger risico op diabetes type 2 en macrovasculaire aandoeningen. Ook geeft het een hoger risico op een ongunstige uitkomst. Leefstijlaanpassingen en antidiabetica verlagen het risico op het ontwikkelen van diabetes type 2 evenals het risico om macrovasculaire aandoeningen te ontwikkelen bij patiënten zonder manifest vaatlijden. Of behandeling van prediabetes ook leidt tot minder macrovasculaire complicaties en verbetering van de uitkomst bij patiënten met al bewezen macrovasculair lijden is nog onzeker.

In hoofdstuk 3 richt ik mij op de prognostische waarde van een gestoord glucosemetabolisme bij patiënten met een beroerte. In deel 3.1 beschrijf ik de relatie tussen prediabetes, nieuw gediagnosticeerde diabetes en functioneel herstel bij patiënten met een beroerte, afkomstig uit de Erasmus Stroke Study (ESS) database. Dit is een registratie van alle patiënten die met een beroerte zijn opgenomen in het Erasmus Medisch Centrum. Patiënten met glucosewaarden passend bij prediabetes en diabetes hadden een verhoogd risico op een slechtere uitkomst na het doormaken van

een beroerte op de korte termijn. Deze bevindingen benadrukken het belang van verder onderzoek naar het vroeg opsporen en de behandeling van deze patiënten.

Het is belangrijk om onderscheid te maken tussen tijdelijk en blijvend gestoord glucosemetabolisme. Een gestoord glucosemetabolisme is geassocieerd met recidief beroerte en andere hart- en vaatziekten en een ongunstige uitkomst na een beroerte. Glucose verlagende behandeling kan in deze groep patiënten gunstig zijn. Daarom is er een voorspellingsmodel ontwikkeld om patiënten te identificeren met een verhoogd risico op een blijvende gestoorde glucosetolerantie. Hierbij werden de volgende factoren gebruikt: leeftijd, huidig roken, statinegebruik, triglyceridegehalte, hypertensie, voorgeschiedenis van hart- en vaatziekten, body mass index en het nuchter glucose. In sectie 3.2 heb ik dit voorspellingsmodel extern gevalideerd en verbeterd vanwege de slechte prestatie van het originele voorspellingsmodel. Het verbeterde voorspellingsmodel bevat BMI, hypertensie, statinegebruik, boezemfibrilleren, glucose 2 uur na belasting, HbA1c en atherosclerose van de grote vaten, en voorspelt blijvend gestoord glucosetolerantie beter. Dit voorspellingsmodel kan gebruikt worden om blijvend gestoord glucosetolerantie te voorspellen bij patiënten met een gestoorde glucosetolerantie direct na een klein herseninfarct of TIA. Dit voorspellingsmodel kan ook gebruikt worden om patiënten te selecteren die mogelijk baat hebben van secundaire preventie.

In hoofdstuk 4 wordt de prognostische waarde van een gestoord glucose metabolisme besproken bij patiënten met een herseninfarct die behandeld worden met intraveneuze trombolyse of intra-arteriële trombectomie (IAT). In deel 4.1 beschrijf ik de relatie tussen glucose bij opname, nuchter glucose en de uitkomst bij patiënten met een herseninfarct die behandeld zijn met intraveneuze alteplase uit de Erasmus Stroke Study (ESS) database. Een gestoord nuchter glucose en hyperglycemie bij opname zijn gerelateerd aan een ongunstige functionele uitkomst op de korte termijn. Het nuchter glucose voorspelde de ongunstige uitkomst beter dan hyperglycemie bij opname.

In deel 4.2 wordt de relatie tussen glucose bij opname en het nuchter glucose met uitkomst weergegeven bij patiënten met een herseninfarct met een occlusie in de voorste circulatie, die behandeld werden met IAT. Deze patiënten waren afkomstig van de pretrial registry van de Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands (MR CLEAN) trial. Dit cohort bevatte alle patiënten met een acuut herseninfarct die IAT ondergingen in Nederland. Hyperglycemie bij opname en een gestoord nuchter glucose zijn gerelateerd aan een ongunstige functionele uitkomst bij ontslag na IAT. Deze bevindingen suggereren mogelijk beïnvloeding van het effect op IAT door glucose in patiënten met een acute beroerte en occlusie in de voorste circulatie.

Daarom werd in deel 4.3 het effect van glucose bij opname op IAT in de MR CLEAN trial onderzocht, waarin patiënten met een acuut herseninfarct en een proximale occlusie in de voorste circulatie werden gerandomiseerd voor IAT of standaard behandeling. De interactie tussen hyperglycemie of glucosewaarden bij opname en het behandeleffect op functioneel herstel was niet significant. Hetzelfde geldt voor het optreden van symptomatische intracerebrale bloedingen na IAT. Glucose lijkt daarom geen effect te hebben op IAT in de MR CLEAN trial. Echter, een meta-analyse van zeven gerandomiseerde studies die IAT vergeleken met de standaard behandeling rapporteerde wel een beïnvloeding van het effect van glucose op IAT, waarbij lagere glucosewaarden gerelateerd waren met een beter effect van IAT vergeleken met de standaard behandeling.

In hoofdstuk 5 beschrijf ik de behandeling van prediabetes bij patiënten met een TIA of klein herseninfarct. Patiënten werden gerandomiseerd voor metformine, sitagliptine of geen medicatie. Er was een significante gemiddelde verandering in de nuchtere glucosewaarden en HbA1c waarden, maar niet in glucose na belasting. Vijftig procent van de patiënten in de metformine groep en 32% in de sitagliptine groep ervaarden bijwerkingen. Eenenzestig procent van de patiënten in de metformine groep en 59% in de sitagliptinegroep voltooiden de behandeling bij 6 maanden. Een minderheid van de patiënten die de behandeling hadden gestaakt, ervaarde bijwerkingen (25%). Achttien procent van de patiënten voltooiden de 6 maanden follow-up niet. Op basis van deze bevindingen concludeer ik dat metformine en sitagliptine veilig en effectief zijn in het verlagen van het nuchter glucose en de HbA1c waarden bij patiënten met een TIA of herseninfarct en een gestoord glucosemetabolisme.

In hoofdstuk 6 worden de klinische en wetenschappelijke implicaties van de verschillende studies in dit proefschrift besproken.

Nieuw gediagnosticeerd gestoord glucosemetabolisme na een herseninfarct of TIA is geassocieerd met ongunstige uitkomst. Prediabetes kan adequaat behandeld worden met leefstijlaanpassingen en/of antidiabetica. Het is echter nog niet bewezen dat deze behandeling het risico op recidief hart- en vaatziekten verlaagt. Daarom is meer onderzoek nodig naar behandeling van prediabetes en of dit bijdraagt aan secundaire preventie na een herseninfarct of TIA. Ook is er meer onderzoek nodig naar glucose verlaging in de acute fase en of dit de uitkomst verbetert in patiënten die intraveneuze trombolytica of intra-arteriële behandeling krijgen.

CHAPTER 8
Epilogue

DANKWOORD

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ABOUT THE AUTHOR

Elizabeth (Lisa) Osei was born 1st of May 1987 in Amsterdam. From 2005 to 2011, she studied medicine at the University of Utrecht. She was an active member of the Medical Students' Board of the University of Utrecht from 2009 to 2011. Also, she was a board member of the National Medical Students' Board in 2010. She obtained her medical degree in 2011. Her first job as a medical doctor was at Tergooiziekenhuizen Blaricum in the Neurology department. In 2013, she started her residency for Neurology at Medisch Spectrum Twente in Enschede (head dr. L.D.A. Dorresteijn). She combined her training with the research underlying this thesis from 2014 to 2020 (under supervision of prof. D.W.J. Dippel, dr. H.M. den Hertog and dr. A.A.M. Zandbergen). She was the trial-coordinator of the Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS)-trial. She finished her neurology residency in October 2019, and now works as a neurologist at Flevoziekenhuis in Almere. She currently resides in Almere with her family.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: Elizabeth Osei
Erasmus MC Department: Neurology
Research School: Cardiovascular Research School Erasmus University Rotterdam (COEUR), Medical School Twente
PhD period: 2013-2020
Promotor: prof. D.W.J. Dippel
Co-promotors: dr. H.M. den Hertog, dr. A.A.M. Zandbergen

	Year	Workload (ECTS)
PhD training		
Good research clinical practice course (Medisch Spectrum Twente, the Netherlands)	2014	1
Epidemiology, Literature and Statistics course (Medical School Twente, the Netherlands)	2014	2
PhD course Technical Writing & Editing (University of Twente, the Netherlands)	2016	1
PhD Course Datamanagement (University of Twente, the Netherlands)	2016	1
In-depth courses		
Supervision internship neurovascular disease (Erasmus MC)	2018	5

Oral Presentations		
MAAS-protocol - Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) - Regional scientific evening neurology Overijssel (Enschede, the Netherlands)	2013 2014	0.5 0.5
Prediabetes en nieuw gediagnosticeerde diabetes leiden tot een verhoogd risico op een ongunstige uitkomst bij patiënten na een beroerte - Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) - Scientific meeting Dutch Society of Neurology (Nunspeet, the Netherlands)	2014	1
Atrial fibrillation is associated with disturbed glucose metabolism in patients with ischemic stroke and TIA - Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) - Neurological Disorders Summit (San Francisco, USA)	2015	1
Gestoord glucose metabolisme is geassocieerd met slecht functioneel herstel bij patiënten na endovasculaire behandeling van een herseninfarct (MR CLEAN Pretrial-cohort) - Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) - Scientific meeting Dutch Society of Neurology (Nunspeet, the Netherlands)	2015	1
Invloed van glucose op het effect van IA-behandeling bij patienten met een acuut herseninfarct - Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands)	2016	0.5

Poster presentations		
Prediabetes and newly diagnosed diabetes have an increased risk on onfavourable outcome after stroke Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) Scientific meeting PhD students Erasmus MC (Rotterdam, the Netherlands) European Stroke Congress (Nice, France)	2014	0.9
Newly-diagnosed diabetes and impaired fasting glucose are associated with unfavorable outcome in ischemic stroke patients treated with intravenous thrombolysis European Stroke Organization Congress (Glasgow, Scotland)	2015	0.3
Atrial fibrillation is associated with disturbed glucose metabolism in patients with ischemic stroke and TIA European Stroke Organization Congress (Glasgow, Scotland)	2015	0.3
Nieuw-gediagnosticeerde diabetes en een gestoord nuchter glucose zijn geassocieerd met ongunstig herstel en overlijden bij patiënten met een herseninfarct behandeld met intraveneuze trombolyse Scientific meeting Dutch Society of Neurology (Nunspeet, the Netherlands)	2015	0.3
Increased admission glucose and impaired fasting glucose are associated with unfavourable short-term outcome after intra-arterial treatment of ischaemic stroke in the MR CLEAN Pretrial-cohort Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) European Stroke Organization Congress (Barcelona, Spain)	2016	0.6
Admission glucose and effect of intra-arterial treatment in patients with acute ischaemic stroke in the MR CLEAN Cohort Scientific meeting department of neurology Medisch Spectrum Twente (Enschede, the Netherlands) European Stroke Organization Congress (Barcelona, Spain) Scientific meeting Dutch Society of Neurology (Nunspeet, the Netherlands)	2016	0.9
Prediction of persistent impaired glucose tolerance in patients with minor ischemic stroke or transient ischemic attack European Stroke Organization Congress (Milan, Italy)	2019	0.5
International conferences and symposia		
European Stroke Congress (Nice, France)	2014	0.9
Neurological Disorders Summit (San Francisco, USA)	2015	0.9
European Stroke Organization Congress (Glasgow, UK)	2015	0.9
" (Barcelona, Spain)	2016	0.9
" (Milan, Italy)	2019	0.9

Seminars and workshops		
Regional scientific evening neurology Overijssel (Enschede, the Netherlands)	2014	0.3
Scientific meeting Dutch Neurovascular Network (Utrecht, the Netherlands)	2014, 2015, 2016, 2020	1.2
Scientific meeting Dutch Society of Neurology (Nunspeet, the Netherlands)	2014, 2015, 2016	1.8
Development and presentation guidelines:		
Subdural hematoma, Medisch Spectrum Twente (Enschede, the Netherlands)	2014	1
Cerebral venous sinus thrombosis, Medisch Spectrum Twente (Enschede, the Netherlands)	2017	1
Richtlijn ongeruptureerd intracranieel aneurysma, Erasmus MC (Rotterdam, the Netherlands)	2018	1
Supervision of students		
Supervising research project of medical students	2014-2015	1
Other		
Peer review for scientific journals	2015-present	1
Total		31.1

LIST OF PUBLICATIONS

Osei E, Fonville S, Zandbergen AA, Brouwers PJ, Mulder LJ, Lingsma HF, Dippel DW, Koudstaal PJ, den Hertog HM. Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial. Trials 2015; 16: 332.

Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos YBWEM, Beumer D, van Oostenbrugge RJ, Schonewille WJ, Boiten J, Zandbergen AAM, Koudstaal PJ, Dippel DWJ, MR CLEAN Pretrial investigators. Increased admission glucose and impaired fasting glucose are associated with unfavorable short-term outcome after intra-arterial treatment of ischemic stroke in the MR CLEAN Pretrial cohort. J Neur Sci 2016; 371: 1-5.

Osei E, Fonville S, Zandbergen AAM, Koudstaal PJ, Dippel DW, den Hertog HM. Glucose in prediabetic and diabetic range and outcome after stroke. Acta Neurol Scand 2017; 135: 170-175.

Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos YBWEM, Beumer D, van Oostenbrugge RJ, Schonewille WJ, Boiten J, Zandbergen AAM, Koudstaal PJ, Dippel DWJ, MR CLEAN investigators. Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke in the MR-CLEAN cohort. Stroke 2017; 48: 1299-1305.

Osei E, Fonville S, Zandbergen AAM, Koudstaal PJ, Dippel DWJ, den Hertog HM. Impaired fasting glucose is associated with unfavorable outcome in ischemic stroke patients treated with intravenous alteplase. J Neurol 2018; 265: 1426-1431.

Kleinherenbrink W, **Osei E**, den Hertog HM, Zandbergen AAM. Prediabetes and macrovascular disease: Review of the association, influence on outcome and effect of treatment. Eur J Intern Med 2018; 55: 6-11.

Chamorro A, Brown S, Amaro S, Hill MD, Muir KW, Dippel DWJ, van Zwam W, Butcher K, Ford G. A, den Hertog H. M, Mitchell P. J, Demchuk A. M, Majoie CBLM, Bracard S, Sibon I, Jadhav, A. P, Lara-Rodriguez, B, van der Lugt A, **Osei E**, Renu A, Richard S, Rodriguez-Luna D, Donnan G. A, Dixit A, Almekhlafi M, Deltour S, Epstein J, Guillon B, Bakchine S, Gomis M, du Mesnil de Rochemont R, Lopes D, Reddy V, Rudel G, Roos YBWEM, Bonafe A, Diener H. C, Berkhemer O. A, Cloud G. C, Davis S. M, van Oostenbrugge R, Guillemin F, Goyal M, Campbell B. C. V, Menon B. K, Hermes Collaborators. Glucose Modifies the Effect of Endovascular Thrombectomy in Patients With Acute Stroke. Stroke 2019; 50: 690-696.

E. Osei, H.M. den Hertog, S. Fonville, P.J.A.M. Brouwers, L.J.M.M. Mulder, P.J. Koudstaal, D.W.J. Dippel, A.A.M. Zandbergen, H.F. Lingsma. Prediction of persistent impaired glucose tolerance in patients with minor ischemic stroke or transient ischemic attack. J Stroke Cerebrovasc. Dis. 2020