

# Novel therapeutic strategies for the prevention of stroke in patients with diabetes mellitus



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Stroke continues to be a major public health problem, being the third most common cause of death in the world and a major cause of long-term disability [1–5]. In the USA alone, there are 731,000 new strokes annually with 4 million stroke survivors [4]. Among these survivors, 4–15% will suffer a recurrent stroke within a year and 25% by the fifth year after incident stroke [3,4]. Although death rates from stroke have declined from the 1970s and '80s, recent reports suggest that the decline in age-standardized mortality rates from stroke have been slowing since 1990 [4]. Strategies to reduce the incidence of stroke include prevention of first-ever and recurrent stroke, and treatment of patients with acute stroke to reduce death and disability. The two main strategies of stroke prevention are the population-based public health (or 'mass') approach and the 'high-risk' approach. The 'mass' approach aims to reduce stroke by lowering the prevalence and mean level of vascular risk factors in the community, by means of public education and government legislation [1,2,5]. This approach is also effective for the primary prevention of stroke and diabetes. For example, lowering the mean blood pressure (BP) and reducing obesity considerably reduces the risk of stroke in a population. Behavioral interventions include dietary modifications, increased physical activities and smoking cessation. Reducing the number of smokers by 1% over a 7-year period was estimated to result in 34,261 fewer hospitalizations for stroke. In addition, simple physical activity of 20min, three times a week can significantly reduce the incidence of stroke [1,2,5].

## Diabetes & stroke risk

Diabetes is one of the most important modifiable risk factors for atherosclerosis and stroke, with increasing significance as the diabetes epidemic continued to grow. The incidence of stroke in people with diabetes is up to three times that of the general population [5,6]. The Framingham study demonstrated that those with glucose

intolerance had twice the risk of brain infarction compared with normoglycemic subjects. Furthermore, there is a high prevalence of both newly diagnosed diabetes as well as impaired glucose tolerance in patients presenting with stroke. In the prospective Honolulu Heart Study, the prevalence of thromboembolic, but not hemorrhagic, stroke was increased in those with serum glucose greater than 120mg/dl at 1h after a 50-g glucose load. Furthermore, certain ethnic backgrounds are associated with a higher risk of stroke, of note, African-Americans have almost a 2.4-fold increased incidence, and Caribbean-Hispanics have almost a twofold increase in stroke incidence. This high risk of stroke is likely a reflection of the greater propensity for both diabetes and hypertension in these populations [5,6].

## Diabetes & the risk of morbidity & mortality in stroke patients

Both short- and long-term mortality is substantially increased in post stroke patients who also have diabetes. In a Finnish Study the survival of patients with diabetes was compared with that of a group of randomly selected, nondiabetic patients and a group of age- and sex-matched nondiabetic controls with stroke. After 5 years, only 20% of those with diabetes were alive compared with 40% of the control groups. In this study, 20% of patients were first diagnosed with diabetes when they presented with stroke. Hyperglycemia also appears to increase the mortality rate following stroke, with several studies indicating a cut-off glycemic level of 120 mg/dl. For example, a study from the UK showed that complete recovery of hemiparesis occurred within the first month, only in patients with a persisting blood glucose of less than 120 mg/dl. Another group reported that in diabetic patients less than 65 years of age, 70% of those with presenting glucose of 120 mg/dl, but only 30% with glucoses greater than 120 mg/dl, were able to eventually return to work. Acute hyperglycemia has also been shown to adversely affect stroke outcome in both diabetic and nondiabetic patients, likely due to increased brain lactate production. Hyperglycemia also facilitates the conversion of hypoperfused at-risk tissue into infarction [5,6].

**Management of modifiable stroke risk factors in diabetic patients**

Current recommendations regarding the management of stroke risk factors in people with diabetes include BP control to lower than 130/80 mmHg and glycemic control with a goal of hemoglobin (Hb)A1c of less than 7%, as well as control of dyslipidemia, particularly with statins, to a low-density lipoprotein (LDL)-cholesterol value of less than 100 mg/dl and 70 mg/dl in diabetic patients with established cardiovascular disease. The recommendations also include smoking cessation and decreased alcohol intake, as well as the use of antiplatelet and anticoagulation therapies [1,2,5,6].

**Novel strategies for reduction of atherosclerosis & risk of stroke in diabetes**

Although therapies targeting BP and lipids have proven efficacy in reducing vascular events, there remains a large amount of residual cardiovascular and cerebrovascular disease in patients with diabetes [5–7]. This provides the basis for investigating additional strategies to reduce vascular events in the diabetic population.

The NIH-sponsored Look Action for Health in Diabetes (AHEAD) trial is a multicenter, randomized clinical trial that will examine the effects of a lifestyle intervention designed to achieve and maintain long-term weight loss through decreased caloric intake and increased exercise (Table 1) [8]. Participants were randomly assigned to lifestyle intervention or diabetes support and education. The follow-up of Look AHEAD patients will be up to 11.5 years with the primary outcome being major vascular events, heart attack, stroke, and cardiovascular-related death. The study will also assess the cost-effectiveness of Lifestyle Intervention relative to Diabetes Support and Education.

The question of whether aggressive versus standard glucose control is associated with the risk reduction of vascular events and mortality will be examined in the currently ongoing NIH-sponsored randomized Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial which will study approximately 10,000 patients with Type 2 diabetes for more than 6 years (Table 1). This trial will also include a secondary randomization to examine the effect of BP and lipid control. The ongoing, large-scale, randomized clinical trial, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) is expected to clarify the effect of LDL cholesterol lowering for recurrent stroke (Table 1) [9].

Additional trials using different statins in patients with diabetes are also ongoing. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial will determine whether treatment with an upcoming statin rosuvastatin can reduce cardiovascular events in healthy, normolipidemic subjects with elevated C-reactive protein (CRP) levels (Table 2). This study will enroll approximately 15,000 subjects and determine whether individuals with a LDL cholesterol level of less than 130 mg/dl and an elevated high-sensitivity CRP (hs-CRP) level greater than 2 mg/L will benefit from statins with reduced cardiovascular end points. An elevated hs-CRP level in diabetes, is a marker of insulin resistance, and has been established as a potent predictor of future cardiovascular events. Another large trial is currently ongoing to examine the effect of fenofibrate on cardiovascular mortality in patients with diabetes. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial will enroll approximately 9,000 patients with diabetes and average levels of total cholesterol (Table 1).

**Table 1. Ongoing clinical trials to evaluate strategies for reducing vascular risk in diabetes mellitus [101].**

<b>Trial</b>	<b>Subject population</b>	<b>Intervention</b>	<b>End point</b>
Look AHEAD	Type 2 DM	Lifestyle intervention vs diabetes support and education	Cardiovascular events, stroke and vascular death/health-related quality of life and cost-effectiveness
ACCORD	Type 2 DM	Aggressive glucose control/aggressive lipid/BP control	Cardiovascular events and mortality/neurocognitive
FIELD	Type 2 DM with average cholesterol level	Fenofibrate vs placebo	Cardiovascular events and mortality
SPARCL	Ischemic stroke/TIA	Atorvastatin	Recurrent stroke

ACCORD: Action to Control Cardiovascular Risk in Diabetes trial; ASCENDENT: A Study of Cardiovascular Events in Diabetes; BP: Blood pressure; DM: Diabetes mellitus; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; Look AHEAD: Action for Health in Diabetes; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA: Transient ischemic attack.

**Table 2. Ongoing clinical trials to evaluate novel strategies for reduction of atherosclerosis and risk of stroke and vascular disease in diabetes mellitus or impaired glucose tolerance [101].**

<b>Trial</b>	<b>Subject population</b>	<b>Intervention</b>	<b>End point</b>
CHICAGO	Type 2 DM	Pioglitazone vs glimepiride	Carotid IMT/ Coronary calcium score
PERISCOPE	Type 2 DM with symptomatic CAD	Pioglitazone vs glimepiride	IVUS, atheroma volume in target coronary artery
PROACTIVE	Type 2 DM with macrovascular diseases	Pioglitazone vs placebo on top of the existing DM therapy	Cardiovascular events and mortality
BARI-2D	Type 2 DM with stabile CAD	Invasive vs medical therapy for glycemic control using insulin sensitizing vs insulin-providing strategy	Cardiovascular events and mortality
FREEDOM	Type 1 or Type 2 DM with symptomatic multivessel CAD or MI	CABG vs multi-vessel stenting using drug-eluting stents	All-cause mortality, nonfatal MI and stroke
STARR/DREAM	IGT/IFG	Ramipril vs rosiglitazone	Carotid IMT/ Progression to diabetes
NAVIGATOR	IGT	Valsartan vs nateglinide	Cardiovascular events and progression to diabetes
IRIS	Insulin resistance with ischemic stroke	Pioglitazone vs placebo	Recurrent stroke or MI
JUPITER	Elevate CRP (insulin resistance, DM)	Rosuvastatin	Cardiovascular events and mortality

*BARI-2D: Bypass Angioplasty Revascularization in Type 2 Diabetes trial; CAD: Coronary artery disease; CHICAGO: Study Evaluating Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone; CRP: C-reactive protein; DM: Diabetes mellitus; DREAM: Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications; FREEDOM: Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease; IMT: Intima-media thickness; IRIS: Insulin Resistance Intervention After Stroke trial; IVUS: Intravascular ultrasound; JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; MI: Myocardial infarction; NAVIGATOR: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial; PERISCOPE: Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; PROACTIVE: Prospective Pioglitazone Clinical Trial in Macrovascular Events; STARR: Study of Atherosclerosis with Ramipril and Rosiglitazone.*

Several trials with newer approaches to reducing vascular disease in patients with diabetes or impaired glucose tolerance (IGT) are ongoing (Table 2). Most of these studies use the thiazolidinedione (TZD) class of drugs as an approach to reducing atherosclerosis and vascular events [10]. This class of drugs has been shown to have beneficial cardiovascular effects in patients with insulin resistance and diabetes, above and beyond glycemic control. These favorable effects of TZDs include decreased platelet reactivity, a decrease in platelet-activating inhibitor-1 levels, and a decrease in fibrinogen levels and inflammatory markers [10]. A number of trials using TZDs to suppress early atherosclerosis and/or cardiovascular events in patients with diabetes or IGT are currently underway and within several years, results from these trials could change our clinical practice.

The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial is a study in which the effect of pioglitazone on carotid intima-medial thickness (IMT) is

being evaluated in patients with Type 2 diabetes (Table 2). This trial will provide new information on how changes in carotid IMT and coronary calcium, as a secondary outcome, respond to therapy with a TZD. Other secondary outcomes measures include the distribution of fat between visceral and subcutaneous deposits, markers of lipoprotein metabolism, markers of inflammation, and coagulation factors. The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial uses an identical study design to the CHICAGO trial, but the primary end point is the measure of intravascular ultrasound of the coronary arteries. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) also uses pioglitazone and has major cardiac events as its primary end point in patients with Type 2 diabetes who have evidence of macrovascular disease. Another ongoing trial that uses TZDs is the Study of Atherosclerosis with Ramipril and Rosiglitazone (STARR), a substudy of the Diabetes Reduction

Approaches with Ramipril and Rosiglitazone Medications (DREAM) trial (Table 2) [11]. The DREAM is a placebo-controlled trial of patients with impaired postprandial or impaired fasting glucose, who are randomized to ramipril and/or rosiglitazone with diabetes as the primary end point. Carotid IMT is the primary end point in the STARR study. In addition to the use of TZDs, STARR is also evaluating an atheroprotective effect of the angiotensin-converting enzyme inhibitor, ramipril [11].

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is an ongoing investigation evaluating strategies to reduce cardiovascular risk in patients with IGT (Table 2). The end point of this trial is cardiovascular events and onset of diabetes. The expectation that valsartan can favorably affect the cardiovascular event rate or conversion to diabetes is derived from studies using ACE inhibitors, as well as retrospective analyses of studies using angiotensin II receptor blockers. The NAVIGATOR trial also investigates a potential beneficial effect of nateglinide, a short-acting insulin secretagog, on cardiovascular event rates in those with IGT.

Finally, the role of invasive therapies for patients with diabetes and coronary artery disease remains controversial. As the patients with diabetes mellitus represent 25–30% of all patients requiring coronary revascularization, the need for an updated clinical trial to prospectively assess and clearly recommend a preferred treatment strategy has become imperative. Therefore the The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI-2D) [12] and Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trials [13] are designed to

determine the optimal form of treatment for individuals with diabetes and coronary artery disease (Table 2). In the FREEDOM trial, eligible patients will be randomized to receive either CABG or multivessel stenting using drug-eluting stents. The recent commercial approval of the first drug-eluting stent in the USA has provided a short but important window of opportunity for the FREEDOM trial. There are no clear guidelines for the clinical use of drug-eluting stents and the adverse clinical consequences of stenting are unknown. Revascularization of the symptomatic and asymptomatic carotid artery stenosis by the means of stenting versus carotid endarterectomy has also been tested in several ongoing randomized clinical trials, although none of them specifically is addressing the revascularization effect on stroke outcome in the diabetic population.

### The road ahead

The road ahead to prevention of stroke and diabetes is not easy but it is bright. It is likely that within several years we will have powerful evidence-based interventions at hand. We must, however, ensure that benefits from our research efforts are effectively translated into clinical practice across various models of healthcare delivery. Further studies are still needed, in particular to quantify the relative effect of glycemic management in people with diabetes and associated cardiovascular risk. In addition, further studies are needed to elucidate the optimal approach to people with diabetes who require multiple treatment strategies. Finally, it is important to emphasize that prevention through a mass public health approach of risk factor and lifestyle modifications in the community remains to be the most important strategy for the prevention of stroke and diabetes [14].

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