**Name of Journal: *World Journal of Diabetes***

**Manuscript NO: 32315**

**Manuscript Type: Review**

**Diabetes mellitus and stroke: A clinical update**

Tun NN *et al*. Diabetes mellitus and stroke

**Nyo Nyo Tun, Ganesan Arunagirinathan, Sunil K Munshi, Joseph M Pappachan**

**Nyo Nyo Tun,** **Ganesan Arunagirinathan,** Department of Endocrinology and Diabetes, Western General Hospital, the University Hospitals Edinburgh NHS Trust, Edinburgh EH2 2XU, United Kingdom

**Sunil K Munshi,** Department of Stroke Medicine, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham NG5 1PB, United Kingdom

**Joseph M Pappachan,** Department of Endocrinology and Diabetes, Royal Lancaster Infirmary, University Hospitals Morecambe NHS Trust, Lancaster LA1 4RP, United Kingdom

**Author contributions**: Pappachan JM and Munshi SK conceived the idea; Tun NN did the initial draft of the paper that was further modified by Arunagirinathan G, Munshi SK and Pappachan JM; all authors contributed to literature search and modification and revision of the paper in the final form; Pappachan JM is the guarantor of the work and takes responsibility of the accuracy of the paper.

**Conflict-of-interest statement:** None.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondence to: Dr. Joseph M Pappachan, MD, MRCP,** **Consultant** in Endocrinology and Diabetes, Department of Endocrinology and Diabetes, Royal Lancaster Infirmary, University Hospitals Morecambe NHS Trust, Ashton Road, Lancaster LA1 4RP, United Kingdom. pappachan.joseph@mbht.nhs.uk

**Telephone:** +44-1524-512482

**Fax:** +44-1524-583447

**Received:** December 31, 2016

**Peer-review started:** January 5, 2017

**First decision:** February 20, 2017

**Revised:** March 27, 2017

**Accepted:** May 3, 2017

**Article in press:**

**Published online:**

**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. Cardiometabolic 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

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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 healthcare professionals. This review updates a scientific approach to patients with diabetes and stroke.

Tun NN, Arunagirinathan G, Munshi SK, Pappachan JM. Diabetes mellitus and stroke: A clinical update. *World J Diabetes* 2017; In press

**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 healthcare 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 (WHO) 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].

**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 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 (PKC) isoforms; and (5) over-activity 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 (HDL), 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 (IRIS) 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 23% (HR 0.76; 95%CI: 0.62 to 0.93, *P* = 0.007), but was also associated with significant adverse drug effects[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 UK Glucose Insulin in Stroke Trial (GIST-UK), 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 hours 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 versus 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% HbA1c 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) 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 [HbA1c < 42 mmol/mol (6.0%) and HbA1c 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].

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. HbA1c reduction does not appear to be equally relevant in T2DM compared to T1DM in reducing stroke outcomes. The most appropriate target for HbA1c 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 HbA1c 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 mm Hg 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 mm Hg, compared with a goal of 140 mm Hg, 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 mm Hg resulted in a 17% risk reduction for stroke. Further meta-regression analysis showed continued risk reduction for stroke with a sBP of < 120 mm Hg but even at levels < 130 mm Hg 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 (HOPE) 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 mm Hg) 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 mm Hg. A more aggressive approach targeting systolic BP < 120 mm Hg 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/m2 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 minutes 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 (SOS) 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 (HSPC) and Collaborative Atorvastatin Diabetes Study (CARDS) have demonstrated how statins 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 CHA2DS2-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 CHA2DS2-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 CHA2DS2-VASc score, as discussed previously, is applied for stroke risk stratification in atrial fibrillation. A study reviewed CHA2DS2-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 (CEA) appears to reduce the risk of stroke in diabetic patients with severe stenosis (*i.e.,* ≥ 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 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.

**REFERENCES**

1. International Diabetes Federation. IDF Diabetes Atlas – 7th Edition. [accessed 2016 Dec 11]. Available from: URL: http: //www.diabetesatlas.org/key-messages.html
2. World Health Organization. Ageing and health. WHO, Geneva. 2015. [accessed 2016 Dec 11]. Available from: URL: http: //www.who.int/mediacentre/factsheets/fs404/en/
3. **Dutton GR**, Lewis CE. The Look AHEAD Trial: Implications for Lifestyle Intervention in Type 2 Diabetes Mellitus. *Prog Cardiovasc Dis* 2015; **58**: 69-75 [PMID: 25936906 DOI: 10.1016/j.pcad.2015.04.002]
4. **Maahs DM**, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, Kelly AS, Nadeau KJ, Martyn-Nemeth P, Osganian SK, Quinn L, Shah AS, Urbina E. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. *Circulation* 2014; **130**: 1532-1558 [PMID: 25170098 DOI: 10.1161/CIR.0000000000000094]
5. **Krishnamurthi RV**, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson LM, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013; **1**: e259-e281 [PMID: 25104492 DOI: 10.1016/S2214-109X(13)70089-5]
6. **Mozaffarian D**, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016; **133**: e38-360 [PMID: 26673558 DOI: 10.1161/CIR.0000000000000350]
7. **Zhu S**, McClure LA, Lau H, Romero JR, White CL, Babikian V, Nguyen T, Benavente OR, Kase CS, Pikula A. Recurrent vascular events in lacunar stroke patients with metabolic syndrome and/or diabetes. *Neurology* 2015; **85**: 935-941 [PMID: 26296518 DOI: 10.1212/WNL.0000000000001933]
8. **Shou J**, Zhou L, Zhu S, Zhang X. Diabetes is an Independent Risk Factor for Stroke Recurrence in Stroke Patients: A Meta-analysis. *J Stroke Cerebrovasc Dis* 2015; **24**: 1961-1968 [PMID: 26166420 DOI: 10.1016/j.jstrokecerebrovasdis.2015.04.004]
9. **Shah AD**, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. *Lancet Diabetes Endocrinol* 2015; **3**: 105-113 [PMID: 25466521 DOI: 10.1016/S2213-8587(14)70219-0.]
10. **Kannel WB**, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; **241**: 2035-2038 [PMID: 430798 DOI: 10.1001/jama.1979.03290450033020]
11. **Abbott RD**, Donahue RP, MacMahon SW, Reed DM, Yano K. Diabetes and the risk of stroke. The Honolulu Heart Program. *JAMA* 1987; **257**: 949-952 [PMID: 3806877 DOI: 10.1001/jama.1987.03390070069025]
12. **Manson JE**, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH. 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 [PMID: 2043016 DOI: 10.1001/archinte.1991.00400060077013]
13. **Kuusisto J**, Mykkänen L, Pyörälä K, Laakso M. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke* 1994; **25**: 1157-1164 [PMID: 8202973 DOI: 10.1161/01.STR.25.6.1157]
14. **Stegmayr B**, Asplund K. Diabetes as a risk factor for stroke. A population perspective. *Diabetologia* 1995; **38**: 1061-1068 [PMID: 8591820 DOI: 10.1007/BF00402176]
15. **Folsom AR**, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss G. 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 [PMID: 10388971 DOI: 10.2337/diacare.22.7.1077]
16. **Wannamethee SG**, Perry IJ, Shaper AG. Nonfasting serum glucose and insulin concentrations and the risk of stroke. *Stroke* 1999; **30**: 1780-1786 [PMID: 10471423 DOI: 10.1161/01.STR.30.9.1780]
17. **Hart CL**, Hole DJ, Smith GD. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley Study in Scotland. *Stroke* 2000; **31**: 1893-1896 [PMID: 10926953 DOI: 10.1161/01.STR.31.8.1893]
18. **Abu-Lebdeh HS**, Hodge DO, Nguyen TT. Predictors of macrovascular disease in patients with type 2 diabetes mellitus. *Mayo Clin Proc* 2001; **76**: 707-712 [PMID: 11444403 DOI: 10.4065/76.7.707]
19. **Aronow WS**, Ahn C. Risk factors for new atherothrombotic brain infarction in older Hispanic men and women. *J Gerontol A Biol Sci Med Sci* 2002; **57**: M61-M63 [PMID: 11773215 DOI: 10.1093/gerona/57.1.M61]
20. **Woodward M**, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, MacMahon S. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 2003; **26**: 360-366 [PMID: 12547863 DOI: 10.2337/diacare.26.2.360]
21. **Hu FB**, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, Nathan DM, Manson JE. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* 2001; **161**: 1717-1723 [PMID: 11485504 DOI: 10.1001/archinte.161.14.1717]
22. **Khoury JC**, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, Broderick JP, Kissela BM. Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. *Stroke* 2013; **44**: 1500-1504 [PMID: 23619130 DOI: 10.1161/STROKEAHA.113.001318]
23. **Karapanayiotides T**, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology* 2004; **62**: 1558-1562 [PMID: 15136681 DOI: 10.1212/01.WNL.0000123252.55688.05]
24. **Vaidya V**, Gangan N, Sheehan J. Impact of cardiovascular complications among patients with Type 2 diabetes mellitus: a systematic review. *Expert Rev Pharmacoecon Outcomes Res* 2015; **15**: 487-497 [PMID: 25824591 DOI: 10.1586/14737167.2015.1024661]
25. **Hata J**, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, Patel A, Neal B, Glasziou P, Hamet P, Mancia G, Poulter N, Williams B, Macmahon S, Chalmers J. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. *Circulation* 2013; **128**: 1325-1334 [PMID: 23926207 DOI: 10.1161/CIRCULATIONAHA.113.002717]
26. **Tuttolomondo A**, Pinto A, Salemi G, Di Raimondo D, Di Sciacca R, Fernandez P, Ragonese P, Savettieri G, Licata G. Diabetic and non-diabetic subjects with ischemic stroke: differences, subtype distribution and outcome. *Nutr Metab Cardiovasc Dis* 2008; **18**: 152-157 [PMID: 17702553 DOI: 10.1016/j.numecd.2007.02.003]
27. **Jørgensen H**, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke* 1994; **25**: 1977-1984 [PMID: 8091441 DOI: 10.1161/01.STR.25.10.1977]
28. **Olsson T**, Viitanen M, Asplund K, Eriksson S, Hägg E. Prognosis after stroke in diabetic patients. A controlled prospective study. *Diabetologia* 1990; **33**: 244-249 [PMID: 2347437 DOI: 10.1007/BF00404803]
29. **Kiers L**, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, Carlin J, Ratnaike S. Stroke topography and outcome in relation to hyperglycaemia and diabetes. *J Neurol Neurosurg Psychiatry* 1992; **55**: 263-270 [PMID: 1583510 DOI: 10.1136/jnnp.55.4.263]
30. **Weir CJ**, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ* 1997; **314**: 1303-1306 [PMID: 9158464 DOI: 10.1136/bmj.314.7090.1303]
31. **Megherbi SE**, Milan C, Minier D, Couvreur G, Osseby GV, Tilling K, Di Carlo A, Inzitari D, Wolfe CD, Moreau T, Giroud M. 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 [PMID: 12624292 DOI: 10.1161/01.STR.0000057975.15221.40]
32. **Arboix A**, Rivas A, García-Eroles L, de Marcos L, Massons J, Oliveres M. Cerebral infarction in diabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. *BMC Neurol* 2005; **5**: 9 [PMID: 15833108 DOI: 10.1186/1471-2377-5-9]
33. **Hankey GJ**, Anderson NE, Ting RD, Veillard AS, Romo M, Wosik M, Sullivan DR, O'Connell RL, Hunt D, Keech AC. Rates and predictors of risk of stroke and its subtypes in diabetes: a prospective observational study. *J Neurol Neurosurg Psychiatry* 2013; **84**: 281-287 [PMID: 23085934 DOI: 10.1136/jnnp-2012-303365]
34. **Capes SE**, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; **32**: 2426-2432 [PMID: 11588337 DOI: 10.1161/hs1001.096194]
35. **Bangen KJ**, Gu Y, Gross AL, Schneider BC, Skinner JC, Benitez A, Sachs BC, Shih R, Sisco S, Schupf N, Mayeux R, Manly JJ, Luchsinger JA. Relationship Between Type 2 Diabetes Mellitus and Cognitive Change in a Multiethnic Elderly Cohort. *J Am Geriatr Soc* 2015; **63**: 1075-1083 [PMID: 26096383 DOI: 10.1111/jgs.13441]
36. **Brownlee M**. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54**: 1615-1625 [PMID: 15919781 DOI: 10.2337/diabetes.54.6.1615]
37. **Nathan DM**, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977-986 [PMID: 8366922 DOI: 10.1056/NEJM199309303291401]
38. **Nathan DM**, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**: 2643-2653 [PMID: 16371630 DOI: 10.1056/NEJMoa052187]
39. **Giacco F**, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010; **107**: 1058-1070 [PMID: 21030723 DOI: 10.1161/CIRCRESAHA.110.223545]
40. **El-Osta A**, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, Cooper ME, Brownlee M. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *J Exp Med* 2008; **205**: 2409-2417 [PMID: 18809715 DOI: 10.1084/jem.20081188]
41. **Ceriello A**, Ihnat MA, Thorpe JE. Clinical review 2: The "metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? *J Clin Endocrinol Metab* 2009; **94**: 410-415 [PMID: 19066300 DOI: 10.1210/jc.2008-1824]
42. **Li AC**, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK. Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2000; **106**: 523-531 [PMID: 10953027 DOI: 10.1172/JCI10370]
43. **Nolan JJ**, Ludvik B, Beerdsen P, Joyce M, Olefsky J. Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *N Engl J Med* 1994; **331**: 1188-1193 [PMID: 7935656 DOI: 10.1056/NEJM199411033311803]
44. **Saremi A**, Schwenke DC, Buchanan TA, Hodis HN, Mack WJ, Banerji M, Bray GA, Clement SC, Henry RR, Kitabchi AE, Mudaliar S, Ratner RE, Stentz FB, Musi N, Tripathy D, DeFronzo RA, Reaven PD. Pioglitazone slows progression of atherosclerosis in prediabetes independent of changes in cardiovascular risk factors. *Arterioscler Thromb Vasc Biol* 2013; **33**: 393-399 [PMID: 23175674 DOI: 10.1161/ATVBAHA.112.300346]
45. **MacDonald MR**, Petrie MC, Home PD, Komajda M, Jones NP, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, Curtis PS, McMurray JJ. Incidence and prevalence of unrecognized myocardial infarction in people with diabetes: a substudy of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study. *Diabetes Care* 2011; **34**: 1394-1396 [PMID: 21562320 DOI: 10.2337/dc10-2398]
46. **Dormandy JA**, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J. 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 [PMID: 16214598 DOI: 10.1016/S0140-6736(05)67528-9]
47. **Kernan WN**, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. *N Engl J Med* 2016; **374**: 1321-1331 [PMID: 26886418 DOI: 10.1056/NEJMoa1506930]
48. **Scott JF**, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Prevalence of admission hyperglycaemia across clinical subtypes of acute stroke. *Lancet* 1999; **353**: 376-377 [PMID: 9950447 DOI: 10.1016/S0140-6736(05)74948-5]
49. **Poppe AY**, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes Care* 2009; **32**: 617-622 [PMID: 19131465 DOI: 10.2337/dc08-1754]
50. **Gray CS**, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007; **6**: 397-406 [PMID: 17434094 DOI: 10.1016/S1474-4422(07)70080-7]
51. **Ntaios G**, Papavasileiou V, Bargiota A, Makaritsis K, Michel P. Intravenous insulin treatment in acute stroke: a systematic review and meta-analysis of randomized controlled trials. *Int J Stroke* 2014; **9**: 489-493 [PMID: 24373425 DOI: 10.1111/ijs.12225]
52. **Jauch EC**, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870-947 [PMID: 23370205 DOI: 10.1161/STR.0b013e318284056a]
53. **Malmberg K**, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J, Hildebrandt P, MacLeod K, Laakso M, Torp-Pedersen C, Waldenström A. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; **26**: 650-661 [PMID: 15728645 DOI: 10.1093/eurheartj/ehi199]
54. **Raz I**, Wilson PW, Strojek K, Kowalska I, Bozikov V, Gitt AK, Jermendy G, Campaigne BN, Kerr L, Milicevic Z, Jacober SJ. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. *Diabetes Care* 2009; **32**: 381-386 [PMID: 19246588 DOI: 10.2337/dc08-1671]
55. **Holman RR**, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577-1589 [PMID: 18784090 DOI: 10.1056/NEJMoa0806470]
56. **Gerstein HC**, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]
57. **Patel A**, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560-2572 [PMID: 18539916 DOI: 10.1056/NEJMoa0802987]
58. **Orchard TJ**, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, Lachin JM. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015; **313**: 45-53 [PMID: 25562265 DOI: 10.1001/jama.2014.16107]
59. **Fox CS**, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, Deedwania P, Eckel RH, Ershow AG, Fradkin J, Inzucchi SE, Kosiborod M, Nelson RG, Patel MJ, Pignone M, Quinn L, Schauer PR, Selvin E, Vafiadis DK. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. *Circulation* 2015; **132**: 691-718 [PMID: 26246173 DOI: 10.1161/CIR.0000000000000230]
60. **de Ferranti SD**, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, Magge SN, Marx N, McGuire DK, Orchard TJ, Zinman B, Eckel RH. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation* 2014; **130**: 1110-1130 [PMID: 25114208 DOI: 10.1161/CIR.0000000000000034]
61. **Duckworth W**, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129-139 [PMID: 19092145 DOI: 10.1056/NEJMoa0808431]
62. **Turnbull FM**, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52**: 2288-2298 [PMID: 19655124 DOI: 10.1007/s00125-009-1470-0]
63. **Gaede P**, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383-393 [PMID: 12556541 DOI: 10.1056/NEJMoa021778]
64. **Hu G**, Sarti C, Jousilahti P, Peltonen M, Qiao Q, Antikainen R, Tuomilehto J. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* 2005; **36**: 2538-2543 [PMID: 16282538 DOI: 10.1161/01.STR.0000190894.30964.75]
65. **de Boer IH**, Kestenbaum B, Rue TC, Steffes MW, Cleary PA, Molitch ME, Lachin JM, Weiss NS, Brunzell JD. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. *Arch Intern Med* 2008; **168**: 1867-1873 [PMID: 18809813 DOI: 10.1001/archinternmed.2008.2]
66. **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.284427]
67. **Chamberlain JJ**, Rhinehart AS, Shaefer CF, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med* 2016; **164**: 542-552 [PMID: 26928912 DOI: 10.7326/M15-3016]
68. **Kernan WN**, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. 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**: 2160-2236 [PMID: 24788967 DOI: 10.1161/STR.0000000000000024]
69. **Cushman WC**, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575-1585 [PMID: 20228401 DOI: 10.1056/NEJMoa1001286]
70. **Bangalore S**, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011; **123**: 2799-810, 9 p following 810 [PMID: 21632497 DOI: 10.1161/CIRCULATIONAHA.110.016337]
71. **Yusuf S**, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145-153 [PMID: 10639539 DOI: 10.1056/NEJM200001203420301]
72. **Bangalore S**, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016; **352**: i438 [PMID: 26868137 DOI: 10.1136/bmj.i438]
73. **Fried LF**, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013; **369**: 1892-1903 [PMID: 24206457 DOI: 10.1056/NEJMoa1303154]
74. **Ng M**, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766-781 [PMID: 24880830 DOI: 10.1016/S0140-6736(14)60460-8]
75. **Strazzullo P**, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke* 2010; **41**: e418-e426 [PMID: 20299666 DOI: 10.1161/STROKEAHA.109.576967]
76. **Hubert HB**, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67**: 968-977 [PMID: 6219830 DOI: 10.1161/01.CIR.67.5.968]
77. **Mitchell AB**, Cole JW, McArdle PF, Cheng YC, Ryan KA, Sparks MJ, Mitchell BD, Kittner SJ. Obesity increases risk of ischemic stroke in young adults. *Stroke* 2015; **46**: 1690-1692 [PMID: 25944320 DOI: 10.1161/STROKEAHA.115.008940]
78. **Clearfield M**, Pearce M, Nibbe Y, Crotty D, Wagner A. The "New Deadly Quartet" for cardiovascular disease in the 21st century: obesity, metabolic syndrome, inflammation and climate change: how does statin therapy fit into this equation? *Curr Atheroscler Rep* 2014; **16**: 380 [PMID: 24338517 DOI: 10.1007/s11883-013-0380-2]
79. **Wing RR**. 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 AHEAD trial. *Arch Intern Med* 2010; **170**: 1566-1575 [PMID: 20876408 DOI: 10.1001/archinternmed.2010.334]
80. **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403 [PMID: 11832527 DOI: 10.1056/NEJMoa012512]
81. **Wing RR**, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145-154 [PMID: 23796131 DOI: 10.1056/NEJMoa1212914]
82. **Sjöström CD**, Lystig T, Lindroos AK. Impact of weight change, secular trends and ageing on cardiovascular risk factors: 10-year experiences from the SOS study. *Int J Obes* (Lond) 2011; **35**: 1413-1420 [PMID: 21266948 DOI: 10.1038/ijo.2010.282]
83. **Sjöström L**, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; **351**: 2683-2693 [PMID: 15616203 DOI: 10.1056/NEJMoa035622]
84. **Sjöström L**, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, Ahlin S, Anveden Å, Bengtsson C, Bergmark G, Bouchard C, Carlsson B, Dahlgren S, Karlsson J, Lindroos AK, Lönroth H, Narbro K, Näslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307**: 56-65 [PMID: 22215166 DOI: 10.1001/jama.2011.1914]
85. **Pappachan JM**, Viswanath AK. Medical Management of Diabesity: Do We Have Realistic Targets? *Curr Diab Rep* 2017; **17**: 4 [PMID: 28101792 DOI: 10.1007/s11892-017-0828-9]
86. **Rubino F**, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, Herman WH, Amiel SA, Kaplan LM, Taroncher-Oldenburg G, Cummings DE. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. *Diabetes Care* 2016; **39**: 861-877 [PMID: 27222544 DOI: 10.2337/dc16-0236]
87. **McCarthy MI**. Genomics, type 2 diabetes, and obesity. *N Engl J Med* 2010; **363**: 2339-2350 [PMID: 21142536 DOI: 10.1056/NEJMra0906948]
88. **Look AHEAD Research Group**. Prospective association of a genetic risk score and lifestyle intervention with cardiovascular morbidity and mortality among individuals with type 2 diabetes: the Look AHEAD randomised controlled trial. *Diabetologia* 2015; **58**: 1803-1813 [PMID: 25972230 DOI: 10.1007/s00125-015-3610-z]
89. **Collins R**, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005-2016 [PMID: 12814710 DOI: 10.1016/S0140-6736(03)13636-7]
90. **Colhoun HM**, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685-696 [PMID: 15325833 DOI: 10.1016/S0140-6736(04)16895-5]
91. **Keech A**, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, Hague W, Beller E, Arulchelvam M, Baker J, Tonkin A. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care* 2003; **26**: 2713-2721 [PMID: 14514569 DOI: 10.2337/diacare.26.10.2713]
92. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) *Lancet* 1994; **344**: 1383-1389 [PMID: 7968073 DOI: 10.1016/S0140-6736(94)90566-5]
93. **Pyŏrälä K**, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) *Diabetes Care* 1997; **20**: 614-620 [PMID: 9096989 DOI: 10.2337/diacare.20.4.614]
94. **Sacks FM**, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**: 1001-1009 [PMID: 8801446 DOI: 10.1056/NEJM199610033351401]
95. **Goldberg RB**, Mellies MJ, Sacks FM, Moyé LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 1998; **98**: 2513-2519 [PMID: 9843456 DOI: 10.1161/01.CIR.98.23.2513]
96. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339**: 1349-1357 [PMID: 9841303 DOI: 10.1056/NEJM199811053391902]
97. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; **288**: 2998-3007 [PMID: 12479764 DOI: 10.1001/jama.288.23.2998]
98. **Sever PS**, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149-1158 [PMID: 12686036 DOI: 10.1016/S0140-6736(03)12948-0]
99. **Sever PS**, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005; **28**: 1151-1157 [PMID: 15855581 DOI: 10.2337/diacare.28.5.1151]
100. **Cannon CP**, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; **372**: 2387-2397 [PMID: 26039521 DOI: 10.1056/NEJMoa1410489]
101. **Keech A**, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366**: 1849-1861 [PMID: 16310551 DOI: 10.1016/S0140-6736(05)67667-2]
102. **Wolf PA**, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; **22**: 983-988 [PMID: 1866765 DOI: 10.1161/01.STR.22.8.983]
103. **January CT**, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; **64**: e1-76 [PMID: 24685669 DOI: 10.1016/j.jacc.2014.03.022]
104. **Lip GY**, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263-272 [PMID: 19762550 DOI: 10.1378/chest.09-1584]
105. **Aksnes TA**, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, Julius S. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). *Am J Cardiol* 2008; **101**: 634-638 [PMID: 18308012 DOI: 10.1016/j.amjcard.2007]
106. **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 [PMID: 21529739 DOI: 10.1016/j.amjcard.2011.03.004]
107. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449-1457 [PMID: 8018000 DOI: 10.1001/archinte.1994.00420130036007]
108. **Go AS**, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med* 1999; **131**: 927-934 [PMID: 10610643 DOI: 10.7326/0003-4819-131-12-199912210-00025]
109. **Sadlon AH**, Tsakiris DA. Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. *Swiss Med Wkly* 2016; **146**: w14356 [PMID: 27683276 DOI: 10.4414/smw.2016.14356]
110. **Brown JD**, Shewale AR, Talbert JC. Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke Prevention in Incident, Treatment-Naïve Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm* 2016; **22**: 1319-1329 [PMID: 27783556 DOI: 10.18553/jmcp.2016.22.11.1319]
111. **Simons LA**, Ortiz M, Freedman SB, Waterhouse BJ, Colquhoun D, Thomas G. Improved persistence with non-vitamin-K oral anticoagulants compared with warfarin in patients with atrial fibrillation: recent Australian experience. *Curr Med Res Opin* 2016; **32**: 1857-1861 [PMID: 27463735 DOI: 10.1080/03007995.2016.1218325]
112. **Alberts VP**, Bos MJ, Koudstaal P, Hofman A, Witteman JC, Stricker B, Breteler M. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol* 2010; **25**: 807-812 [PMID: 21061046 DOI: 10.1007/s10654-010-9520-y]
113. **Masrur S**, Cox M, Bhatt DL, Smith EE, Ellrodt G, Fonarow GC, Schwamm L. Association of Acute and Chronic Hyperglycemia With Acute Ischemic Stroke Outcomes Post-Thrombolysis: Findings From Get With The Guidelines-Stroke. *J Am Heart Assoc* 2015; **4**: e002193 [PMID: 26408015 DOI: 10.1161/JAHA.115.002193]
114. **Melgaard L**, Gorst-Rasmussen A, Søgaard P, Rasmussen LH, Lip GY, Larsen TB. Diabetes mellitus and risk of ischemic stroke in patients with heart failure and no atrial fibrillation. *Int J Cardiol* 2016; **209**: 1-6 [PMID: 26874450 DOI: 10.1016/j.ijcard.2016.02.004]
115. **Melgaard L**, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. *JAMA* 2015; **314**: 1030-1038 [PMID: 26318604 DOI: 10.1001/jama.2015.10725]
116. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996; **348**: 1329-1339 [PMID: 8918275 DOI: 10.1016/S0140-6736(96)09457-3]
117. **Wang Y**, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; **369**: 11-19 [PMID: 23803136 DOI: 10.1056/NEJMoa1215340]
118. **Palacio S**, Hart RG, Pearce LA, Anderson DC, Sharma M, Birnbaum LA, Benavente OR. Effect of addition of clopidogrel to aspirin on stroke incidence: Meta-analysis of randomized trials. *Int J Stroke* 2015; **10**: 686-691 [PMID: 23692560 DOI: 10.1111/ijs.12050]
119. **Rothwell PM**, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004; **363**: 915-924 [PMID: 15043958 DOI: 10.1016/S0140-6736(04)15785-1]
120. **Adegbala O**, Martin KD, Otuada D, Akinyemiju T. Diabetes Mellitus with Chronic Complications in Relation to Carotid Endarterectomy and Carotid Artery Stenting Outcomes. *J Stroke Cerebrovasc Dis* 2017; **26**: 217-224 [PMID: 27810149 DOI: 10.1016/j.jstrokecerebrovasdis.2016.09.012]
121. **Zinman B**, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-2128 [PMID: 26378978 DOI: 10.1056/NEJMoa1504720]
122. **Wanner C**, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 323-334 [PMID: 27299675 DOI: 10.1056/NEJMoa1515920]
123. **Marso SP**, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-322 [PMID: 27295427 DOI: 10.1056/NEJMoa1603827]
124. **Marso SP**, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016; **375**: 1834-1844 [PMID: 27633186 DOI: 10.1056/NEJMoa1607141]
125. Royal College of Physicians; Intercollegiate Working Party. National Clinical Guidelines for Stroke – Fifth Edition 2016. [accessed 2016 Dec 11]. Available from: URL: https: //www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5th-ed.pdf
126. **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140-149 [PMID: 25538310 DOI: 10.2337/dc14-2441]
127. **Baigent C**, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ* 1998; **316**: 1337-1343 [PMID: 9563981 DOI: 10.1136/bmj.316.7141.1337]
128. **Ogawa H**, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; **300**: 2134-2141 [PMID: 18997198 DOI: 10.1001/jama.2008.623]
129. **Wolff T**, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; **150**: 405-410 [PMID: 19293073 DOI: 10.7326/0003-4819-150-6-200903170-00009]

**P-Reviewer:** Dinc M, Alamgir MA **S-Editor:** Kong JX **L-Editor: E-Editor:**

**Specialty type:** Endocrinology and metabolism

**Country of origin:** United Kingdom

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**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 | 5.4 (3.3-9.0) |
| 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.

**Table 2** **Stroke patterns and risk factors in diabetes *vs* non-diabetes group1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Investigators, stroke type** | **Stroke**  **study population** | **Stroke patterns diabetes *vs* non-diabetes** | **Significant stroke risk factors in diabetes** |
| Jorgensen 1994, all strokes[27] | 233 diabetes  902 non-diabetes | ICH 2% *vs* 9%  Infarct 52% *vs* 60% | Hypertension |
| Olsson 1990, all strokes[28] | 121 diabetes  584 non-diabetes | ICH 6% *vs* 9%  Infarct 59% *vs* 55% | Heart failure, ischaemic heart disease |
| Kiers 1992, all strokes[29] | 50 diabetes  126 non-diabetes | ICH 12% *vs* 18%  Infarct N/A | N/A |
| Weir 1997, all strokes[30] | 61 diabetes  750 non-diabetes | ICH 7% *vs* 14%  Infarct N/A | Hypertension, hyperglycaemia |
| Megherbi 2003, all storkes[31] | 937 diabetes  3544 non-diabetes | ICH 8.5% *vs* 11.5%  Infarct 78% *vs* 72% | Hypertension |
| Arboix 2005, ischaemic strokes[32] | 393 diabetes  1447 non-diabetes | Infarct 76% *vs* 51% | Ischaemic heart disease, previous ischaemic stroke, dyslipidaemia |
| Hankey 2013, all strokes[33] | 9795 diabetes | ICH 10%  Infarct 82% | Hypertension, previous ischaemic stroke, ischaemic heart disease, nephropathy, high LDL cholesterol |

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

**Table 3 Blood glucose targets for non-pregnant adults with diabetes1**

|  |
| --- |
| 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 |

1More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycaemia.

**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 mm Hg) | 1.29 (1.13*-*1.46) |
| Hypertension only (sBP ≥ 160/95 mm Hg) | 1.93 (1.48*-*4.16) |
| Diabetes only | 2.48 (1.48*-*4.16) |
| Diabetes and hypertension  (sBP 140-159 mm Hg) | 4.26 (2.90*-*6.25) |
| Diabetes and hypertension  (sBP ≥ 160 mm Hg) | 4.90 (3.87*-*6.21) |

sBP: Systolic blood pressure.

**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  (4.5%) | S20-40 | 5.4 | 37% |
| CARE[94,95] | 4159,  21-75 years old | Secondary | 586  (14.1%) | 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 | 12% |
| 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.

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

|  |  |
| --- | --- |
| **Condition** | **Supporting literature** |
| **Hyperglycaemia** |  |
| Targeting HbA1c 6%*-*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 < 130 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] |