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REVIEW

Diabetes mellitus and stroke: A clinical update

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Abstract

Cardiovascular disease including stroke is a major complication that tremendously increases the morbidity and mortality in patients with diabetes mellitus (DM). DM poses about four times higher risk for stroke. Cardio-metabolic risk factors including obesity, hypertension, and dyslipidaemia often co-exist in patients with DM that add on to stroke risk. Because of the strong association between DM and other stroke risk factors, physicians and diabetologists managing patients should have thorough understanding of these risk factors and management. This review is an evidence-based approach to the epidemiological aspects, pathophysiology, diagnostic work up and management algorithms for patients with diabetes and stroke.

Key words: Diabetes mellitus; Stroke; Metabolic memory; Cardiovascular disease; Glycaemic management

Core tip: With the current global prevalence of more than 415 million, diabetes mellitus (DM) poses very high risk for cardiovascular diseases including stroke. Associated risk factors for stroke such as obesity, hypertension and dyslipidaemia are also high among DM cases especially in those with type 2 diabetes that further increases stroke risk. Thorough understanding of the epidemiology, pathophysiology and management options for patients with DM and co-morbidities is imperative for a rational medical practice among health-care professionals. This review updates a scientific approach to patients with diabetes and stroke.

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INTRODUCTION

Diabetes mellitus is a major risk factor for cardiovascular disease (CVD) including stroke. In 2015, the global prevalence of diabetes was estimated to be 415 million adults, with 12% of global expenditure (US$ 673 billion) on health spent for diabetes care alone[1]. Steady increase in the incidence of type 2 diabetes mellitus (T2DM) related to adverse eating habits, obesity and inadequate physical activity resulted in an exponential rise in diabetes-related cardiovascular morbidity worldwide in recent years. This trend is expected to escalate further with the improvement in life expectancy from advancements in science, technology and health-care resources that resulted in a sharp rise in the proportion of older individuals in the global population with higher prevalence of T2DM and hypertension. World Health Organization's current estimate of 900 million people aged ⩾ 60 years (12% of global population in 2015) is expected to cross 2 billion by 2050 (22% of world population), with 80% of these individuals in the low- and middle-income countries would catalyze the explosiveness of this alarming situation[2].

Being a disease mainly associated with lifestyle, patients with T2DM usually have additional risk factors for stroke such as obesity, hypertension and dyslipidaemia that multiplies the vascular risk in these patients[3]. Type 1 diabetes mellitus (T1DM) also increases the stroke risk although to a lesser degree. Management of diabetes immediately after a stroke and in the long-term follow up period poses significant challenges to clinicians. Inappropriate management of diabetes also increases immediate and long-term morbidity and mortality associated with stroke, and significantly elevates the risk for recurrent strokes[4]. We outline the evidence base for the epidemiological aspects, pathophysiology, diagnostic work up and management algorithms for diabetes and stroke to help clinicians for a rational approach to patients through this comprehensive article.

DIABETES AND STROKE: EPIDEMIOLOGY

Globally, stroke mortality rates have fallen, but stroke incidence and its sequelae have significantly increased over the last three decades[5,6]. Diabetes is a recognized independent risk factor for stroke and is associated with higher morbidity and mortality[7-9]. Table 1 summarises the results of relevant prospective studies demonstrating the relative risk of ischaemic stroke in different diabetes populations worldwide[10-20]. Cardiometabolic risk factors including obesity, hypertension, and dyslipidaemia often co-exist with T2DM and can contribute to the higher reported relative stroke risks when compared to patients with similar risk profile without diabetes[8,21-23].

Table 1 Risk of stroke in diabetes mellitus from different study populations

Study population	Follow-up (yr)	Relative risk (95%CI), gender
Framingham study, 5209 persons, 30-62 years old[10]	20	2.5 (M) 3.6 (F)
Honolulu Heart Program, 7598 men, 45-70 years old[11]	12	2.0 (1.4-3.0)
United States, Nurse Study, 116177 women, 30-55 years old[12]	8	3.0 (1.6-5.7)
Finland, 1298 persons, 65-74 years old[13]	3.5	1.36 (0.44-4.18) M 2.25 (1.65-3.06) F
Sweden, 241000 persons, 35-74 years old[14]	8	4.1 (95%CI: 3.2-5.2) M 5.8 (95%CI: 3.7-6.9) F
United States (ARIC), 15792 persons, 45-64 years old[15]	6-8	2.22 (1.5-3.2)
United Kingdom, 7735 men, 40-59 years old[16]	16.8	2.27 (1.23-4.20)
Renfrew/Paisley, Scotland, 15406 person, 45-64 years old[17]	20	1.52 (0.72-3.21) M 2.83 (1.63-4.90) F
Oldmsted County, Minnesota, 9936 persons, 40-70 years old[18]	15	3.5
United States, Hispanics, 503 persons, 70-90 years old[19]	3.5	3.5 M 5.0 F
Asia, Australia, New Zealand, 161214 persons[20]	5.4	2.09 2.49 Asian population

M: Male; F: Female.

CLINICAL PATTERN OF STROKE IN PATIENTS WITH DIABETES

There are clear differences in stroke patterns between patients with diabetes and those without diabetes. Patients with diabetes have a higher proportion of ischaemic stroke compared to haemorrhagic strokes, and lacunar infarcts (*i.e.*, small 0.2 to 15 mm, non-cortical infarcts) is the most common stroke type. This may be due to the higher prevalence of microvascular disease and the co-existence of hypertension seen in this patient group[24-26]. Table 2 summarises prospective studies highlighting stroke patterns and risk factors identified in patients with diabetes. Prognostic features also differ from normal stroke population as diabetes is associated with an increased risk of subsequent strokes, greater functional disability, longer in-hospital stay, and increased mortality[8,34]. A higher risk of developing stroke-related dementia has also been reported[35].

PATHOPHYSIOLOGICAL CONSIDERATIONS

Hyperglycaemia

It is now evident hyperglycaemia increases oxidative

Table 2 Stroke patterns and risk factors in diabetes *vs* non-diabetes group[1]

Investigators, stroke type	Stroke study population	Stroke patterns diabetes *vs* non-diabetes	Significant stroke risk factors in diabetes
Jørgensen *et al*[27], 1994, all strokes	233 diabetes 902 non-diabetes	ICH 1% *vs* 9% Infarct 60% *vs* 68%	Hypertension
Olsson *et al*[28], 1990, all strokes	121 diabetes 584 non-diabetes	ICH 6% *vs* 9% Infarct 59% *vs* 55%	Heart failure, ischaemic heart disease
Kiers *et al*[29], 1992, all strokes	27 diabetes 100 non-diabetes	ICH 19% *vs* 21% Infarct N/A	N/A
Weir *et al*[30], 1997, all strokes	61 diabetes 750 non-diabetes	ICH 7% *vs* 14% Infarct N/A	Hypertension, hyperglycaemia
Megherbi *et al*[31], 2003, all storkes	937 diabetes 3544 non-diabetes	ICH 8.5% *vs* 11.5% Infarct 78% *vs* 72%	Hypertension
Arboix *et al*[32], 2005, ischaemic strokes	393 diabetes 1447 non-diabetes	Infarct 76% *vs* 51%	Ischaemic heart disease, previous ischaemic stroke, dyslipidaemia
Hankey *et al*[33], 2013, all strokes	9795 diabetes	ICH 10% Infarct 82%	Hypertension, previous ischaemic stroke, ischaemic heart disease, nephropathy, high LDL cholesterol

[1]Prospective series reported in the literature. ICH: Intracerebral haemorrhage; LDL: Low-density lipoprotein; N/A: Not available.

stress leading to several pathological processes involved in diabetes-related microvascular complications[36]. Hyperglycaemia-induced overproduction of reactive oxygen species (ROS) inhibits the action of glyceraldehyde 3-phosphate dehydrogenase (GADPH), a key enzyme in glycolysis. When free radicals induce DNA strand break, ROS activates the DNA repair enzyme Poly(ADP-ribose) polymerase (PARP). Active PARP then modifies GAPDH and inhibits its activity. This results in the accumulation of glycolytic intermediates upstream of GAPDH which drive 5 pathogenic pathways contributing to endothelial dysfunction and diabetes complications: (1) polyol pathway flux; (2) increased formation of advanced glycation end products (AGEs); (3) increased expression of receptors for AGEs; (4) activation of protein kinase C isoforms; and (5) overactivity of hexosamine pathway[36].

Vasculopathy induced by chronic hyperglycaemia related endothelial damage results in acceleration of atherosclerosis inherent to diabetes. Therefore, higher prevalence and incidence of cardiovascular disease including stroke are common in the diabetic population.

Metabolic memory

The term "metabolic memory" is derived from the findings of DCCT/EDIC study and describes how the beneficial effects of immediate intensive treatment for hyperglycaemia is maintained for several years, regardless of future course of glycaemia[37,38]. More recent evidence indicates hyperglycaemia-induced ROS production triggers persistent epigenetic changes in nuclear factor-κB (NF-κB) within endothelial cells despite return to euglycaemic state. NF-κB mediates expression of inflammatory genes[39]. Epigenetic changes involve chromatin remodeling and changes in levels of gene expression[40]. This suggests even short-term hyperglycaemic spikes have a substantial impact on endothelial dysfunction independent of long-term glycaemic control. Switching off the metabolic memory effect of hyperglycemia-induced ROS is an important strategy in the prevention of cardiovascular complications related to diabetes.

Therefore, early management of hyperglycaemia in new onset diabetes should be advocated to halt the hyperglycaemia-induced pathological processes described earlier[36]. Unfortunately, maintaining good glycaemic control still does not prevent the progression of complications. So, new therapeutic strategies are being considered to prevent the overproduction of free radicals[39,41].

Insulin resistance

Insulin resistance plays a major role in the pathology of cardiovascular disease. In the context of excess adipose tissue, insulin is unable to suppress lipolysis activity, which results in free fatty acid (FFA) mobilization. The influx of FFA inhibits insulin stimulated peripheral glucose uptake in the liver, skeletal muscle, and other organs. In the vascular endothelial cells, FFA influx leads to mitochondrial overproduction of ROS, which activates the same pathogenic processes as hyperglycaemia. Increased FFA release also results in an adverse lipid profile characterized by raised triglycerides, reduced high-density lipoprotein cholesterol, and increased levels of small dense low-density lipoprotein (LDL) particles that accumulate in the arterial wall. In the context of insulin resistance, increased FFA and defective insulin signaling receptors on the macrophages contribute to macrophage apoptosis and poor clearance of LDL by phagocytosis. Consequently, necrotic breakdown of advanced lipid-rich plaques occurs, which lead to the progression of clinically relevant atherosclerotic lesions[39].

Preclinical studies have identified peroxisome-proliferator-activated receptor γ (PPARγ) in macrophage foam cells, endothelial cells, and smooth muscle cells in atherosclerotic lesions[42]. PPARγ is a nuclear receptor that regulates lipid metabolism and glucose homeostasis.

Thiazolidinediones, initially identified as drugs for T2DM by reducing systemic insulin resistance[43], are PPARγ ligands that have been shown to have protective effects against atherosclerosis progression in animal models and clinical studies[42,44]. Unfortunately, studies reviewing the use of thiazolidinediones in patients with T2DM have not consistently shown this effect[45,46]. The more recent Insulin Resistance Intervention after Stroke trial reviewed the use of the thiazolidinedione pioglitazone in patients without established T2DM but with markers of insulin resistance. Pioglitazone significantly reduced total cardiovascular events by 24% (HR = 0.76; 95%CI: 0.62-0.93, *P* =0.007), but was also associated with significant adverse drug effects contributing to nonadherence in the intervention arm[44,47].

GLYCAEMIC MANAGEMENT DURING THE ACUTE PHASE OF STROKE

Hyperglycaemia is frequently seen in acute stroke patients, irrespective of diabetes diagnosis, and it is associated with increased morbidity and mortality[30,48]. In many patients, the first diagnosis of diabetes is often made in the event of an acute stroke and especially in the elderly. Numerous observational studies have shown that acute hyperglycaemia in stroke is associated with larger infarct volumes, longer in-hospital stay, poor functional recovery, and increased 30-d mortality[33].

There is limited evidence to suggest active glucose reduction with intravenous insulin therapy improves stroke outcomes[49,50]. The largest efficacy trial to date, the United Kingdom Glucose Insulin in Stroke Trial, showed no difference in mortality or functional outcomes in patients with mild to moderate blood glucose elevations (median 7.8 mmol/L). Episodes of hypoglycaemia were also observed in 41% of subjects in the treatment arm. Therefore, the use of insulin infusion regimens with mild to moderate hyperglycaemia is not advisable. Current guidelines recommend maintaining blood glucose levels in range of 140-180 mg/dL (7.8-10.0 mmol/L), and it is common practice to use intravenous glucose/potassium/insulin (GKI) in the first 24 h after stroke[50-52].

The evidence of glycaemic management in the following days after a stroke is less clear as enteral feeding and oral intake can cause fluctuations in post-prandial glucose excursions. No randomised, prospective intervention studies have proven insulin administration for diurnal glycaemic variability translates to clinical benefits[53,54]. The Heart2D trial specifically reviewed the impact of prandial glucose spikes after an acute myocardial infarction and found that subcutaneous insulin regimens targeting prandial *vs* fasting glycaemic control in diabetes subjects did not result in any differences in risk for future cardiovascular events (HR = 0.98, 95%CI: 0.8-1.21)[54]. The use of subcutaneous or intravenous insulin or oral agents will need to be balanced with the clinical presentation and risk of hypoglycemia[52].

LONG-TERM GLYCAEMIC CONTROL

There is reasonable evidence to suggest a period of intensive glycaemic control results in sustained reduction of microvascular complications in those with T1DM and T2DM because of the effects on metabolic memory[38,41,55]. However, it is less clear how beneficial long-term glycaemic control is on cardiovascular outcomes including stroke[55-59].

The DCCT/EDIC study showed that intensive glycaemic control resulted in significant reduction in cardiovascular events in recently diagnosed T1DM subjects[38]. Study patients without any cardiovascular risk factors who were treated in the intensive arm had a 57% reduction in major cardiovascular disease outcomes during the 17 years of follow-up. This study suggested poor glycaemic control is associated with increased cardiovascular risk and intensive treatment reduces such risk in individuals with T1DM. Subsequent follow-up in the DCCT/EDIC cohort, now 27 years, demonstrates the continuing importance of early optimal glycaemic control with reduced overall mortality risk observed in the intensive group (*P* = 0.045), albeit with a small absolute risk reduction (approximately 1/1000 patient years)[58].

The increase and early risk of cardiovascular disease in T1DM has been well-documented in the literature. Even with early institution of intensive glycaemic control, its prevention and management require target-driven optimisation of individual cardiovascular risk factors (dyslipidaemia, hypertension, hypercoagulability, renal impairment). However, the specific risks toward cardiovascular disease in the T1DM population still needs to be elucidated, and active research in this patient group will be important in determining future clinical care as emphasized by the current AHA/ADA scientific statement on T1DM and cardiovascular disease[60].

The clinical relevance of glycaemia course in early diabetes diagnosis was further reviewed in T2DM. The delayed benefits of intensive glycaemic therapy observed in the DCCT/EDIC study was also seen in the 10-year follow-up of UKPDS. Newly diagnosed T2DM subjects in the intensive arm had a reduction in microvascular complications (15%, *P* = 0.01), myocardial infarction (15%, *P* = 0.01), and all-cause mortality (13%, *P* = 0.007). Stroke incidence, however, did not decline[55].

Since then, several studies addressed whether the degree of glycaemic control improved longer-term cardiovascular outcomes. The Veterans Affairs Diabetes Trial (VADT) showed intensive glycaemic control (1.5% HbA_{1c} reduction) was not associated with any significant difference in cardiovascular outcomes or in the rate of all-cause mortality (HR = 1.07; 95%CI: 0.81-1.42, *P* = 0.62) in poorly-controlled (baseline mean HbA1c 9.4%) veterans with established T2DM (mean, 11.5 years)[61].

To further evaluate the effects of lowering glucose to near-normal levels on cardiovascular outcomes, Action to Control Cardiovascular Risk in Diabetes (ACCORD)

Table 3 Blood glucose targets for non-pregnant adults with diabetes[1]

More stringent target (< 6.5%)
Short diabetes duration
Long life expectancy
T2DM treated with lifestyle or metformin only
No significant CVD/vascular complications
Less stringent target (< 8.0%)
Severe hypoglycaemia history
Limited life expectancy
Advanced microvascular or macrovascular complications
Extensive comorbidities
Long-term diabetes in whom general HbA1c targets are difficult to attain
Targets may be individualized based on:
Age/life expectancy
Comorbid conditions
Diabetes duration
Hypoglycaemia status
Individual patient considerations

[1]More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycaemia. CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; HbA1c: Glycated hemoglobin.

and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials were performed on subjects with long-standing T2DM (median 10 years duration) and already established cardiovascular risk[56,57]. Both ACCORD and ADVANCE did not demonstrate that intensive glycaemic control [HbA_{1c} < 42 mmol/mol (6.0%) and HbA_{1c} ⩽ 48 mmol/mol (6.5%) respectively] in the first few years significantly reduced cardiovascular events including strokes. Intensive therapy was associated with no risk reduction in non-fatal strokes in ADVANCE (HR = 0.97; 95%CI: 0.81-1.16) and a nonsignificant increase risk in ACCORD (HR = 1.06; 95%CI: 0.75-1.50, *P* = 0.74). The ACCORD trial also identified a clear difference in mortality within the first two years and was terminated early after demonstrating an increase in total (22%) and cardiovascular (35%) mortality rates in the intensive-therapy group[56].

Finally, a meta-analysis performed on 27,049 participants involved in UKPDS, ACCORD, ADVANCE, and VADT suggested a small reduction in major cardiovascular events (HR = 0.91, 95%CI: 0.84-0.99) but no difference in cardiovascular (HR 1.10, 95%CI: 0.84-1.42) or all-cause (HR = 1.04, 95%CI: 0.90-1.20) mortality[62]. These studies tell a cautionary tale and underscore how active intensification of glycaemic control can cause harm with early, increase mortality, particularly in T2DM patients with pre-existing cardiovascular disease.

Rather than treating a single factor, intensive intervention should include multiple risk factors that can influence cardiovascular outcomes and mortality. In support of this, the Steno-2 Study showed long-term (mean, 7.8 years), focused intervention for multiple risk factors (hyperglycaemia, hypertension, dyslipidaemia, BMI > 25, smoking) led to reduction of cardiovascular events among patients with established T2DM and microalbuminuria[63].

Table 4 Relative risk for ischaemic stroke incidence dependent on history of hypertension and diabetes at baseline[64]

Variables	Relative risk (95%CI)
Hypertension only (sBP 140-159 mmHg)	1.29 (1.13-1.46)
Hypertension only (sBP ⩾ 160/95 mmHg)	1.93 (1.48-4.16)
Diabetes only	2.48 (1.48-4.16)
Diabetes and hypertension (sBP 140-159 mmHg)	4.26 (2.90-6.25)
Diabetes and hypertension (sBP ⩾ 160 mmHg)	4.90 (3.87-6.21)

sBP: Systolic blood pressure.

There are several conclusions that can be inferred from these large, well-documented studies. Establishing good glycaemic control is certainly important in reducing diabetes complications, but there is no justification for targeting glucose levels to near-normal physiological parameters. Such an approach would not benefit patients with long-standing diabetes and established cardiovascular disease. HbA_{1c} reduction does not appear to be equally relevant in T2DM compared to T1DM in reducing stroke outcomes. The most appropriate target for HbA_{1c} should remain 53 mmol/mol (7%) with some caveat towards individualised targets as based on ADA guidelines summarised in Table 3[59]. More stringent targets may be appropriate, but requires an assessment to balance the expected benefits with the increased rates of adverse outcomes. Ultimately, the perception of diabetes management extends from hyperglycaemia and insulin resistance to considering other aspects of metabolic disorder which contribute to cardiovascular disease.

MANAGEMENT OF COMORBID CONDITIONS IN PATIENTS WITH DIABETES AND STROKE

Hypertension

Hypertension is a potent, treatable risk factor for stroke and more so in those with diabetes. Table 4 shows relative risk of stroke in patients with diabetes, hypertension or both[64]. In the DCCT/EDIC trial, higher HbA_{1c} was associated with a 25% increased risk of hypertension at EDIC follow-up (HR = 1.25; 95%CI: 1.14-1.37). However, intensive glycaemic therapy only reduced long-term risk of hypertension by 24% (HR = 0.76; 95%CI: 0.64-0.92). This suggests that standard cardiovascular risk factors gain more importance as glycaemic control improves[65].

Multiple studies have shown blood pressure (BP) control is important in reducing stroke risk in subjects with diabetes. In the UKPDS, T2DM patients in the tight control arm had a significantly lower BP (144/82 mmHg) compared with those in the standard control arm (154/87 mmHg) and this was associated with a

44% reduction in stroke[55].

Most guidelines, including AHA/ASA, recommend a BP target of < 140/90 mmHg in patients[66-68]. Lower targeted BP values have been evaluated with promising cardiovascular benefits but limited by adverse side effects, at least in diabetic patients at high risk of a cardiovascular event. The ACCORD BP trial reported intensive systolic BP (sBP) control to 120 mmHg, compared with a goal of 140 mmHg, among T2DM patients was associated with a significant reduction in total stroke (HR = 0.59; 95%CI: 0.39-0.89, P = 0.01) and nonfatal stroke (HR = 0.63; 95%CI: 0.41-0.96, P = 0.03)[69]. However, the intensive arm also had a significant number of adverse events. A meta-analysis in subjects with T2DM analyzed less modest BP targets than ACCORD and showed targeting a systolic BP ⩽ 135 mmHg resulted in a 17% risk reduction for stroke. Further meta-regression analysis showed continued risk reduction for stroke with a sBP of < 120 mmHg but even at levels < 130 mmHg there was a 40% increase in serious adverse events without any other cardiovascular benefits besides stroke[70].

There is enough evidence to suggest an antagonist of the renin-angiotensin system has cardiovascular benefits[71,72]. The Heart Outcomes Prevention Evaluation study reviewed the use of an ACE-inhibitor in high risk patients for cardiovascular event[71]. In the subgroup of patients with diabetes, there was a 25% reduction in primary outcome of MI, stroke, and cardiovascular mortality (95%CI: 12%-36%; P = 0.0004) in the ACE-inhibitor treated arm.

Overall, these studies suggest hypertension management (BP < 140/90 mmHg) improves stroke risk in subjects with diabetes independent of glycaemic control. Young people with diabetes and those with microalbuminuria should aim for BP control ⩽ 130/80 mmHg. A more aggressive approach targeting systolic BP < 120 mmHg in patients already at high risk for a cardiovascular event can be limited by adverse side effects and does not translate to further reduction in cardiovascular outcomes besides stroke.

Pharmacotherapy should include an antagonist of the renin-angiotensin system (unless contraindicated), either an ACE-inhibitor or an angiotensin-receptor blocker but not both[67,73]. Other common antihypertensive agents include calcium channel antagonists, beta blockers and diuretics. AHA/ASA guidelines recommend the choice of antihypertensive be individualised to the patient with specific consideration based on clinical indication[68].

Obesity

Obesity is a growing epidemic in developed and developing countries. The proportion of adults with a body mass index (BMI) ⩾ 25 kg/m^2 has increased from 28.8% (95%CI: 28.4-29.3) in 1980 to 36.9% (36.3-37.4) in 2013 in men and from 29.8% (29.3-30.2) to 38.0 (37.5-38.5) in women[74]. Obesity increases the risk of T2DM, ischaemic heart disease, stroke, and mortality[75-77]. It is also associated with the metabolic syndrome, which is a constellation of cardiovascular factors including dyslipidaemia, hypertension, hyperinsulinaemia, and insulin resistance[78].

Weight reduction of ⩾ 5% of initial body weight improves control of diabetes and hypertension, reduces risk of diabetes and hypertension incidence, and reduces other metabolic risk factors[79,80]. The difficulties faced in any weight loss intervention is ensuring this can translate to long term health benefits. The Look AHEAD research group evaluated the role of Intensive lifestyle intervention which included a healthy diet with a calorie goal of 1200 to 1800 kcal per day (with < 30 % of calories from fat and > 15% from protein) and at least 175 min of moderate-intensity physical activity per week in contributing to weight loss[81]. They observed that intensive lifestyle intervention resulted in greater sustained weight loss than in the control group (8.6% *vs* 0.7% at 1 year; 6.0% *vs* 3.5% at study end). However, this weight loss did not reduce the rate of cardiovascular morbidity and mortality in overweight or obese adults with T2DM at 10-year follow-up (HR = 0.95; 95%CI: 0.82-1.09; P = 0.51).

The degree of long-term weight reduction may be important to overall cardiovascular benefit. The Swedish Obese Subjects study had shown cardiovascular risk factor improvement over 10 years required sustained, large (*i.e.,* 10-40 kg) weight loss that could not be achievable with intensive lifestyle intervention alone[82,83]. Metabolic surgery has been associated with reduced number of cardiovascular deaths (HR = 0.47; 95%CI: 0.29-0.76; P = 0.002) and reduced total first incidence (fatal or nonfatal) of myocardial infarction or stroke (HR = 0.67; 95%CI: 0.54-0.83; P < 0.001)[84].

Most efforts to achieve sustainable weight reduction with lifestyle intervention and medical therapy have been unsuccessful. Lifestyle intervention still conveys other potential benefits by improving physical functioning and quality of life; therefore, it is integral for good health outcomes[3]. Pharmacotherapy for glucose management should consider weight loss or weight neutral medications in preference to those promoting weight gain. Concomitant medications should be rationalized to minimize weight gain[85]. Metabolic surgery for obese individuals with T2DM has shown cardiovascular benefits and is an important clinical consideration in obese (BMI > 40) T2DM individuals[86]. Identifying new pathways leading to safe and effective weight reduction continues to be sought. In recent years, there has been focus in gene variants predisposing individuals to type 2 diabetes and obesity[87]. Investigators from the Look AHEAD trial reported how genetic variants can help predict cardiovascular morbidity and mortality[88]. Such information on genetic studies continues to be garnered and can potentially allow for new targets for pharmaceutical intervention in the future[87,88].

Dyslipidaemia

The Heart Protection Study and Collaborative Atorvastatin Diabetes Study have demonstrated how statins

Table 5 Trials of statin therapy with individual participant data and relative reduction of cardiovascular event rate including stroke

Study	Randomized participants, age	Type of Prevention	Diabetes participants (%)	Intervention (mg/d)	Follow-up (yr)	Relative reduction of CVE rate
4S[92,93]	4444, 35-70 years old	Secondary	202 (4.50%)	S20-40	5.4	37%
CARE[94,95]	4159, 21-75 years old	Secondary	586 (14.10%)	P40	5.0	25%
LIPID[91,96]	9014, 31-75 years old	Secondary	1077 (11.9%)	P40	6.1	21%
ALLHAT-LLT[97]	10355, ⩾ 55 years old	Primary	3638 (35%)	P40	4.8	11%
HSPC[89]	20536, 40-80 years old	Primary, secondary	5963 (29%)	S40	4.8	22% total 33% primary
ASCOT-LLA[98,99]	19342, 40-79 years old	Primary	2532 (13%)	A10	3.3	23%
CARDS[90]	2838, 40-75 years old	Primary	2838 (100%)	A10	3.9	37%

CVE: Cardiovascular event; S: Simvastatin; P: Pravastatin; A: Atorvastatin.

improve cardiovascular risk in patients with diabetes by lowering LDL cholesterol[89,90]. Stroke incidence was significantly higher among those with diabetes and impaired fasting glucose, and treatment of dyslipidaemia was more effective for secondary prevention in these groups compared to subjects with normal fasting glucose[91]. Statin therapy should now be considered routinely for all diabetes patients beyond 40 years of age and earlier in high risk groups, irrespective of their initial cholesterol concentrations. Table 5 summarises major clinical trials showing the benefits of statin therapy in diabetes participants[92-99].

Ezetimibe with statin therapy can provide additional cardiovascular benefits as it reduces LDL cholesterol levels by a further 24%. A recent study showed cardiovascular benefits with this dual therapy particularly in patients with a recent acute coronary syndrome[100]. The addition of fibrate has not been shown to significantly improve cardiovascular outcomes but it can be considered in a subgroup of T2DM subjects with mixed dyslipidaemia[101].

Atrial fibrillation

Atrial fibrillation (AF) is associated with a 4- to 5-fold increase risk for ischaemic stroke[102]. In patients with AF, clinical predictive risk scores have been useful in stratifying patients for anticoagulation therapy. The primary example is the CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ⩾ 75 years (doubled), diabetes, stroke/transient ischaemic attack/thromboembolism (doubled), vascular disease, age 65-74 years, sex (female)] which has been recommended in clinical practice guidelines[103,104].

Diabetes has been associated with an increased risk of developing persistent AF[105]. A meta-analysis reviewed this association and reported that approximately 25% of diabetes patients will have AF[106]. The relevance of diabetes with AF on stroke risk is not clearly determined, although a diagnosis of diabetes is included in the CHA_2DS_2-VASc score[107]. To ascertain whether aspects of diabetes influence risk, a study reviewed the role of glycaemic control and duration of diabetes on stroke risk in subjects from the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) cohort during a period off anticoagulation therapy[108]. The study reported an increased rate of ischaemic stroke with longer duration of diabetes (adjusted HR = 1.74, 95%CI: 1.10-2.76) but not with increased HbA1c. Further studies reviewing aspects of diabetes may prove useful in stratifying stroke risk in AF patients and refining current stroke risk models.

Clinical trials and practice-based experience with newer oral anticoagulants (NOAC) such as rivaroxaban, edoxaban, apixaban and dabigatran in recent years showed beneficial effects in prevention of stroke in patients with AF. Ease of administration without regular monitoring, better patient adherence, and probable improved efficacy and safety make NOAC more favourable to physicians in treating AF and venous thromboembolism in the present day clinical practice[109]. Although there is no data to show higher efficacy of NOAC in comparison with warfarin for stroke prevention in patients having AF with or without diabetes, better patient adherence and therefore, possibly improved clinical outcomes are shown in recent studies[110,111].

Heart failure

Incident heart failure is also associated with increased risk of ischaemic stroke, even without atrial fibrillation[112,113]. Heart failure is common in subjects with diabetes that is associated with higher risk for stroke. A recent study demonstrated heart failure patients with diabetes and no AF was associated with a 27% increased relative risk of ischaemic stroke[114]. While this study tried to stratify the degree of risk by duration of diabetes, no clear relationship could be elucidated; this may be attributed to the limited sample sizes in the subgroups and the short follow-up time.

The CHA_2DS_2-VASc score, as discussed previously, is applied for stroke risk stratification in atrial fibrillation. A study reviewed CHA_2DS_2-VASc score in patients with heart failure without atrial fibrillation and found that the absolute risk of thromboembolic complications was higher in this group compared to patients with concomitant AF[115]. Currently, patients with heart failure and no AF are not routinely recommended to take antiplatelet or anticoagulation therapy. If further studies support the finding of increased stroke and thromboembolic disease in heart failure patients with diabetes, consideration of anticoagulation in a subgroup of these patients may be

clinically relevant.

Antiplatelet therapy

Antiplatelet therapy significantly reduces recurrent cardiovascular events outcomes among patients with diabetes. The CAPRIE trial demonstrated clopidogrel is superior to aspirin in reducing cardiovascular events and causing few bleeding complications in diabetic patients with established atherosclerotic disease[116]. Unfortunately, these clinical benefits do not extend to primary prevention. Short-term dual therapy with Aspirin and Clopidogrel improves stroke outcomes in patients presenting with an acute TIA or minor stroke[117]. The use of long-term dual therapy is still unclear; while there may be a relative risk reduction of stroke this is unbalanced by the increased haemorrhagic risk[118].

CAROTID ENDARTERECTOMY

Some patients with symptomatic carotid stenosis would benefit from surgical intervention. Carotid endarterectomy appears to reduce the risk of stroke in diabetic patients with severe stenosis (*i.e.,* $\geqslant$ 70% stenosis) on long-term follow up[119]. Mild to moderate stenosis (*i.e.,* < 70%) was not associated with such clinical benefits. However, a recent study demonstrated that diabetes with chronic complications increased the risk for myocardial infarction, stroke, perioperative infections, longer hospital stay and mortality compared to nondiabetics treated with carotid endarterectomy although diabetics without complications did not show this risk[120].

DIABETES AND STROKE: RECENT DEVELOPMENTS

With the emergence of newer oral and injectable anti-diabetic agents in the management of T2DM, the use of older agents with hypoglycaemia risk such as insulin and sulphonylureas as well as glinides is less favoured by physicians recently. While metformin and pioglitazone have demonstrated cerebrovascular benefit in the insulin resistant population, the GLP-1 analogues have proved their efficacy in cardiovascular outcomes along with weight and blood pressure reduction. The EMPA-REG Trial showed significant cardiovascular benefit with weight and blood pressure reduction though there was a marginal signal of higher stroke rates[121]. Improvement of renal outcomes was another promising benefit of empagliflozin use demonstrated recently that may translate into better cardiovascular outcomes in T2DM patients with diabetic nephropathy[122].

The newer cardiovascular outcome trials LEADER and SUSTAIN-6 using GLP-1 analogues have shown reduction in stroke and cardiovascular event risk as well as lower nephropathy and hypoglycaemia rates in patients with longstanding diabetes and very high cardiovascular risk adding to the armamentarium of agents with low risk of hypoglycemia or weight gain[123,124]. Technological advances in insulin delivery and glucose monitoring have improved the prospects of glycaemic management of T1DM and may reduce the future risk of stroke.

The United Kingdom National Clinical Guidelines for Stroke have been recently updated and provide an elaborate care plan for patients with stroke[125]. Individualised care plan for stroke patients depending on the clinical scenario should be tailored with considerations of disease co-morbidities including diabetes. An up to date scientific evidence should always lead the clinicians to optimise such care plan.

CURRENT RECOMMENDATIONS FOR MANAGEMENT OF CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH DIABETES

The Joint European-American diabetes guidelines has given a nice illustration of the target HbA1c in different scenarios[126]. While aiming for a tighter control in those who are young, fit, and very motivated with recent onset diabetes and on agents with no risk of hypoglycemia, a less stringent target should be adopted for those who are frail, elderly and with long duration of diabetes on agents causing hypoglycemia as well as those with cognitive decline. Randomised controlled trials ACCORD and ADVANCE have shown that it is safe to aim for a HbA1c of 53 mmol/mol (7.0%) in those with long duration of diabetes and established cardiovascular disease rather than tighter control[56,57]. An evidence-based recommendation for management of patients with cardiovascular risk factors is summarised in Table 6[127-129].

CONCLUSION

The incidence of stroke and its sequelae are on the rise. Patients with diabetes are particularly at a significantly higher risk of stroke and have a higher mortality. Initiating good glycaemic control at first diagnosis of diabetes, irrespective of type, is essential for sustained cardiovascular benefits (*i.e.*, metabolic memory) and for the reduction of hyperglycaemia-induced pathogenic processes implicated in atherosclerotic vascular disease. However, long term tight glycaemic control has not been shown to improve cardiovascular outcomes and therefore, subsequent management should focus on modifiable cardiovascular risk factors. We have summarised a few recommendations with relevant supporting literature to help clinicians to approach patients with diabetes and stroke as outlined in Table 6. As the population is ageing, the "time-bomb" of diabetes in older people is becoming more and more obvious. The economic, physical, medical, nursing, and psycho-social implications of diabetes and stroke will be immense

Table 6 Recommendations for cardiovascular risk factor management in patients with diabetes

Condition	Supporting literature
Hyperglycaemia	
Targeting HbA1c < 6.5% to reduce cardiovascular events is not beneficial and is harmful when compared with a target of 7.0%	ACCORD[56], ADVANCE[57]
Hypertension	
BP < 140/90 mmHg improves risk of cardiovascular and cerebrovascular outcomes (33)	UKPDS[55]
Targeting sBP < 120 does not improve cardiovascular outcomes and is associated with increased risk of adverse side effects	ACCORD-BP[69]
Antagonist of renin-angiotensin system is associated with cardiovascular benefits	HOPE[71]
Dyslipidaemia	
All patients age > 40 yr, with or without history of atherosclerotic vascular disease, should receive statin therapy	HPSC[89], CARDS[90]
Use of ezetimibe with statin therapy can improve cardiovascular outcome in patients with a recent acute coronary syndrome and LDL > 50 mg/dL (1.3 mmol/L)	IMPROVE-IT[100]
Use of fibrates may be effective in selected patients with HDL < 34 mg/dL (0.9 mmol/L) and triglycerides > 204 mg/dL (2.3 mmol/L)	FIELD[101]
Obesity	
Intensive lifestyle intervention with diet, physical activity, and medical therapy improves quality of life and physical function	Look AHEAD[81]
Metabolic surgery has been shown to improve long-term cardiovascular outcomes	SOS[82]
Antiplatelet therapy	
Aspirin use in acute coronary syndrome treatment and in secondary prevention has been established	ISIS-2[127]
Clopidogrel use in secondary prevention reduces more cardiovascular outcomes and causes fewer bleeding complications compared to aspirin in diabetic patients	CAPRIE[116]
In patients with acute TIA or minor stroke, combination of clopidogrel and aspirin is superior to aspirin alone for reducing risk of stroke in the first 90 d without increasing risk of haemorrhage	CHANCE[117]
Use of aspirin in primary prevention has not been shown to improve cardiovascular outcomes	JPAD[128]
Low-dose aspirin use for primary prevention of cardiovascular disease in adults who have a 10% or greater 10-yr cardiovascular risk, are not at increased risk of bleeding, and are willing to take daily aspirin for at least 10 yr	USPSTF[129]

ACCORD: Action to Control Cardiovascular Risk in Diabetes; UKPDS: United Kingdom Prospective Diabetes Study; ACCORD-BP: Action to Control Cardiovascular Risk in Diabetes-Blood Pressure; HOPE: Heart Outcomes Prevention Evaluation; CARDS: Collaborative AtoRvastatin Diabetes Study; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; Look AHEAD: Look Action for HEAlth in Diabetes; CAPRIE: Clopidogrel *vs* Aspirin in Patients at Risk of Ischemic Events; CHANCE: Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events; JPAD: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; USPSTF: United States Preventive Services Task Force;; sBP: Systolic blood pressure; LDL: Low-density lipoprotein; HDL: high density lipoprotein.

in the future. Health authorities and policy makers throughout the world will need to pay special attention to the duo of diabetes and stroke to alleviate or prevent the resultant complications.

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