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Cerebrovascular Disease in Diabetes

Prof Samar Banerjee

Dept of Medicine, Vivekananda Institute of Medical Sciences Kolkata. – President RSSDI

***Abstract:** Cerebrovascular disease (CeVD) is the fourth leading cause of death among all adults and a leading cause of death among patients with diabetes mellitus (DM).[1,2] Approximately 50% of the diabetic patients who survive a stroke, will have long-term disability.[3] Physicians therefore, should know about the optimal strategies for primary prevention, acute treatment, and secondary prevention of CeVD. Majority of the preventive and treatment strategies in diabetes are similar to those for nondiabetic patients. But, there are distinct metabolic derangements and vascular pathology in diabetes which stimulate us to examine specific therapeutic strategies and propose important considerations in the evaluation and management of these patients. New evidence is rapidly generating regarding the improved care for stroke patients with diabetes.*

Introduction

Diabetes is a risk factor for first and recurrent ischemic stroke, transient ischemic attack (TIA), or intra cerebral hemorrhage (ICH). Stroke onset is approximately 2 years earlier.[4] But stroke patients over 85 years of age are less likely to present with diabetes compared with stroke patients aged 65–84 years.[5]

The relation between abnormal glucose metabolism and ischemic stroke is vice-versa. On the one hand, people with diabetes have more than double the risk of ischemic stroke after correction for other risk factors, compared with people without diabetes. On the other hand, acute stroke can give rise to abnormalities in glucose metabolism (either stress hyperglycemia or aggravating the existing one), which in turn could affect the outcome. Moreover, the relation between disturbed glucose metabolism and CeVD is not limited to acute ischemic stroke.

Diabetes is also associated with more insidious ischemic damage to the brain, mainly manifesting as small-vessel disease and increased risk of cognitive decline and dementia.[6] In diabetic stroke models, hyperglycemia exaggerates the following damaging processes: acidosis, accumulation of reactive oxygen species/reactive nitrogen, inflammation and mitochondrial dysfunction.

Moreover, a relation between admission hyperglycemia and poor outcome has been noted for hemorrhagic stroke, in particular aneurysmal subarachnoid haemorrhage.[7]

Epidemiology of CeVD in Diabetes Mellitus

Honolulu Heart Study first in 1968, reported an adjusted relative risk for ischemic stroke of 2.45 (95% CI 1.73–3.47) among patients with diabetes, compared to non-diabetic individuals.[8] This risk has been consistently verified in diverse populations[9] across various age groups, and involving both genders.[10,11] In addition, the duration of diabetes seems to independently increase the risk of ischemic stroke.[12] In those patients who younger than 60 years, the relative risk of stroke compared to those without diabetes is double that of individuals older than 70 years. Sex and ethnic origin also influence the risk of stroke in people with diabetes. The risk is higher in women (hazard ratio 2.8, 95% CI 2.4–3.4) than in men (2.2, 1.8–2.5).[13]

It appears that hyperglycemia ≥155 mg/dL in patients with stroke, with or without diabetes, is associated with a three-fold higher risk of short-term mortality and reduced chance of recovery.[14] When compared to normoglycemic stroke patients, hyperglycemia may also lead to more severe neurological deficits.[15]

Pre-diabetic conditions, including insulin resistance and impaired glucose tolerance, are also associated with increased risk for stroke.[16] Data suggest a selective relationship between serum uric acid and stroke in type 2 diabetes. Whether treatment aimed at reducing serum uric acid can be useful to prevent acute cerebrovascular events in these patients, remains to be ascertained.[19]

The risk of developing stroke, with every year of diabetes duration increases by 3%.[12] Prediabetic conditions are also associated with increased risk for stroke.[20] Compared with nondiabetic patients, diabetic patients have at least twice the risk for stroke. Hyperglycemia has been shown to increase the size of ischemic stroke and worsen the clinical outcome following a stroke.[21] Diabetes may be associated with increased risk for hemorrhagic stroke, although there remains substantial controversy.[22]

Two case-control studies came to conflicting conclusions, but the difference may be explained by research methodology. In 2005, an analysis from the Hemorrhagic Stroke Project reported an adjusted odds ratio for diabetes of 2.4 (95% CI 1.15–5.01.[23] In 2010, the results of a case-control analysis from the INTERSTROKE study reported no association between hemorrhagic stroke and risk for diabetes (OR 00.87, 95% CI 0.60–1.24).[24] However, INTERSTROKE used hospital controls and proxy respondents, two common sources of error and bias in case–control research not used in Hemorrhagic Stroke Project.

DM in Stroke Patients

Diabetes is present in about 10–25% of people with stroke. Stress related hyperglycemia is found in up to two-thirds of people with an acute stroke.[25]

Minnesota Heart Survey estimated the prevalence of diabetes in people hospitalized for stroke, 22.4% in men and 24.7% in women.[26]

The Cardiovascular Heart Study found diabetes in 12.6% for men and 12.7% for women.[27] After a completed stroke, diabetes doubles the risk for a recurrent event.[28] The presence of severe diabetic retinopathy and diabetic nephropathy, independently, increases the risk of stroke,cerebral infarction, and cerebral hemorrhage in patients with type 1 diabetes.[29]

Comorbid Illnesses in Stroke

Diabetic patients are more likely to have hypertension, coronary artery disease, obesity, and dyslipdemia and have a high risk for recurrent stroke in diabetes.[30]

Mechanisms Linking Diabetes to CeVD

Diabetes causes atherosclerotic changes in the heart and the cerebropetal arteries and is associated with different subtypes of ischemic stroke, including lacunar, large artery occlusive, and thromboembolic strokes. Moreover, the risk of atrial fibrillation—a major cause of thromboembolic stroke—is increased by 40% in individuals with diabetes.[31] Diabetes related risk factors for stroke include not only diabetes-specific factors (eg, hyperglycemia) and vascular risk factors (eg, hypertension, dyslipidemia) but also genetic, demographic, and lifestyle factors. The contribution of these factors, many of which are strongly inter-related, is likely to vary according to diabetes type and age. HbA1c concentrations of greater than 6% increases the risk of stroke between two and three times in adults without diabetes, taking into account about the potential confounding effects of other vascular risk factors.[32]

Hitman *et al*. assessed the impact of the diabetes-specific factors like microalbuminuria and glycemic control on the risk of stroke or transient ischemic attack in 2838 participants in the Collaborative Atorvastatin Diabetes Study (CARDS), a placebo-controlled randomized trial evaluating atorvastatin in diabetic subjects free of macrovascular disease.[33] Over a follow-up period of about 4 years, 60 first-ever cerebrovascular events were observed. Subjects with HbA1c greater than 10% had more than double the odds of stroke versus those with lower HbA1c levels. Microalbuminuria was measured using an albumin–creatinine ratio (ACR), with normal ranges for this measure being 1 to 2.5 mg/mmol. An ACR above 2.5 conferred twice the risk of a stroke than in those with a lower ACR.

A Chinese study of 6445 persons followed for more than 5 years showed that an HbA1c greater than 6.2% and macroalbuminuria had a synergistic adverse impact on stroke risk.[34] The Strong Heart Study, based on 4549 Native Americans age 45 to 74 years at baseline, noted that FBG, and haemoglobin A1c (HbA1c) were risk factors for incident stroke along with age, diastolic blood pressure, smoking, albuminuria, hypertension, and prehypertension.[35]

Diabetes accelerated atherosclerosis, may contribute to atrial fibrillation and small vessel disease in deep penetrating branches of the cerebral arteries. Both large and small blood vessels are affected. Diabetes has been associated with a variety of other structural and functional changes in the cerebrovascular circulation that may contribute to poorer outcomes in the setting of cerebral ischemia.

Pathophysiology

Meta-analyses of experimental studies have shown that infarcts were relatively larger in animal models of hyperglycemia, and this effect was more striking for streptozotocin than after dextrose infusion (140% larger *vs* 48% larger).[36] Till date hyperglycemia—in amounts that can be encountered in patients has not been proven definitively to be a causal factor for impaired outcome after stroke, several mechanisms have been observed by which, hyperglycemia could aggravate cerebral damage in ischemic stroke, including impaired re-canalisation and reperfusion injury. Impaired recanalization may be due to disturbances in coagulation and in fibrinolytic pathways.

These pathways have been investigated in people at prediabetic stages, with persistent dysglycemia, and who are resistant to insulin but infrequently in those with acute stroke. Amounts of plasminogen activator inhibitor 1 and tissue-type plasminogen activator antigens, were found to be higher in patients with glucose intolerance compared with those with normal glucose tolerance. The raised levels of fasting insulin are also linked to impaired fibrinolysis and hypercoagulability in individuals with normal glucose tolerance. Acute and chronic hyperglycemia both, show important similarities in their effects on coagulation activation and impaired fibrinolysis.[37]

Hyperinsulinemia is associated mainly with impaired fibrinolysis in people with glucose intolerance. In patients with acute stroke, such disturbances could impinge on the efficacy of fibrinolytic treatment. Indeed, findings of transcranial Doppler imaging studies show that hyperglycemia is associated with persistent arterial occlusion after thrombolytic treatment in individuals with ischemic stroke.[38]

Acute and chronic hyperglycemia both are associated with gross abnormalities in blood vessels that can affect blood flow and vascular reactivity. The results of the disturbed metabolism of endothelium-derived nitric oxide probably have a vital role in these vessel abnormalities, which become more detrimental when blood flow is acutely compromised, during acute cerebral ischemia. The hyperglycemia further threaten the tissue, through augmented reperfusion injury when perfusion is restored. This process is triggered by increased oxidative stress and inflammation, arising from hyperglycemia.[39]

Moreover, increased risk of hemorrhagic complications after thrombolytic treatment probably depend upon the admission hyperglycemia as seen in an observational study of alarge series of patients with acute ischemic stroke treated with intravenous thrombolysis, the increased risk of hemorrhage was only raised significantly when admission glucose concentrations were greater than 10 mmol/L. This study points towards the need of tight control of blood glucose in the hyper-acute phase after thrombolysis, but data from randomised trials are needed.[40]

In cases of large-vessel thromboembolic stroke, hyperglycemia are likely to affect salvage of the penumbra, the part of the ischemic area which can still potentially recover if adequate reperfusion is restored within hours after stroke onset. Available MRI studies show that reduced penumbral salvage is a key contributor to increased infarct size in patients with hyperglycemia at admission.[41]

As a penumbra is usually not present in the cases of lacunar stroke, hyperglycemiais not associated with worse outcome. Moreover, lactate produced by astrocytes has been suggested to be an important rescue source of energy for axons in the basal ganglia region. Enhanced lactate production due to hyperglycemia in lacunar stroke might fuel and salvage axons.

Proposed mechanisms for the association diabetes, stroke with atherosclerosis are as follows:

- In experimental models of stroke diabetes increases cerebral edema, neovascularization, and protease expression that may damage endothelial integrity.[42]
- Diabetes has a relative increased risk for intracranial stenosis and internal carotid artery stenosis associated with a very high risk for stroke recurrence.[43]

Stroke in Type 1 and Type 2 Diabetes

The risk of stroke related to diabetes is assessed mostly in people with type 2 diabetes, because in the age group in which most strokes take place, type 2 diabetes is much more common than type 1 diabetes. Studies involving direct comparison between both types of diabetes show that the relative risk of stroke in people with type 1 diabetes is at least similar or maybe even higher than in individuals with type 2 diabetes.[44]

In the Nurses' Health Study, incidence of stroke is four fold higher in type 1 and two fold higher among type 2 than for nondiabetic.[45] Ischemic stroke increased six fold in type 1 and twofold in type 2. Risks for large-artery infarction and lacunar stroke were similar. Type 1 diabetes is significantly associated with the risk of hemorrhagic stroke (3.8 [1.2–11.8]), but type 2 diabetes was not (1.0 [0.7–1.4]).

Outcomes Following CeVD

The average case-fatality rate for ischemic stroke is 8% to 12%. ICH is much higher, ranging from 38% to 45%.[46] This may be due to certain clinical features more common in diabetic patients with ICH, such as

- higher incidence of infectious complications
- higher incidence of intraventricular hemorrhage[47]

Patients with diabetes after ischemic stroke are more likely to suffer loss of independence and have residual disability. Even with early rehabilitation, disability at 3, 6, and 18 months is increased for patients with diabetes.[48]

Nonetheless, diabetic patients do improve with rehabilitation after stroke and initiation of physical therapy for disability should be no different for patients with diabetes and stroke.

The average case-fatality rate for ICH is much higher; with reliable estimates ranging from 38% to 45%.[49] Diabetes is an independent risk factor for in-hospital mortality from acute spontaneous intracerebral hemorrhage. This may be due to certain clinical features more common in diabetic patients with ICH, such as higher incidence of infectious complications and intraventricular hemorrhage. Of note, acute hyperglycemia itself is an important determinant of stroke outcome in patients both with and without

diabetes.[51–54] Hyperglycemia is associated with both higher mortality and worse functional outcomes.[55–58]

Indicators of Unfavorable Prognosis Following Stroke

In the UKPDS trial, levels of chronic hyperglycemia, monitored using HbA1c levels, were shown to be a continuous risk factor for stroke fatality. The odds ratio for case fatality in stroke was 1.37 per 1% increase in HbA1c.[59] Additionally, sex, systolic blood pressure, recurrent stroke and white cell count were predictors for stroke case fatality in a multivariate analysis. The Copenhagen stroke study identified AF and hypertension as being predictors of poorer prognosis, along with male gender and a history of TIAs.[60]

Patients with diabetes are even more vulnerable once they have suffered an initial stroke. In such patients the risk of a recurrent stroke is increased 12-fold and therefore more than doubled as compared with non-diabetic patients with a history of stroke.[61] Diabetic patients with TIA have an increased stroke risk during the first week after a TIA.[62]

Presentation of Cerebrovascular Events in patients with Diabetes

Patients with diabetes have higher rates of ischemic stroke and lower or similar rates of hemorrhagic stroke compared with nondiabetic patients. In a large European cohort study of first-ever strokes, patients with diabetes were more likely to have limb weakness and dysarthria on presentation after stroke. Aphasia was more common in nondiabetic patients.[63]

Diabetics probably have higher proportion of stroke in the posterior circulation. The overall proportion of strokes attributable to lacunar infarction is probably no different between diabetic and nondiabetic patients, but may present with a higher burden of multiple lacunar stroke.[64]

The present author made a comparative evaluation of diabetic and non diabetic stroke and studied the effect of glycaemia on outcome of CeVd.[65] 450 Patients were categorised into two groups. Group I consisted of patients (171 cases) with previous history of diabetes or being newly diagnosed with HbA1c more than 7%.Group II (279 cases) consisted of 2 subgroups as follows:

= (a) Patients without previous or present history of diabetes [260 cases(93.25)]

= (b)Patients with reactive hyperglycemiahyperglycemia showing a plasma glucose level between 140 and 160 *mg/dl* and HbAIc level of less than 7% [19 cases (6.8%)]

In group I, compared to group II there were more ischemic stroke (p<0.00l). The lacunar infarcts were also more (p<0.05). Old infarct on CT brain were seen in 63 (36.8%) in group I and 59 (21.1%) in group II, (p<0.00l).The mortality in haemorrhagic stroke in group I was 55.8%and in group II was 49.6% (p<O.05) followed upto 4 weeks. The ischemic stroke, in group I was 26.3%and in group II were 14.8% which was highly significant (p<0.00 1).

Amongst the group I out of total mortality of 60 in group I from all causes, 35.08% had HbA1C in the range of 9.5–11.6% just after admission. Main comorbid events in group I were:

- diabetic nephropathy (15.7%),
- ischemic heart disease (lHD) in (8.8%)
- deep vein thrombosis (DVT) with pulmonary thromboembolism (1.75%).

In this study it was observed that diabetics suffer from stroke at an average lower age, 51.2 years as compared to 67 years for non-diabetics. Similar findings were observed in the UKPDS study. There was female preponderance in diabetic stroke which was not corroborated in previous studies.

In the Framingham study higher risk of myocardial infarction in women was seen but relative risk of stroke in diabetes was same in men and women.[66] The incidence of ischemic stroke was higher in group I (69%) as compared to group II (45.8%). Hypertension being the most important risk factor for stroke in the general population, it is possible therefore that diabetes exerts its effect on stroke indirectly by way of its effect on BP. Hypercholesterolemia above 175 mg/dL was present in higher percentage of cases of diabetes (30.9%) compared to non-diabetic (21.1%).Stroke is associated with age, hypertension, and plasma cholesterol in men, age, hypertension, BMI and plasma cholesterol in women. Moreover it was observed that 35.08% of diabetics who died had uncontrolled diabetes (HbA1c>9.5%) at the time of stroke.

Correlation between mortality from stroke and level of hyperglycemia was observed in a major study by Fullerton *et al.*[67] It was found that plasma glucose < 156.6 mg/dl was associated with good recovery but above that death occurred within six months. In this study it was observed that diabetics who died within two weeks of stroke had HbAlc>9.5%.

The present author also studied the carotid intima medial thickness (CIMT) and stroke in diabetes.[68] Twenty four DM and a matched population of 14 patients each of PDM and NDM strokes were studied. Each group was compared as whole and by gender and stroke segregation. Study parameters were right and left CIMTs (CIMTR, CIMTL), insulin resistance (IR), age, BMI and lipids, correlations between CIMTs and CIMTs with risk markers. CIMTR was higher in DM and PDM compared to NDM, but CIMTLs did not differ. CIMTs were similar in genders and stroke types of each group. The IR was significantly high only in DM.

Age and BMI correlations were predominantly positive and lipids variable except in PDM. Age and IR had better impacts on CIMTs in DM while BMI was poor. Females and infarcts had a more congruous CIMT increment in DM and PDM but male and haemorrhage in NDM. With similar levels of risk markers, their impacts on the CIMTs are highly variable at various levels of glycemia.

CIMTs were similar in the genders and stroke types of each group, irrespective of the glycemic status. In the three

groups of patients, incidents CIMTs were higher in DM strokes. The IR level and age of the patient probably plays some role in CIMT status modulation in DM, while it of lesser significance in PDM and NDM.

The incident lipids were similar in the three groups; however they correlated best with the CIMT status only in PDM.

Diagnostic Assessments

Assess modifiable risk factors for stroke progression, recurrent stroke, or complications. Assess for carotid stenosis, AF, myocardial infarction, hypovolemia, hypoglycemia, body temperature, and dysphagia. Screen for carotid stenosis with carotid ultrasound, CT angiography, or magnetic resonance angiography and carotid end-arterectomy (CEA) or stenting. Continuous cardiac monitoring for 1 to 4 weeks at this point is reasonable as Type 2 diabetes has been associated with a significant increase in the risk of AF.

Complications Following CeVD

The frequent and important cause of morbidity and mortality after CeVD in a case of diabetes are:

- urinary tract infections (UTI),
- deep venous thromboses,
- pneumonia,
- difficulty patients experience in ambulating
- difficulty in swallowing

Medical complications following stroke are a frequent and important cause of morbidity and mortality. Urinary tract infections (UTI), deep venous thromboses, and pneumonia are of particular concern, given the frequent difficulty patients experience in ambulating and swallowing following stroke. In a study of 992 stroke registry patients, 30% of whom had diabetes, diabetic patients had an increased rate of UTI, extra cerebral bleeding, and any medical complications. There was no statistically significant difference between risk of deep venous thrombosis or pneumonia but it is important to note that patients with diabetes were given significantly more antibiotics (31% vs 23%, P=0.0075) than patients without diabetes.[6]

Diabetes and Long-Term Outcome After Stroke

There is no difference in mortality during the first 3 months after ischemic stroke, in patients with diabetes compared with those without. But the mortality more than 1 year after stroke was slightly increased (hazard ratio 1.2, 95% CI 1.1–1.2).[70] Additionally the risk of recurrent stroke is raised (1.8, 1.2–2.8),38 which could be even more marked in patients with diabetes younger than 50 years.[71]

Finally, diabetes is associated with augmented risk of long-term functional deficits after stroke (odds ratio 1.5, 95% CI 1.1–1.9), including an increased risk of post-stroke dementia (1.5, 1.1–2.3).[72]

The cumulative 5-year mortality was 40.0 and 54.2%in diabetic men and women, 32.3 and 38.1% in the nondiabetics. Significantly associated mortality was seen with:[73]

- increasing age,
- hemorrhagic stroke,
- renal failure (only in men),
- levels of care dependency,
- number of prescribed medications

Yang Luo *et al.* found that low and high e GFRs (<45 or >120 mL/min/1.73 m^2, respectively) are independent predictors of all-cause mortality and other poor outcomes after acute stroke in patients with type 2 diabetes.[74]

Diagnostic Assessments

Diagnostic procedures should be targeted in ischemic stroke are to assess modifiable risk factors for stroke progression, recurrent stroke, or complications: assessment for carotid stenosis, atrial fibrillation (AF), myocardial infarction, hypovolemia, hypoglycemia, body temperature, and dysphagia screening]. All of these assessments should be considered in patients with diabetes and stroke, and many of them are more likely to be present in a patient with diabetes, such as hypoglycemia, carotid stenosis, and AF.

Due to a possible increased risk of internal carotid artery stenosis, it is even more important to screen for carotid stenosis with carotid ultrasound, CT angiography, or magnetic resonance angiography; in appropriate patients carotid end-arterectomy or stenting can markedly reduce the risk of recurrent stroke.

Type 2 diabetes has been associated with a significant increase in the risk of AF.[75] Therefore, screening with continuous heart monitoring likely has a higher yield in patients with diabetes. The ideal type and duration of cardiac monitoring in ischemic stroke has yet to be determined, but continuous cardiac monitoring for 1 to 4 weeks at this point is reasonable. In those with diabetes and AF, the risk of stroke is higher than those with AF and no diabetes; therefore, these patients will more likely benefit from anticoagulation.

Diagnosis of ICH in diabetic patients does not differ than those without diabetes. It includes rapid imaging with CT or MRI of the brain to distinguish it from ischemic stroke, and use of CT or magnetic resonance angiography to determine the etiology.

Management of Stroke in Diabetics

Management of stroke consist of treatment of strokes in the acute state and subsequent measures to prevent propagation of acute stroke as well as its recurrence.

Management in Acute State

Hyperglycemia damages neurons in the hypo-perfused area (penumbra) during an acute incomplete stroke. The penumbra can either undergo permanent injury or be completely restored depending upon the approach. Hyperglycemia

and hypoxia both can lead to lactic acidosis, which further reduces perfusion and causes infarct expansion. Early and aggressive management of stroke reduces infarct size and neurological deficit.

The priority in treatment consist of strict glycemic control, adequate fluid administration, body temperature control, oral feeding, and start of antiplatelet agents within the first 48 hours of stroke onset.

If glucose and insulin are administered intravenously to improve glycemic control, the aerobic glycolytic path is promoted, ATP synthesis is augmented, and lactic acid production resulting from anaerobic glycolysis is minimised. This results in better perfusion rates and reduces the infarction size. Insulin-induced vasodilation may also play an additional action. Proposed guidelines for the early management of hyperglycemia during ischemic stroke is to initiate insulin therapy when plasma glucose is >140–180 mg/dL with therapeutic target of plasma glucose between 80–140 mg/dL.

Acute Thrombolytic Treatment

Outcomes for patients with diabetes after tissue plasminogen activator (tPA) appear to be similar to those in patients without diabetes.[76,77] Diabetes may be associated with increased risk for symptomatic ICH after tPA.[78] However, this association is not certain, and studies have not resolved the controversy.

Glycemic Management

Tight glycemic control appears to be safe in acute ischemic stroke. However, the effectiveness for improving outcome has not been proven, despite the aforementioned positive relationship between glucose levels and stroke outcomes in the acute setting. An older trial of glucose potassium insulin infusion in acute ischemic stroke found that it lowered blood glucose, but did not affect cerebral infarct growth, was associated with a high incidence of asymptomatic hypoglycemia.[79]

Two more trials using very developed monitoring protocols found no significant safety concerns.[80,81] In acute stroke, treat persistent hyperglycemia (> 140 mg/dL) with insulin and monitoring to avoid hypoglycaemia.[82] The effectiveness of tight glycemic control with standardized safety monitoring is being evaluated in the SHINE trial that is scheduled to be completed by 2018.

Intensive versus standard control

Currently, there is no evidence that tighter chronic glycemic control prevents first or recurrent stroke, even among high risk persons. Three large secondary prevention trials have examined tight control, compared with conventional control, for prevention of macrovascular events in patients with type 2 diabetes. In the ADVANCE study no difference was found between the intensive versus standard control group with respect to the rate of nonfatal stroke (3.8% in both treatment groups), major cerebrovascular events (4.3% vs 4.4%), or all cerebrovascular events (6.3% vs 5.9%).[83]

In the ACCORD study, there was no difference in nonfatal or fatal stroke rate between the two treatment groups.[84] The third trial, the VADT showed no difference in cardiovascular events or all-cause mortality, including stroke, between the two treatment groups.[85]

It is important to note that none of these trials were designed specifically to examine secondary prevention of stroke in patients with diabetes. Instead, they examined stroke as one in a composite of macrovascular outcomes. In the setting of acute stroke and hyperglycemia aggressive management of glucose has also failed to demonstrate benefit. The largest trial to date, the Glucose Insulin in Stroke Trial (GIST), did not show benefit in 90 days mortality, which was the primary end point, or severe disability, the secondary end point.[86]

Why no benefit?

The Glucose Regulation in Acute Stroke patients (GRASP) study, showed a strong association with hypoglycemia and tight glucose control in the acute post stroke setting.[87] Further hypoglycemia, especially if severe and repeated, is associated with cognitive impairment. Possible explanation is hypoglycemia induces cerebrovascular damage, via direct hypoglycemic induced neuronal damage.[88]

While more evidence is gathered, diabetic patients with stroke or TIA should be treated with existing American Heart Association (AHA) and American Diabetes Association (ADA) guidelines for glycemic control. That is, in the hospital setting, stroke patients should be treated with insulin to a goal of blood glucose less than 140 mg/dL in noncritical and less than 180 mg/dL in critical patients respectively, if it can be safely achieved.[89] In the post-acute setting, non-pregnant adults with TIA or stroke should be treated to a goal HbA1c of less than 7%. A less stringent goal HbA1C of less than 8% can be used in older individuals who have a limited life expectancy and others who may not benefit from tighter control. Certainly the glycemic control targets must be individualized to account for overall health, risk for hypoglycemia, polypharmacy and cognitive impairment. Treatment in the acute setting of ICH is the same as in ischemic stroke or TIA.[90]

Other Choice of Antidiabetics

The first study on oral antidiabetics in stroke was the UKPDS. The metformin group had a reduction in stroke compared to the sulfonylurea or insulin group, respectively, ($p = 0.032$). When metformin was compared to conventional (diet) therapy, there was a 30% lower risk for all macrovascular disease, showing some benefit in the primary prevention of stroke in patients with diabetes. But the incidence of stroke was not statistically different. These results suggest that first-line treatment with metformin shows some benefit in the primary prevention of stroke in patients with diabetes.[91]

In the PROactiveTrial with a history of stroke, pioglitazone therapy was associated with a 47% relative risk reduction for future stroke.[92] The US National Institutes of Neurological Disorders and Stroke has started the IRIS (Insulin Resistance Intervention After Stroke) trial to assess the effect of pioglitazone on stroke risk. Results from this international study involving nearly 4000 non-diabetic, insulin-resistant patients are expected in 2015.

Antiplatelet Therapy

Platelets from subjects with DM, particularly from those with type 2 diabetes, exhibit

- increased reactivity
- aspirin resistance

Trial data does not support the routine use of aspirin as a primary prevention. For the secondary prevention of stroke, the evidence base comparing aspirin and clopidogrel in the diabetic person is relatively sparse. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study looked specifically at their diabetic participants and suggested that clopidogrel was better than aspirin for diabetic people.[93]

Currently, there is no evidence to suggest that a combination of aspirin and clopidogrel, even in high risk people, such as those with diabetes, has any therapeutic advantage and may actually be harmful. In the Mexican-American Trial of Community Health workers (MATCH) trial individuals already taking clopidogrel were randomised to receive either aspirin or placebo, in addition to clopidogrel, but failed to show a reduction in its composite cardiovascular end point (which included stroke) but did demonstrate increased rates of bleeding when using a combination of the two.[94]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study, did not show any benefit of clopidogrel and aspirin combined, when compared to aspirin alone.[95] The American Diabetes Association (ADA) and the American Heart Association (AHA) guidelines recommend aspirin therapy (75–162 mg/day) for secondary prevention of stroke in patients with diabetes and previous stroke or TIA. In patients who are allergic to aspirin, clopidogrel can be used.[89]

These agents, in addition to aspirin/dipyridamole, on an average reduce the risk of stroke by 22%.[96] The CAPRIE study in a subgroup analysis of previously suffered stroke, showed that the relative risk reduction of recurrent stroke was 7.3% but was not statistically significant.[97] As a standard practice the the ADA and AHA guidelines should be followed in patients with diabetes who have suffered a stroke or TIA as follows:[89]

- receive aspirin therapy (50–325 mg/day) for secondary prevention of stroke,
- with clopidogrel 75 mg/day or aspirin/dipyridamole 25/200 mg twice daily as acceptable alternatives.

Blood Pressure Management

In acute ischemic stroke, there appears to be a "U-shaped" relationship between blood pressure (BP) and outcomes, with both high and low associated with worse outcomes, but no trial has yet demonstrated improved outcomes with treatment of high or low BP in either patient with or without diabetes. Therefore, until other evidence becomes available, BP in acute stroke should be monitored and only treated above 220/120 mmHg, except in patients receiving tPA who should have BP above 185/110 mmHg treated.[98]

In the non acute setting, the evidence for treatment of BP after stroke is much clearer. No specific different guidelines for patients with diabetes who have also suffered a previous stroke have been recommended at this time.[99]

Recent stroke secondary prevention guidelines generally support the JNC recommendations but emphasize that specific treatment goals should be individualized. Two important trials have been published that examine BP goals among patients with diabetes (beyond the acute period).

The ACCORD trial included a BP arm with history of cardiovascular disease (including stroke) and investigated more stringent BP goals (systolic BP goal <120 vs <140 mmHg) on cardiovascular event outcome.[100] Although the study found overall no reduction in cardiovascular death, it did find that annual rates of stroke were 0.32% in the intensive treatment group and 0.53% in the standard therapy group (HR 0.59, 95% CI 0.39–0.89; P=0.01).

The ADVANCE trial also investigated BP but no statistically significant difference in the total cerebrovascular event rate (5.1% in the treatment group and 5.4% in the placebo group) between the treatment and placebo groups (RR 6%; 95% CI −10–20%, P0 0.42).[101]

No trial has looked specifically at BP goals or specific medications used for secondary prevention of stroke in patients with diabetes. Anyone with BP higher than the optimal 120/80 mmHg may be more likely to have a stroke, according to a new meta-analysis published in the March 12, 2014, online issue of *Neurology*, the medical journal of the American Academy of Neurology.

Newer trial data indicate that patients with diabetes who have suffered a stroke should have a goal BP of less than 130/80 mmHg, with allowance for individual circumstances. The JNC 8 has not recommended any separate guideline for stroke. As most patients with diabetes require three or more antihypertensive agents, a combination that includes angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and diuretic therapy may be required.[102] Evidence suggests similar treatment of ICH in diabetic patients as in ischemic stroke.[90]

Cholesterol Management

The goal of cholesterol therapy is more stringent in patients with diabetes who have suffered a stroke. The Heart Protection Study (HPS) with simvastatin 40 mg daily in

diabetic sub group, showed that there was a 24% (95% CI; 19–28%; P<0.0001) reduction in first occurrence of major coronary event, stroke, and revascularization.[103]

The Adult Treatment Panel (ATP) III recommendations were modified for high-risk patients to include an optional low-density lipoprotein (LDL) goal of less than 70 mg/dL, rather than less than 100 mg/dL.[104] Patients with diabetes who have previously suffered a stroke should be considered high risk and therefore should have statin therapy with a goal LDL of less than 70 mg/dl. As baseline LDL did not impact the positive outcome, initiating statin therapy in these patients regardless of their LDL level may be considered.

Current[96] AHA guidelines recommend statin therapy for those:

- ischemic stroke or TIA
- who have evidence of atherosclerosis,
- an LDL cholesterol level greater than 100 mg/dL,
- who are without known coronary heart disease,
- with a reasonable target of 50% LDL reduction or less than 70 mg/dL.

Atrial Fibrillation

The risk of embolic stroke disease varies between individuals and diabetes being one risk factor. The use of warfarin, has been shown conclusively to reduce stroke.[105]

However, warfarin increases bleeding risk, takes time to work, and is not suitable for all people. Hence, aspirin is often prescribed as a suitable, if less efficacious, alternative. Recently factor IIa (thrombin) inhibitors have been developed as alternatives to warfarin. Trials such as RE-LY, have demonstrated that these medications are as efficacious as warfarin.[106]

Lifestyle Modifications

Intensive lifestyle interventions, improve cardiovascular risk factors. A low-fat, low-carbohydrate diet can assist with weight control. These lifestyle modifications can potentially reduce adverse vascular events by curing diabetes or reducing its severity. Hsieh F et al noted that PPAR y2821C allele is a strong predictor of ischemic stroke for diabetic patients, and PPAR may serve as a potential target for treating ischemic stroke.[107]

Stroke Prevention

Several risk factors leading to stroke in patients with diabetes are modifiable. They are lifestyle factors, glucose concentrations, blood pressure, and dyslipidemia. Stroke prevention is distinguished as primary prevention (eg, prevention of first stroke) and secondary prevention (eg, prevention after transient ischemic attack or ischemic stroke.. Lifestyle probably has the highest effect on risk of stroke. Smoking, obesity, inactivity, excessive alcohol intake, and unhealthy diets should be strongly avoided. Lifestyle modification in the diabetic population is associated with a substantial decline in stroke incidence (hazard ratio 0.62, 95% CI 0.39–0.98).[108] Moreover, modest weight loss (5–10% of bodyweight) in individuals with type 2 diabetes has shown a substantial improvement of cardiovascular risk factors and glycemic control.[109] As yet, aggressively treating hyperglycemia has not been shown to have beneficial outcomes in either primary or secondary prevention in stroke. Aggressive management of hypertension, however, has been shown to be particularly efficacious in diabetics. Currently, evidence would suggest target BP should be 140/80 mmHg at maximum but perhaps not lower than 120 mmHg systolic.

A meta-analysis of 14 randomized trials of statins involving more than 18,600 subjects demonstrated a significant (21%) reduction in stroke risk among diabetics who were taking statins versus those who were not (OR, 0.79; 95% CI, 0.67–0.93).[110] Statin treatment in diabetics appeared to protect against stroke and are relatively safe and are widely used.

Also an ACE-I would usually be a suitable first line agent in this population. Cholesterol should be reduced, regardless of its starting point in diabetic people.

The latest AHA and American Stroke Association Recommendations of 2014 for stroke prevention in patients with diabetes are as follows:[111]

1. After a TIA or ischemic stroke, all patients should probably be screened for diabetes with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post event period *(Class IIa; Level of Evidence C*). (New recommendation).
2. Use of existing guidelines from the ADA for glycemic control and cardiovascular risk factor management is r*ecommended for patients with an* ischemic stroke or TIA who also have DM or pre-DM.

Conclusion

CeVD is a significant cause of morbidity and mortality among patients with diabetes. The diagnosis and management of stroke is almost identical in diabetic as in nondiabetics, with the exception of monitoring and treatment of blood glucose according to ADA standards of medical care in diabetes. Those standards include, for most patients, lowering the HbA1c to ≤7%.

For patients with type 2 diabetes who require drug therapy, metformin is recommended for initial therapy. For diabetic patients with an acute stroke, hospital care should include measurement of HbA1c on admission, regular monitoring of preprandial blood glucose throughout the stay, and treatment with basal and prandial insulin. For critically

ill patients, a goal of 140 to 180 mg/dL (7.8–10.0 mmol/L) is recommended.[88]

For most noncritically ill patients a goal of less than 140 mg/dL (< 7.8 mmol/L) is reasonable, if it can be safely achieved. More intensive glucose management is not recommended at this time. AHA guidelines should be followed for patients with diabetes and CeVD, including the assessment of risk factors such as AF, carotid stenosis, among others; treatment with tPA if appropriate; and management of hypertension, lipids, and smoking cessation.

It is possible to reduce the risk of stroke among people with diabetes. Both the systolic and diastolic BP should be measured and controlled. Lipid levels should be monitored and LDL cholesterol lowered to at least 130 mg/dL and probably to 100 mg/dL in most diabetic subjects by diet or drug therapy. Any attempt to raise HDL cholesterol by increasing exercise and/or weight reduction or drugs should be considered. Smoking cessation must be mandatory and assessment of asymptomatic vascular disease and symptomatology, especially transient cerebral ischemia, atrial fibrillation, and peripheral vascular disease, should be encouraged. The view that stroke is an inevitable consequence of diabetes and aging should be replaced by aggressive efforts to prevent stroke.

There is a distinct lack of evidence specific for secondary stroke prevention, and it is important that further studies be conducted specifically examining this cohort of high cerebrovascular risk individuals. We need targeted studies to identify biomarkers that may predict future stroke in diabetics, to evaluate stroke risk in prediabetic states, and to examine additional therapeutic interventions among persons at an increased risk for developing diabetes.

References

1. Heron M Deaths. Leading causes for 2007. *Natl Vital Stat Rep* 2011;59:1–95.
2. de Marco R, Locatelli F, Zoppini G, *et al*. Cause-specific mortality in type 2 diabetes. The verona diabetes study. *Diabetes Care* 1999;22:756–761.
3. Hankey GJ, Spiesser J, Hakimi Z, *et al*. Rate, degree, and predictors of recovery from disability following ischemic stroke. *Neurology* 2007;68:1583– 1587.
4. Kissela BM, Khoury J, Kleindorfer D, *et al*. Epidemiology of ischemic stroke in patients with diabetes: The greater cincinnati/northern kentucky stroke study. *Diabetes Care* 2005;28:355–359.
5. Auriel E, Gur AY, Uralev O, *et al*. Characteristics of first ever ischemic stroke in the very elderly: Profile of vascular risk factors and clinical outcome. *Clin Neurol Neurosurg* 2011;113(8):654–657.
6. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol* 2008;7:184–190.
7. Kruyt ND, Biessels GJ, DeVries JH, *et al*. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. *J Cereb Blood Flow Metab* 2010;30:1577–1587.
8. Burchfiel CM, Curb JD, Rodriguez BL, *et al*. Glucose intolerance and 22-year stroke incidence. The Honolulu heart program. *Stroke* 1994;25:951–957.
9. Folsom AR, Rasmussen ML, Chambless LE, *et al*. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The atherosclerosis risk in communities (aric) study investigators. *Diabetes Care* 1999;22:1077–1083.
10. Kissela BM, Khoury J, Kleindorfer D, *et al*. Epidemiology of ischemic stroke in patients with diabetes: The greater cincinnati/northern kentucky stroke study. *Diabetes Care* 2005;28:355–359.
11. Manson JE, Colditz GA, Stampfer MJ, *et al*. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991;151:1141–1147.
12. Banerjee C, Moon YP, Paik MC, *et al*. Duration of diabetes and risk of ischemic stroke: The Northern Manhattan study. *Stroke* 2012;43(5):1212–1217.
13. The Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, *et al*. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–2222.
14. Capes SE, Hunt D, Malmberg K, *et al*. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001;32(10):2426–2432.
15. Elgebaly MM, Ogbi S, Li W, *et al*. Neurovascular injury in acute hyperglycemia and diabetes: A comparative analysis in experimental stroke. Transl. *Stroke Res* 2011;2(3):391–398.
16. Thacker EL, Psaty BM, McKnight B, *et al*. Fasting and postglucose load measures of insulin resistance and risk of ischemic stroke in older adults. *Stroke* 2011;42(12):3347–3351.
17. Tuomilehto J, Rastenyte D, Jousilahti P, *et al*. Diabetes mellitus asa risk factor for death from stroke. Prospective study of the middle-aged finnish population. *Stroke* 1996;27:210–215.
18. Furie K, Inzucchi SE. Diabetes mellitus, insulin resistance, hyperglycemia,and stroke. *Curr Neurol Neurosci Rep* 2008;8:12–19.
19. Seghieri G, Moruzzo D, Fascetti S, *et al*. Increase In Serum Uric Acid Is Selectively Associated With Stroke In Type 2 Diabetes. *Diabetes Care* 2002;25(6):1095.
20. Kernan WN, Inzucchi SE. Metabolic rehabilitation: Science gathers to support a new intervention to prevent stroke. *Stroke* 2011;42:3333–3335.
21. Kothari V, Stevens RJ, Adler AI, *et al*. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 2002;33(7)1776–1781.
22. Janghorbani M, Hu F, Willett W, *et al*. Prospective Study of Type 1 and Type 2 Diabetes and Risk of Stroke Subtypes. *Diabetes Care* 2007;30:1730–1735.
23. Feldmann E, Broderick JP, Kernan WN, *et al*. Major risk factors for intracerebral hemorrhage in the young are modifiable. *Stroke* 2005;36:1881–1885.
24. O'Donnell MJ, Xavier D, Liu L, *et al*. Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): A case–control study. *Lancet* 2010;376:112–123.
25. Scott JF, RobinsonG M, French JM, *et al*. Prevalence of admission hyperglycemia across clinical subtypes of acute stroke,. *The Lancet* 1999;353(9150)376–377.
26. Sprafka JM, Virnig BA, Shahar E, McGovern PG. Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival. The Minnesota Heart Survey. *Diabetic Medicine* 1994;11(7)678–684.
27. Barzilay JI, Spiekerman CF, Kuller LH, *et al*. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the cardiovascular health study. *Diabetes Care*, 2001;24(7)1233–1239.

28. Petty GW, Brown Jr RD, Whisnant JP, *et al*. Survival and recurrence after first cerebral infarction: A population-based study in rochester, minnesota, 1975 through 1989. *Neurology* 1998;50:208–216.
29. HÄGG S. Incidence of stroke according to presence of diabetic nephropathy and severe diabetic retinopathy in patients with Type 1 Diabetes. *Diabetes Care* 2013;36:4140–4146.
30. Kissela BM, Khoury J, Kleindorfer D, *et al*. Epidemiology of ischemic stroke in patients with diabetes: The greater cincinnati/northern kentucky stroke study. *Diabetes Care* 2005;28:355–359.
31. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am J Cardiol* 2011;108:56–62.
32. Selvin E, Steffes MW, Zhu H, *et al*. Glycated hemoglobin, diabetes,and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800–811.
33. Hitman GA, Colhoun H, Newman C, *et al*. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabet Med* 2007;24:1313–1321.
34. Yang X, Ko GT, So WY, *et al*. Additive interaction of hyperglycemia and albuminuria on risk of ischemic stroke in type 2 diabetes mellitus - Hong Kong Diabetes Registry. *Diabetes Care* 2008;31(12):2294–2300.
35. Zhang Y, Galloway JM, Welty TK, *et al*. Incidence and risk factors for stroke in American Indians. The Strong Heart Study. *Circulation* 2008;118:1577–1584.
36. MacDougall NJ, Muir KW. Hyperglycemia and infarct size in animal models of middle cerebral artery occlusion: systematic review and meta-analysis. *J Cereb Blood Flow Metab* 2011;31:807–818.
37. Lemkes BA, Hermanides J, Devries JH, *et al*. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost* 2010;8:1663–1669.
38. Pandolfi A, Giaccari A, Cilli C, *et al*. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta Diabetol* 2001;38:71–76.
39. Quast MJ, Wei J, Huang NC, *et al*. Perfusion deficit parallels exacerbation of cerebral ischemia/reperfusion injury in hyperglycemic rats. *J Cereb Blood Flow Metab* 1997;17:553–559.
40. Ahmed N, Davalos A, Eriksson N, *et al*. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). *Arch Neurol* 2010;67:1123–1130.
41. Parsons MW, Barber PA, Desmond PM, *et al*. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol* 2002;52:20–28.
42. Ergul A, Kelly-Cobbs A, Abdalla M, Fagan SC. Cerebrovascular complications of diabetes: Focus on stroke. *Endocr Metab Immune Disord Drug Targets* 2012;12(2):148–158.
43. Turan TN, Makki AA, Tsappidi S, *et al*. Risk factors associated with severity and location of intracranial arterial stenosis. *Stroke* 2010;41:1636–1640.
44. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001;44 (suppl 2):S54–S64.
45. Janghorbani M, Hu FB, Willett WC, *et al*. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. *Diabetes Care* 2007;30:1730–1735.
46. Roger VL, Go AS, Lloyd-Jones DM, *et al*. Heart disease and stroke statistics–2012 update: A report from the american heart association. *Circulation* 2012;125:e2–e220.
47. Tetri S, Juvela S, Saloheimo P, *et al*. Hypertension and diabetes as predictors of early death after spontaneous intracerebral hemorrhage. *Neurosurg* 2009;110:411–417.
47. Arboix A, Massons J, Garcia-Eroles L, *et al*. Diabetes is an independent risk factor for in-hospital mortality from acute spontaneous intra-cerebral hemorrhage. *Diabetes Care* 2000;23:1527–1532.
48. Protopsaltis J, Kokkoris S, Korantzopoulos P, *et al*. Prediction of long-term functional outcome in patients with acute ischemic non-embolic stroke. *Atherosclerosis* 2009;203:228–235.
49. Roger VL, Go AS, Lloyd-Jones DM, *et al*. Heart disease and stroke statistics–2012 update: A report from the american heart association. *Circulation* 2012;125:e2–e220.
50. Arboix A, Massons J, Garcia-Eroles L, *et al*. Diabetes is an independent risk factor for in-hospital mortality from acute spontaneous intracerebral hemorrhage. *Diabetes Care* 2000;23:1527–1532.
51. Capes SE, Hunt D, Malmberg K, *et al*. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* 2001;32:2426–2432.
52. Hatzitolios AI, Didangelos TP, Zantidis AT, *et al*. Diabetes mellitus and CeVD: Which are the actual data? *J Diabetes Complications* 2009;23:283–296.
53. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ* 1997;314:1303–1306.
54. Williams LS, Rotich J, Qi R, *et al*. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 2002;59:67–71.
55. Ahmed N, Dávalos A, Eriksson N, *et al*. Blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register. *Arch Neurol* 2010;67(9):1123–1130.
56. Baird TA, Parsons MW, Phanh T, *et al*. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003;34:2208–2214.
57. Jorgensen HS, Reith J, Nakayama H, *et al*. Potentially reversible factors during the very acute phase of stroke and their impact on the prognosis: Is there a large therapeutic potential to be explored? *Cerebrovasc Dis* 2001;11:207–211.
58. Parsons MW, Barber PA, Desmond PM, *et al*. Acute hyperglycemia adversely affects stroke outcome: A magnetic resonance imaging and spectroscopy study. *Ann Neurol* 2002;52:20–28.
59. Adler AI: UKPDS-modelling of cardiovascular risk assessment and lifetime simulation of outcomes. *Diabet Med* 2008;25(Suppl 2):41–46.
60. Jorgensen HS, Nakayama H, Reith J, *et al*. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. *Neurology* 1997;48:891–5.
61. Idris I, Thomson GA, Sharma JC. Diabetes mellitus and stroke. *Int J Clin Pract* 2006;60:48–56.
62. Johnston SC, Rothwell PM, Nguyen-Huynh MN, *et al*. Validation and refinement of scores to predict very early stroke risk after transient ischemic attack. *Lancet* 2007;369:283–292.
63. Megherbi SE, Milan C, Minier D, *et al*. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: Data from the european biomed stroke project. *Stroke* 2003;34:688–694.

64. Arauz A, Murillo L, Cantu C, *et al*. Prospective study of single and multiple lacunar infarcts using magnetic resonance imaging: Risk factors, recurrence, and outcome in 175 consecutive cases. *Stroke* 2003;34:2453–2458.
65. Sarkar R N, Banerjee S, Basu A. Comparative Evaluation of Diabetic and Non diabetic Stroke - Effect of Glycaemia on Outcome. *JIMA* 2004;102:551–553.
66. Kannel WB, Me Gee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979;59,8–13.
67. Fullerton KJ, Mackenzie G, Stout RW. Prognostic indices in stroke. *Q J Med* 1988;66:147–162.
68. Ghosh US, Chattopadhyay P, Banerjee S, *et al*. Status of carotid intima-media thickness and associated risk factors in diabetic, prediabetic and non diabetic acute stroke. *JAPI* 2012;60:26–29.
69. Stöllberger C, Exner I, Finsterer J, *et al*. Stroke in diabetic and non-diabetic patients: Course and prognostic value of admission serum glucose. *Ann Med* 2005;37:357–364.
70. Kamalesh M, Shen J, Eckert GJ. Long term postischemic strokemortality in diabetes: a veteran cohort analysis. *Stroke* 2008;39:2727–2731.
71. Putaala J, Liebkind R, Gordin D, *et al*. Diabetes mellitus and ischemic stroke in the young: clinical features and long-term prognosis. *Neurology* 2011;76:1831–1837.
72. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009;81006–1018.
73. Icks A, Claessen H, Morbach S, *et al*. Time-Dependent Impact of Diabetes on Mortality in Patients With Stroke. *Diabetes Care* 2012;35:1868–1875.
74. Luo Y, Wang X, Wang Y, *et al*. Association of Glomerular filtration Rate With Outcomes of Acute Stroke in Type 2 Diabetic Patients: Results From the China National Stroke Registry. *Diabetes Care* 2014;37:173–179.
75. Huxley RR, Alonso A, Lopez FL, *et al*. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: The atherosclerosis risk in communities study. *Heart* 2012;98:133–138.
76. Mishra NK, Ahmed N, Davalos A, *et al*. Thrombolysis outcomes in acute ischemic stroke patients with prior stroke and diabetes mellitus. *Neurology* 2011;77:1866–1872.
77. Mishra NK, Davis SM, Kaste M, Lees KR. Comparison of outcomes following thrombolytic therapy among patients with prior stroke and diabetes in the Virtual International Stroke Trials Archive (Vista). *Diabetes Care* 2010;33:2531–2537.
78. Jaillard A, Cornu C, Durieux A, *et al*. Hemorrhagic transformation in acute ischemic stroke. The mast-e study. Mast-e group. *Stroke* 1999;30:1326–32. Celik Y, Utku U, Asil T, Balci K. Factors affecting haemorrhagic transformation in middle cerebral artery infarctions. J ClinNeurosci. 2004;11:656–8.
79. McCormick M, Hadley D, McLean JR, *et al*. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol* 2010;67:570–578.
80. Bruno A, Kent TA, Coull BM, *et al*. Treatment of hyperglycemia in ischemic stroke (this) a randomized pilot trial. *Stroke* 2008;39:384–389.
81. Johnston KC, Hall CE, Kissela BM, *et al*. Glucose regulation in acute stroke patients (grasp) trial: A randomized pilot trial. *Stroke* 2009;40:3804– 3809.
82. Adams Jr HP, del Zoppo G, Alberts MJ, *et al*. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association stroke council, clinical cardiology council, cardiovascular radiology and intervention council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups. *Circulation* 2007;115:e478–534.
83. Effects of intensive glucose lowering in type 2 diabetes. New England Journal of Medicine 2008, 358:2545–59; Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 2008;358:2560–72;.
84. The Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358(24):2545–2559.
85. Duckworth W, Abraira C, Moritz T, *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360129–139.
86. Gray CS, Hildreth AJ, Sandercock PA. *et al*. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurology*, 2007;(6)5:397–406.
87. Johnston KC, Hall CE, Kissela BM, *et al*. Glucose regulation in acute stroke patients (grasp) trial: a randomized pilot trial. *Stroke* 2009;40(12)3804–3809.
88. Whitmer RA, Karter AJ, Yaffe K. *et al*. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301(15):1565–1572.
89. Moghissi ES, Korytkowski MT, DiNardo M, *et al*. American Association of Clinical Endocrinologists and American Diabetes Association onsensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–1131.
90. Morgenstern LB, Hemphill 3rd JC, Anderson C, *et al*. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke* 2010;41:2108–129.
91. UKPDS group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes ukpds 34). *The Lancet* 1998;352:854–865.
92. Dormandy JA, Charbonnel B, Eckland DJ, *et al*. Secondary prevention of macrovascular events in patients with type 2 diabetes in the proactive study (prospective pioglitazone clinical trial in macrovascular events): A randomised controlled trial. *Lancet* 2005;366:1279–1289.
93. Bhatt DL, Marso SP, Hirsch AT, *et al*. Amplified benefit of Clopidogrel versus Aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002;90(6):625–628.
94. Diener PHC, Bogousslavsky PJ, Brass PLM, *et al*., Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *The Lancet* 2004;364(9431)331–337.
95. Bhatt DL, Fox KAA, Hacke W, *et al*. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354(16):1706–1717.
96. Furie KL, Kasner SE, Adams RJ, *et al*. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227–276.
97. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (caprie). *The Lancet* 1996;348:1329–39.
98. Adams Jr HP, delZoppo G, Alberts MJ, *et al*. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 2007;115:e478–534.

99. Standards of medical care in diabetes—2014ADA guidelines for management of diabetes,with a review of the evidence. *Diabetes Care* 2014;37(Suppl 1).
100. Cushman WC, Evans GW, Byington RP, *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585.
101. Anushka P. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *The Lancet* 2007;370:829–840.
102. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003;51(5 Suppl Guidelines):S265–S280.
103. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo controlled trial. *The Lancet* 2003;361:2005–2016.
104. Grundy SM, Cleeman JI, Merz CN, *et al*. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. *Circulation* 2004;110:227–239.
105. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine* 2007;146(12)857–867.
106. Connolly SJ, Ezekowitz MD, Yusuf S. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151.
107. Hsieh F, Lo WC, Lin HJ, *et al*. Significant Synergistic Effect Of Peroxisome Proliferator–Activated Receptor C-2821t And Diabetes On The Risk Of Ischemic Stroke. *Et Al*. *Diabetes Care* 2009;32:2033–2035.
108. Sone H, Tanaka S, Iimuro S, *et al*. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). *Diabetologia* 2010;53:419–428.
109. The Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEADtrial. *Arch Intern Med* 2010;170:1566–1575.
110. Kearney PM, Blackwell L, Collins R, *et al*. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117–125.
111. Walter N. Kernan WN, *et al*. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2014;45:00-00.