

8. Secondary Prevention of Stroke

Katherine Salter BA, Robert Teasell MD, Norine Foley MSc, Sanjit Bhogal MSc, Mark Speechley PhD

Managing Diabetes

Key Points

Intensive glycemic control therapies may be associated with reduced risk for cardiovascular complications, but may have less impact on risk for stroke.

For a specific group of high-risk individuals with Type 2 DM and a history of stroke, addition of pioglitazone is associated with reduced risk for recurrent stroke.

Treatment of hypertension reduces the risk for stroke in patients with diabetes.

Although use of statins may prevent recurrent coronary events in individuals with diabetes, It is not clear whether the use of statins is associated with reduced risk for recurrent stroke.

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The Evidence-Based Review of Stroke Rehabilitation (EBRSR) reviews current practices in stroke rehabilitation.

Contacts:

Dr. Robert Teasell
801 Commissioners
Road East

London, Ontario,
Canada

N6C 5J1

Phone:
519.685.4000

Web:
www.ebrsr.com

Email:
Robert.teasell@sjhc.london.on.ca

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8.4 Managing Diabetes

8.4.1 Significance of Diabetes

Diabetics have an increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia. The presence of glucose intolerance has been shown to double the risk of a stroke (Sacco 2001). Sacco (2001) notes "Diabetes is a determinant of atherosclerosis and microangiopathy of the coronary, peripheral and cerebral arteries. Death from cerebrovascular disease is greatly increased among subjects with elevated blood glucose values (Balkan et al. 1998). Cohort studies have demonstrated an independent effect of diabetes on stroke risk after controlling for other risk factors with relative risks ranging from 1.5 to 3.0 (Sacco et al. 1997, Wolf et al. 1991, Barrett-Connor et al. 1988, Kuller et al. 1985)." A recent study based on data from the FINNSTROKE study (Kaarisalo et al. 2005) found that the presence of diabetes mellitus was associated with a higher risk for death and disability by day 28 following stroke (OR = 1.20 and 1.51 respectively).

As noted in reviews undertaken by Stern (1998) and Sacco (2001), conflicting information exists regarding the relative risk of stroke in diabetic women (i.e. vs. non-diabetic women) when compared to the relative risk for men with diabetes. Stern (1998) cited a summary of 16 studies on the mortality and diabetes in which only half reported an increased risk for cardiovascular disease in women as opposed to men. A recent analysis of data pooled from 9 large epidemiological studies (n=27,269) conducted in the United States, revealed that diabetic women had a 3.37-fold increased risk of fatal stroke

(Women's Pooling Project; Ho et al. 2003). After adjustment for additional factors such as total cholesterol, BMI, systolic and diastolic blood pressure, blood pressure medication use, smoking, educational status, age and race, diabetic women had a similar risk for fatal stroke as non-diabetic women who had suffered a previous stroke (hazard ratio = 3.07 vs. 4.67; p=0.43). Subjects with both diabetes and a history of stroke were found to be 7.95 times more likely to experience a fatal stroke than women with no history of diabetes or stroke. Ho et al. (2003) recommended that, given their analysis, women with diabetes should be considered a high-risk group for fatal stroke and, therefore, be treated as aggressively as patients with a history of previous stroke.

8.4.2 Glycemic Control and Macrovascular Complications of Diabetes

By definition, macrovascular complications of diabetes are stroke, myocardial infarction and peripheral arterial disease. Sacco (2001) noted "*Intensive treatment of both type I and type II diabetes, aimed at maintaining near normal levels of blood glucose can substantially reduce the risk of microvascular complications such as retinopathy, nephropathy and neuropathy, but it has not been conclusively shown to reduce macrovascular complications including stroke (Diabetes Control and Complications Research Group 1993, 1995, UK Prospective Diabetes Study Group 1998). There is therefore strong evidence that maintaining tight glycemic control reduces microvascular complications. Although unproven, there is a presumption that tight*

glycemic control is associated with stroke reduction”.

A fasting plasma glucose level of ≥ 126 mg/dL is associated with the diagnosis of diabetes while impaired fasting glucose is identified as plasma glucose levels of 100 – 125 mg/dL (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). A recent, large ($n=13,999$) prospective study of patients with pre-existing atherosclerotic disease reported a J-shaped relationship between fasting plasma glucose levels and the risk of first ischaemic stroke or TIA (Tanne et al. 2004). Patients with low fasting glucose levels (<80 mg/dL) demonstrated an increased risk for stroke (OR=1.47) as did patients with levels >100 mg/dL (OR ranged from 1.27 for patients with glucose of 100 – 109 mg/dL to 2.82 for patients with fasting glucose >140 mg/dL). Comparisons were made with the majority of participants whose glucose levels measured 90 – 99 mg/dL and who also exhibited the lowest risk of ischaemic cerebrovascular disease (Tanne et al. 2004).

In the Northern Manhattan Study (NOMAS), 572 participants reported a diagnosis of diabetes. Of these, 338 had fasting blood glucose (FBG) levels ≥ 126 mg/dL. Of the documented 62 ischemic stroke events, 48 occurred in the group of patients with uncontrolled diabetes. On analysis, elevated FBG was significantly associated with increased risk for stroke (HR=2.7, 95% CI 1.9-3.8) while FBG at the target level (<126 mg/dL) was not significantly associated with increased risk, after adjustment for age, race, sex, insurance status, education, hypertension, coronary artery disease, lipid levels, obesity, physical inactivity,

alcohol intake and smoking (Boden-Albala et al. 2008).

8.4.2.1 Impact of interventions for Glycemic Control on Risk for Stroke

A report from the UK Prospective Diabetes Study (UKPDS 33) demonstrated that the use of intensive blood glucose measures (sulphonylurea or insulin) was associated with a significant ($p=0.029$), 12% reduction of risk for any diabetes-related endpoint when compared to conventional treatment (UKPDS Study Group, 1998). Most of this effect could be attributed to a significant reduction in microvascular events. Examination of risk for stroke, in particular, revealed no significant risk reduction associated with intensive glycemic control (RR = 1.11 95% CI 0.81, 1.51). However, a secondary analysis of 342 obese patients treated with metformin (UKPDS 34) revealed significant decreases in diabetes-related endpoints ($p=0.0034$), mortality ($p=0.021$) and stroke ($p=0.032$) when compared to conventional intensive interventions for blood glucose control including chlorpropamide, glibenclamide and insulin (UKPDS Study Group, 1998).

In a recent systematic review and meta-analysis, Stettler et al. (2006) examined the reported findings of 8 randomized controlled trials assessing the effects of improved glycemic control in individuals with Type 1 and Type 2 diabetes mellitus (DM). Treatments included sulphonylurea, metformin, insulin, multiple insulin injection therapy, continuous subcutaneous insulin infusion (Type I only) and intensive self-monitoring of blood glucose. The authors determined that improved glycemic control was associated with reduced

risk for macrovascular complications (IRR = 0.38 for Type 1 and 0.81 for Type 2 DM). For individuals with Type 1 DM, benefits were most evident in the reduction of cardiac and peripheral vascular events, while in Type 2 DM, reductions were observed in peripheral vascular disease and stroke. In addition, improved glycemic control was most beneficial in younger patients who had DM of shorter duration. Overall, in a 10-year period,

the number of patients one would need to treat with enhanced glycemic control measures in order to prevent a single macrovascular event were reported to be 16 for Type 1, 14 for low-risk Type 2 and 7 for high-risk Type 2 DM (Stettler et al. 2006).

Studies examining the impact of interventions for glycemic control on risk for stroke in high-risk individuals are summarized in Table 8.12.

Table 8.12 Interventions for Glycemic Control and Risk of Stroke

Author, Year Country Pedro Score	Methods	Outcomes
PROactive Dormandy et al. 2005 International 10 (RCT)	5,238 patients with Type 2 DM and evidence of macrovascular disease were assigned to treatment with pioglitazone (15mg to 45 mg, n=2,605) or matching placebo (n=2,633) in addition to their established medication regimen (diabetic and cardiovascular). Primary outcome = composite of mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention (coronary or leg arteries), amputation above the ankle. Secondary outcome = composite of mortality, non-fatal MI and stroke. Mean follow-up = 34.5 months.	19% of participants in each group had a history of previous stroke. Treatment with pioglitazone was associated with a significant reduction in risk for the secondary composite endpoint (HR=0.84, 95% CI 0.72-0.98), after adjustment for baseline variables including use of other treatments for glycemic control (insulin, metformin and sulphonylurea). Results for the primary endpoint were non significant (HR = 0.90, 0.80-1.02). Examination of elements of the composite endpoints revealed a non-significant trend toward reduction in risk for stroke (HR=0.81, 0.61-1.07). Treatment compliance was in excess of 95% in both groups. Increased rates of edema and heart failure were reported in the pioglitazone group, but there were no significant differences in mortality and fewer hospital admissions.
Wilcox et al. 2007 PROactive subgroup analysis	Evaluated risk for stroke and cardiovascular endpoints in participants with (n=984) vs without (n=4254) prior stroke.	In the subgroup of patients with previous stroke, treatment with pioglitazone was associated with significantly reduced risk of the composite endpoint of cardiovascular death, nonfatal stroke or nonfatal MI (HR=0.72. 95% CI 0.5-1.00). This benefit was driven primarily by reduced risk for fatal or non-fatal stroke. Stroke event rates in the pioglitazone group were 5.6% vs. 10.2% in the placebo group (HR=0.53, 0.35-0.85). In patients with no history of previous stroke, there were no significant benefits noted for any endpoints including fatal or nonfatal stroke (HR = 0.86, 0.71 -

		1.04). On multivariate analysis, only pioglitazone use ($p=0.0076$) and treatment with statins ($p=0.0126$) had significant effects on reduction in stroke risk among patients with previous stroke.
ACCORD Study Group Gerstein et al. 2008 International 7 (RCT)	10,251 patients with type 2 diabetes and either a previous history of cardiovascular events or evidence of increased risk for cardiovascular events were randomly assigned to receive either intensive (HbA_{1c} to $<6.0\%$) or standard (HbA_{1c} to $7.0 - 7.9\%$) glucose-lowering treatment strategies. Treatment formularies/ algorithms were provided. Primary study outcome was the composite of nonfatal MI, nonfatal stroke or death from cardiovascular causes. Mean length of follow-up was 3.5 years (due to early study termination based on mortality trends suggesting increased rate of death from any cause associated with intensive therapy). 35% of participants had a history of previous cardiovascular events at the time of study enrolment.	Stable HbA_{1c} levels were obtained in each group by one year (6.4% & 7.5% in the intensive and standard therapy groups, respectively). Fewer primary events were recorded in the intensive therapy group (352 vs. 371), but this difference was not significant (HR = 0.90, 95% CI 0.78 - 1/04, $p=0.16$). More nonfatal strokes were recorded in the intensive therapy group than standard therapy (67 vs 61, HR = 1.06, 95% CI 0.75 - 1.50, $p=0.74$). Increased mortality from any cause was associated with intensive therapy (HR = 1.22, 95% CI 1.01-1.46, $p=0.04$); however the number of deaths from stroke was not significantly different between groups. Intensive therapy was also associated with higher rates of hypoglycaemia, weight gain and fluid retention ($p<0.001$). On subgroup analysis, patients with history of previous cardiovascular events (including stroke) had more events when treated with intensive therapy.
ADVANCE Collaborative Group Patel et al. 2008 International 10 (RCT)	11,140 patients with Type 2 diabetes were randomly assigned to receive either intensive glucose control (gliclazide + other drugs as necessary to achieve $HbA_{1c} \leq 6.5\%$) or standard glucose control. Primary study outcomes were composites of death from cardiovascular causes, nonfatal MI, nonfatal stroke and major microvascular events. Median follow-up period = 5.0 years. 32% of participants reported a history of major macrovascular events including stroke (approximately 9%).	Compared to standard therapy, intensive glucose control was associated with a significant reduction in microvascular (HR = 0.86, 95% CI 0.77 - 0.97, $p=0.01$) but not macrovascular events (HR = 0.94, 95% CI 0.84 - 1.06), $p=0.32$). Examination of components of the combined primary outcome (macrovascular) revealed that more nonfatal strokes (as well as cerebrovascular events in general) were reported for patients receiving intensive therapy than standard, although this difference did not represent a significant increase in risk. There was no significant effect associated with intensive vs. standard therapy in the subgroup of participants with previous macrovascular events. Severe hypoglycaemia was significantly more frequent in the intensive treatment group (HR=1.86, 95%CI 1.42-2.40, $p<0.001$).
VADT Duckworth et al. 2009 USA 8 (RCT)	In an open label study, 1791 veterans with Type 2 diabetes (and suboptimal response to previous therapy) were randomly assigned to either intensive (maximum doses, $n=892$) or standard	Median glyated hemoglobin levels were 6.9% and 8.4% in the intensive and standard therapy groups, respectively. There were no significant differences reported for the primary composite

	<p>therapy (1/2 maximum doses, n=899). Therapy was determined by BMI. Patients with BMI\geq27 were given metformin + rosiglitazone; those with BMI < 27 received glimepiride + rosiglitazone. Primary outcome was time to first event cardiovascular event. 40% of participants reported history of previous cardiovascular event. Median length of follow-up =5.6 years.</p>	<p>outcome for intensive vs. standard therapy (HR = 0.88, 95% CI 0.74-1.05; p=0.14) or for any of the individual components of the primary outcome including stroke (28 vs. 36 stroke events, HR=0.78, 95% CI 0.48 – 1.28; p=0.32). More adverse events (most frequently hypoglycemia) were reported among individuals receiving intensive therapy (24.1% vs. 17.6%; p<0.001). No subgroup analyses for individuals with previous macrovascular events were reported.</p>
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Discussion

A recent meta-analysis of patient-level data from 19 trials examining the use of pioglitazone in a broad population of high and lower-risk individuals with Type 2 DM demonstrated a significantly reduced risk for the composite outcome of death, myocardial infarction and stroke (HR= 0.82 95% CI 0.72-0.94) (Lincoff et al. 2007). However, when elements of the composite outcome were examined individually, treatment with pioglitazone was not associated with a significant reduction in risk for stroke (HR=0.80, 95% CI 0.62 – 1.04). It should be noted that treatment was associated with a significantly higher risk for serious heart failure (HR = 1.41, (%95 CI 1.14-1.76); however, incidence of heart failure was not associated with increased mortality (Lincoff et al. 2007).

In the PROactive study, which focused on high-risk individuals with established macrovascular disease, there was also a significant reduction in risk for the secondary composite endpoint of all-cause mortality, MI and stroke (HR = 0.84), but no significant reduction in risk for stroke alone (Dormandy et al. 2005). Reduction in risk was associated with treatment given in addition to existing care that included antiplatelets, anti-

hypertensives, lipid-lowering agents and glucose-lowering medications. Over a 3-year period, one would need to treat 48 patients in order to avoid a single major cardiovascular event. Treatment with pioglitazone was not associated with increased mortality or liver toxicity, but was associated with increased rates of edema and heart failure (Dormandy et al. 2007).

Almost one-half of the patients included in PROactive had a previous history of myocardial infarction whereas only 19% had previous stroke. An analysis of this subgroup revealed a significant reduction in risk for stroke of 47%. In individuals with no history of stroke, the addition of pioglitazone had no significant effect on risk for any composite outcome, stroke or all-cause mortality. Among individuals with previous stroke, rates of serious adverse events were similar across treatment conditions (pioglitazone vs. placebo) and, although there were more hospitalizations for heart failure in the pioglitazone group, this difference was not significant (p=0.09) (Wilcox et al. 2007). Based on the results of the PROactive trial, the European Stroke Organization has recommended treatment with pioglitazone in patients with type 2 DM who do not need insulin (Ringleb et al. 2008).

Since that time, however, several more studies (ACCORD 2008, ADVANCE 2008, VADT 2009) examining the impact of intensive vs. standard glucose-lowering therapies have been published. Each of these has included a significant proportion (32% - 40%) of patients with history of previous macrovascular disease (including stroke). In a meta-analysis examining the effect of intensive control of glucose on cardiovascular outcomes in Type 2 DM that included all of the studies summarized here, Ray et al. (2009) demonstrated that intensive treatment was not associated with reduced risk for stroke when compared with standard therapy. In addition, both the ACCORD and ADVANCE studies included subgroup analyses that demonstrated no advantage associated with intensive treatment in terms of risk for macrovascular events.

Conclusions Regarding Interventions for Glycemic Control and Risk for Stroke

There is evidence, based on a systematic review and 2 meta-analyses, that improved glycemic control is associated with reduced risk for macrovascular complications in both Type 1 and Type 2 diabetes. However, benefit in terms of reduced risk for stroke is less clear.

There is also evidence from a recent meta-analysis that, while intensive treatment has cardiovascular benefits, it is not more effective than standard therapy in reducing risk for stroke in individuals with Type 2 diabetes. There is strong (Level 1a) evidence that intensive glucose-lowering therapy is not more effective than standard therapy in reducing risk for macrovascular events in individuals with previous macrovascular disease.

There is moderate (Level 1b) evidence, based on subgroup analysis from a single RCT that the addition of pioglitazone to the treatment regimen of individuals with Type 2 diabetes and a history of previous stroke is associated with reduced risk for recurrent stroke

There is strong (Level 1a) evidence that intensive glucose-lowering therapy is associated with increased episodes of hypoglycaemia.

Intensive glycemic control therapies may be associated with reduced risk for cardiovascular complications, but may have less impact on risk for stroke.

For a specific group of high-risk individuals with Type 2 DM and a history of stroke, addition of pioglitazone is associated with reduced risk for recurrent stroke.

8.4.3 Diabetes and the Treatment of Hypertension

There is recent evidence that stroke patients with diabetes are at significantly increased risk of disability and mortality (Otiniano et al. 2003; Ho et al. 2003). Despite the lack of conclusive evidence proving a causal link between tight glycemic control and stroke risk reduction, there is evidence that aggressive treatment of blood pressure (<150/85 mm Hg) among patients with type II diabetes significantly reduces the risk of stroke by 44% (UK Prospective Diabetes Study Group 1998). The Syst-Eur Investigators (1999) and HOPE Study investigators (2000) reported substantial reductions in stroke risk with anti-hypertensive therapies (73% and 33% respectively). Details of individual studies are summarized in Table 8.13.

Table 8.13 Studies Assessing Control of Blood Pressure and Stroke Risk in Diabetic Patients

Author, Year Country Pedro Score	Methods	Outcomes
UK Prospective Diabetes Study Group (UKPDS 38) 1998 UK 7 (RCT)	A total of 1148 hypertensive patients with Type II diabetes (mean age = 56 yrs) were randomly assigned to tight control vs. less tight control of blood pressure groups. Tight control patients received either captopril 25 – 50 mg twice daily (n=400) or atenolol 50 – 100 mg/day (n=358) to achieve a BP of <150/<85 mmHg. Less tight control patients (n=390) were treated to achieve a BP of <180/<105 without the use of an ACE-inhibitor or β -blocker. Patients were stratified according to previous treatment (yes/no) for hypertension.	Mean blood pressure during follow-up was significantly lower in the tight control group than the less tight group ($p<0.0001$). Tight BP control resulted in a risk reduction for stroke of 44% ($p=0.013$). In addition, diabetes related events were reduced in the tight BP control group compared to the less tightly controlled group (24%; $p=0.046$) as were deaths related to diabetes (32%, $p=0.19$). After nine years of follow-up, 29% of patients in the tight control group required 3 or more agents to maintain target BP.
UK Prospective Diabetes Study Group (UKPDS 39) 1998 UK 7 (RCT)	A total of 1148 hypertensive patients with Type II diabetes (mean age = 56 yrs) were randomly assigned to tight control vs. less tight control of blood pressure groups. Tight control patients received either captopril 25 – 50 mg twice daily (n=400) or atenolol 50 – 100 mg/day (n=358) to achieve a BP of <150/<85 mmHg. Less tight control patients (n=390) were treated to achieve a BP of <180/<105 without the use of an ACE-inhibitor or β -blocker.	Patients were followed for up to 9 years. Patients allocated to receive captopril or atenolol had similarly reduced blood pressures (14/8 mmHg change vs. 14/7 mmHg). For patients receiving neither drug, mean change was 16/7 mmHg over nine years. Comparing captopril to atenolol, there were fewer strokes among patients receiving atenolol, but this was not significant (RR=1.12, $p=0.74$). Both agents appeared equally effective in lowering blood pressure in patients with Type II diabetes.
ABCD Estacio et al. 1998 USA 8 (RCT)	470 patients with hypertension and non-insulin-dependent DM were randomly assigned to receive treatment with either nisoldipine or enalapril. In addition, patients received either intensive treatment (target diastolic BP = 75 mmHg) or moderate treatment (target diastolic BP = 80 – 89 mmHg). Open label antihypertensive medications were used if target BP could not be reached with study medications (with the exceptions of other calcium-channel blockers or ACE-inhibitors). Primary study outcome was effect of blood-pressure control on change in 24-hour creatinine clearance assessed every 6 months. Secondary end points	At 67 months, nisoldipine therapy in hypertensive patients was discontinued on the basis of significant difference in rate of cardiovascular events. No significant differences were seen between medication groups in terms of level of blood pressure control. There were more deaths from cardiovascular causes associated with nisoldipine therapy vs. enalapril (10 vs 5, adj. RR = 1.4, 95% CI 0.4 – 5.1). Similarly, there was a greater risk for stroke associated with nisoldipine therapy (Adj. RR = 2.2, 95% CI 0.7 – 7.1). There was a significantly lower rate of myocardial infarctions among patients receiving ACE-inhibitors vs. the calcium-channel blocker. Headaches were a more frequent cause of discontinuation in the nisoldipine group

	included fatal & nonfatal cardiovascular events. Follow-up=5 years.	(p=0.009) while fatigue and uncontrolled hypertension were more common in patients treated with enalapril (p=0.04)
Syst-Eur Investigators Tuomilehto et al. 1999 Finland, Belgium 8 (RCT)	4695 patients (aged ≥ 60 and having systolic hypertension) were randomized to receive either active treatment with nitrendipine 10 – 40 mg/day with the possible addition of enalapril or hydrochlorothiazide or both; n=252 diabetic & 2146 non-diabetic patients) or matching placebo (n=240 diabetic & 2057 non-diabetic patients). Patients with diabetes were included if blood glucose concentrations were controlled.	After 2 years, systolic & diastolic blood pressures in the active treatment vs. placebo groups differed by 8.6 mmHg & 3.9 mmHg for diabetic patients and 10.3 & 4.5 mmHg for non-diabetic patients. Active treatment was found to reduce the rate of fatal & nonfatal stroke by 73% among diabetic patients and 38% among non-diabetic patients. Reduction in overall mortality, mortality from CVD and all cardiovascular events was greater among diabetic patients than among non-diabetic patients (p=0.04, 0.02 & 0.01).
HOPE Study Investigators 2000 International 8 (RCT)	Population studied was diabetic stroke patients. 1,808 patients received 10 mg Ramipril and 400 IU vitamin E while 1769 received a placebo daily.	The study stopped 6 months early because of consistent benefit of Ramipril compared to placebo. Ramipril lowered risk of combined primary outcome by 25% (p=.0004), myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, overt nephropathy by 24%.
STOP-2 Lindholm et al. 2000 Sweden 7 (RCT)	719 of the 6,614 participants in the STOP-2 trial had diabetes mellitus as well as hypertension at baseline. Random allocation resulted in 253, 235 and 231 patients receiving conventional, ACE inhibitor and calcium antagonist-based therapies for the treatment of hypertension. Primary study outcome was fatal cardiovascular disease (including MI and stroke).	The impact of treatment on blood pressure was similar in all treatment groups. There were no significant differences in risk for fatal cardiovascular events between groups. There were also no significant differences between the three antihypertensive regimens in terms of combined fatal & nonfatal stroke. For Ca-antagonists vs. conventional therapy the adjusted RR for all stroke was 0.80 (95% CI 0.49 – 1.29), for ACE inhibitors vs conventional therapy RR = 0.88 (95% CI 0.56 – 1.40) and for ACE inhibitors vs. Ca-antagonists RR=1.16 (95% CI 0.71 – 1.91). However, treatment with an ACE inhibitor was associated with significantly fewer MIs when compared to Ca-antagonist therapy (RR=0.51, 95% CI 0.28 – 0.92).
ALLHAT Collaborative Research Group 2002 USA/Canada 9 (RCT)	31,512 adults aged 55 and over with HTN were stratified into 3 groups; those with diabetes mellitus (n=13,101), those with impaired fasting glucose levels (IFG, n=1,399) and normoglycemics (NG, n=17,012). Participants were randomly assigned to receive chlorthalidone (2.5 to 10 mg o.d), amlodipine desylate (2.5 – 10 mg o.d) or lisinopril (10 – 40 mg	Overall, there were few significant treatment and glyceic interactions identified. In DM and NG participants assigned to receive amlodipine and lisinopril, there was no significant difference in risk for the primary outcome when compared to chlorthalidone. There was a significant reduction in risk for primary outcome in IFG patients assigned to receive amlodipine vs. chlorthalidone.

	o.d.) Reduction in BP was achieved by titrating study drug dose, then adding one of atenolol, clonidine hydrochloride or reserpine and hydralazine hydrochloride as needed. Primary outcomes included fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, fatal and nonfatal stroke, combined CHD and combined CVD.	When stroke and CVD were considered, both outcomes were found to be more common in normoglycemic patients receiving lisinopril than chlorthalidone (RR=1.31 & RR=1.13 respectively). There was little evidence to support the superiority of treatment with either lisinopril or amlodipine when compared to chlorthalidone.
ADVANCE Collaborative Group, 2007 International 10 (RCT)	11,140 patients with type 2 diabetes (9% of whom had previous stroke) were randomized to receive either a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) (n=5569) or matching placebo (n=5571) following a 6-week run-in period. After 3 months, treatment doses were doubled (4 mg/1.24 mg vs. matching placebo). Patients were not necessarily hypertensive and mean BP at baseline was 145/81 in both groups. Mean follow-up = 4.3 years. Primary endpoints were composites of major macro and microvascular events.	A reduction in relative risk for the combined outcome of macro or microvascular disease event was associated with treatment (HR=0.91, 95% CI 0.83-1.00, p=0.04). However, when considering macrovascular events alone, no significant difference was noted between groups (HR=0.92, -4.0 to 20). Similarly, there was no significant reduction reported in risk for major cerebrovascular events (HR=0.98, (-18 to 19).

Discussion

There is strong evidence supporting the effectiveness of blood pressure control in dramatically reducing the risk for both fatal and nonfatal stroke in individuals with diabetes. Agents assessed for use with diabetic populations include ACE-inhibitors (captopril, enalapril, perindopril and ramipril), β -blockers (atenolol) and calcium channel blockers (nitrendipine, nisoldipine). Given the relative effectiveness of the agents tested, and the reported benefits of a tightly controlled blood pressure (UKDPS 1998), it has been suggested that the choice of medication may be less important than reaching and maintaining an optimal targeted blood pressure (Vinik & Flemmer 2002).

A meta-analysis of twenty-seven trials examined the effectiveness of blood

pressure reduction on major cardiovascular events in adults with diabetes (Turnbull et al. 2005). The authors found that for the outcome of stroke, there was no difference in the effects of treatment regimens based on the use of ACE-inhibitors, calcium antagonists, angiotensin receptor blockers, beta-blockers and diuretics between individuals with and without diabetes. All regimens appeared comparable in their ability to reduce the short to medium-term risks of macrovascular complications. Lower target blood pressures resulted in fewer major cardiovascular events and cardiovascular deaths in patients with diabetes compared to those without diabetes (p=0.03 and 0.02, respectively).

Conclusions Regarding Diabetes and the Treatment of Hypertension

There is strong (Level 1a) evidence that treatment of hypertension in diabetic patients reduces the risk of stroke.

There is strong evidence (Level 1a) that calcium-channel blocker and ACE-inhibitor-based regimens provide no additional benefit over conventional therapies in terms of both blood pressure control and prevention of macrovascular events including stroke in individuals with Type 2 diabetes.

Treatment of hypertension reduces the risk for stroke in patients with diabetes.

8.4.4 Diabetes and the Treatment of Dyslipidemia

In many cases, Type 2 diabetes is associated with plasma lipid and lipid protein abnormalities that include low concentrations of HDL cholesterol, increases in small, dense, atherogenic LDL particles and elevated triglycerides (Krauss 2004). Each of these abnormalities is associated with increased cardiovascular risk. Lehto et al. (1996) demonstrated that HDL cholesterol levels less than 0.9 mmol/L were associated with 1.9 fold increase in risk for stroke in diabetic patients and triglyceride levels of >2.3 mmol/L with a 2.1 fold increase in risk. However, in a study of stroke risk factors from the United Kingdom Prospective Diabetes Study (UKPDS, Davis et al. 1999), dyslipidemia was not identified as a significant risk factor. Significant risk factors included

age, male sex, hypertension and atrial fibrillation.

Although behavioural or lifestyle interventions such as diet, weight loss and physical activity may improve features of diabetic dyslipidemia to some extent, pharmacological treatment may be required. In a recent meta-analysis of cholesterol-lowering therapy with statins using data from 14 randomized controlled trials, it was demonstrated that significant reductions in major vascular events, including major coronary events (RR = 0.78, 99% CI 0.69-0.87), coronary revascularizations (RR=0.75, 99% CI 0.64-0.88) and stroke (RR=0.79, 0.67-0.93) were associated with statin treatment (Cholesterol Treatment Trialists' Collaborators, 2008). Among patients with diabetes and a history of vascular disease (including cerebrovascular and peripheral vascular disease but not CHD), risk for major vascular events was also reduced (RR=0.80, 99% CI 0.61-1.03). For patients with known vascular disease at baseline, treatment with statins over a 5-year period resulted in 57 fewer events per 1000 per mmol/L LDL cholesterol reduction (Cholesterol Treatment Trialists' Collaborators, 2008). It should be noted that, while 37% of patients with diabetes included in the analysis had known vascular disease at baseline, only 5% had a history of previous stroke.

Individual studies examining the use of statin in patients with diabetes and previous history of vascular disease and the prevention of stroke are summarized in Table 8.14

8.14 Studies Assessing Use of Statins for Secondary Prevention in Individuals with Diabetes

Author, Year Country Pedro Score	Methods	Outcomes
Scandinavian Simvastatin Survival Study (4S) Pyorala et al. 1997 Sweden/Finland 8 (RCT)	A <i>posthoc</i> , subgroup analysis of 202 diabetic and 4,242 nondiabetic patients with previous MI or angina who participated in the 4S study. Patients were assigned to treatment with simvastatin, 20 mg/day titrated to 40 mg (n=105 diabetic patients), or placebo (n=97). Study endpoints included mortality, major CHD events, other acute atherosclerotic events and myocardial revascularization procedures. Median follow-up = 5.4 years.	In diabetic patients assigned to treatment with simvastatin, risk of cerebrovascular disease events was not significantly reduced compared to those receiving placebo (RR = 0.38, p=0.71). However, treatment with simvastatin was associated with a significant reduction in risk for major CHD events (RR = 0.45, p=0.002), any CHD events (RR=0.61, p=0.015) or any atherosclerotic events (RR=0.63, p=0.018). Risk reductions associated with treatment were not dependent on baseline levels of total, LDL, HDL cholesterol or triglycerides.
CARE trial Goldberg et al. 1998 USA 8 (RCT)	Subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial. 586 (14.1%) of patients enrolled in CARE had a clinical diagnosis of diabetes at baseline. 6% of these had a history of previous stroke. The primary study endpoint was the composite of death from CHD and nonfatal MI. Mean follow-up was 5 years.	Pravastatin treatment was associated with a non-significant reduction in relative risk of 13% for the primary study endpoint in patients with diabetes. For the endpoint of stroke, treatment was associated with a non-significant reduction of 14%. However, treatment was associated with a 25% reduction of risk for coronary events (CHD death, nonfatal MI, CABG and PTCA) (p=0.004). Expressed in absolute terms, this represents an 8.1% risk reduction for coronary events.
LIPID Trial White et al. 2000, Keech et al. 2003 New Zealand 9 (RCT)	9,014 patients with previous MI or unstable angina during the previous 3 months to 3 years, with hyperlipidemia were randomized to receive either 40 mg of Pravastatin (n=4512) or placebo (n=4502). 1,077 had a history of diabetes (542 received pravastatin), 940 had impaired fasting glucose (IFG) (474 received pravastatin). The remainder were classified as normal fasting glucose (NFG). 6% of patients with diabetes had a previous history of stroke at baseline. The primary study end point was death due to coronary artery disease.	Mean follow-up period was six years. The response of lipids to treatment was similar in all 3 groups (diabetes, IFG & NFG), but level of triglycerides fell most in the diabetic group. In the placebo group, absolute excess risk in patients with diabetes (vs NFG) for death or nonfatal MI was 8.9% and 6.3% for stroke. In patients with diabetes, treatment with pravastatin was associated with a 19% reduction in risk for the primary study outcome (p=0.11). However, treatment with pravastatin reduced the risk for stroke from 9.9 to 6.3% (RRR = 39%, p=0.02; NNT = 53) in patients with diabetes and 5.3% to 3.4% (RRR=42%, p=0.09; NNT = 97) in patients with IFG.

<p>PROSPER Study Group Shepherd et al. 2002 International 8 (RCT)</p>	<p>5,804 patients, aged 70 – 82, with pre-existing vascular disease (coronary, cerebral or peripheral) or increased risk (smoking, HTN or diabetes) were randomized to receive pravastatin 40 mg/day or matching placebo. 11% of patients in the placebo groups & 1.5% in the treatment group had a history of diabetes. The proportion of these who also had a history of vascular disease or stroke is not known. Mean length of follow-up = 3.2 years.</p>	<p>Pravastatin lowered LDL by 34%, overall. For all participants, risk for the combined primary study outcome of coronary death, non-fatal MI and fatal or non-fatal stroke was significantly reduced (HR = 0.85, p=0.014). When considered alone, risk of stroke appeared unaffected by the intervention (hazard ratio = 1.03). For patients with diabetes, risk of the primary outcome was increased, though non-significantly, in the treatment group (hazard ratio = 0.1.27, 95% CI 0.90-1.80).</p>
<p>GREACE Athiros et al. 2003 International 6 (RCT)</p>	<p>Of 1600 patients eligible for the GREACE study, 313 had DM and a history of CHD. These patients were randomized to receive either structured care or usual care for hyperlipidaemia. Patients in the structured care group received atorvastatin titrated up to a maximum dose of 80 mg/day to reach the National Cholesterol Education Program goal of LDL-C <2.6 mmol/L and were followed by the university clinic. Usual care was according to own physician's standard. Follow-up was conducted by the healthcare professional of the patient's choice outside of the hospital. Primary study endpoints were all-cause and coronary mortality, coronary morbidity and stroke. Mean follow-up was 3 years.</p>	<p>In structured care, 97% of patients took atorvastatin daily and lipid level targets were achieved by 93% of patients. In the usual care group, 17% were received long-term treatment with a lipid lowering drug and only 4% reached guideline targets. Fewer patients receiving structured VS standard care experienced primary outcome events (RRR = 58%, p<0.0001). Reported relative risk reduction of 68% was reported for stroke (p<0.002).</p>
<p>MRC/BHF Heart Protection Study 2003 UK 8 (RCT)</p>	<p>5963 adults with diabetes and an additional 14 573 adults with no diabetes but having occlusive arterial disease were randomly assigned to receive 40 mg/day Simvastatin or matching placebo. 19% of participants with diabetes reported a history a history of MI, 14% of other CHD and 18% of other occlusive arterial disease. Mean duration of follow-up was 4.8 years.</p>	<p>Overall, there was a 24% reduction in first non-fatal or fatal stroke among diabetic patients (p<0.0001), overall. For patients with no previous occlusive arterial disease, risk reduction associated with treatment was 33% (p=0.002). Absolute risk reduction for individual with diabetes and occlusive arterial disease was 18.4% (p=0.002). 66 major vascular events/1000 patients treated could be avoided in a 5 year period. For diabetic patients with LDL levels <3 mmol/L, the vascular event rate was reduced by 27%. The results suggest that therapy with Simvastatin is beneficial for diabetic patients with/without previous occlusive arterial disease and with/without elevated LDL.</p>

<p>ASCOT-LLA Sever et al. 2005 International 8 (RCT)</p>	<p>A subgroup analysis of the 2,532 patients with Type 2 diabetes enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were randomly allocated to a treatment group (10 mg Atorvastatin daily) or placebo group. 7.4% and 7.7% of patients with diabetes in the treatment and control groups, respectively, had a history of previous stroke or TIA. Median follow-up = 3.3 years.</p>	<p>Treatment with atorvastatin was associated with a significant reduction in risk (HR = 0.77, p=0.036) for total cardiovascular events and procedures among individuals with diabetes. However, there was no significant reduction in risk for fatal or non-fatal stroke (HR = 0.67, 95% CI 0.41-1.09). However, effective comparisons may have been limited by early stoppage of the trial, thereby reducing the number of endpoint events and limiting the power of tests to compare treatment effect.</p>
<p>ASPEN Study Knopp et al. 2006 International 9 (RCT)</p>	<p>2,410 patients with Type 2 diabetes were randomly assigned to treatment with 10 mg/day atorvastatin or matching placebo. 252 patients in the treatment group and 253 in the placebo group were considered "secondary prevention" patients. Of these 9% & 12% (treatment & placebo respectively) had a history of CVD. Primary study endpoint was a clinical composite that included fatal and non fatal stroke. Median follow-up = 4 years.</p>	<p>Risk for the composite primary endpoint was not significantly reduced with treatment vs. placebo (HR=0.90, p=0.34). When elements of the primary endpoint were examined individually, treatment with atorvastatin was not associated with a significant reduction in risk for fatal or non-fatal stroke in either primary or secondary prevention patients.</p>

Discussion

The majority of studies summarized above provided subgroup analyses of individuals with Type 2 diabetes mellitus. Only two, the MRC/BHF Heart Protection Study and the ASPEN trial, examined the effect of statin within individuals with Type 2 DM exclusively. However, within these two trials, reported results regarding risk for stroke in patients with existing vascular disease. The MRC/BHF Heart Protection Study reported that 18% of all diabetic participants had a history of "occlusive arterial disease" (vs. 33% with previous MI or other CHD) and within this subgroup, statin use was associated with a significant reduction in risk for stroke of 18.4% (Heart Protection Study Collaborative 2003). However, in the ASPEN trial, treatment with atorvastatin was not associated with a significant reduction in risk for stroke in that study's secondary

prevention subgroup (Knopp et al. 2006).

Based on all of the available analyses included in Table 8.14, studies examining the impact of treatment with statins on risk for recurrent stroke in individuals with diabetes and a history of vascular disease have provided mixed results. Whereas the benefit of statin treatment for patients with diabetes and existing coronary heart disease seems clear, in terms of reduced risk for subsequent coronary events, the benefit for secondary prevention of stroke is less apparent. The CARE, PROSPER, ASCOT-LLA and ASPEN studies reported no significant reduction in risk for stroke among individuals with diabetes and history of previous vascular disease, while the remaining trials reported significant reductions in risk for stroke. However, the majority of patients with existing vascular disease have reported a

history of previous MI, angina or other coronary disease, while relatively few have had previous stroke. The LIPID trial, for instance, reported significant reductions for risk of stroke but only 6% of the 1,077 patients with diabetes in that trial also had a history of previous stroke (Keech et al. 2003).

8.4.4.1 Fibrates

Fibrates are PPAR α agonists that decrease plasma triglycerides and increase HDL levels and, therefore, may provide different protective effects in terms of cardiovascular risk than statins (Saha et al. 2007). A

1998 meta-analysis of 28 studies examining the effects of interventions on risk for non-haemorrhagic stroke demonstrated that treatment with statins reduced the risk for fatal and nonfatal stroke (OR=0.76) while fibrates, resins and dietary interventions to lower cholesterol did not reduce stroke risk (OR=1.02) (Bucher et al. 1998). However, the results of several large clinical trials, all of which included patients with diabetes mellitus, have been published subsequent to that analysis (Table 8.15).

Table 8.15. Use of Fibrates in Hyperlipidemia and Stroke Prevention

Author, Year Country Pedro Score	Methods	Outcomes
VA-HIT Study Group Rubins et al. 1999 USA 9 (RCT)	2531 men under the age of 74 (mean age = 64) with a history of coronary heart disease and an LDL of less than 3.6 mmol/L were randomly allocated to either treatment (1 slow-release gemfibrozil 1200 mg/day) or placebo groups. Median duration of follow-up was 5.1 years.	After one year, HDL levels were 6% higher in the treatment group relative to the placebo; triglyceride levels were 31% lower, but LDL levels did not differ significantly between groups. Comparing the treatment group to placebo, there was a reduction of 22% for a primary event (p=0.006), 25% for stroke (p=0.10) and 59% for TIA (p<0.001).
BIP Study Group (2000) Israel 7 (RCT)	3090 patients with previous MI or stable angina, total cholesterol of 180 – 250 mg/dL, HDL-C \leq 45 mg/dL, triglycerides \leq 300 mg/dL, LDL \leq 180 mg/dL and who had been placed on a lipid-lowering diet were randomly assigned to either treatment (400 mg bezafibrate/day) or placebo. Primary study outcomes were fatal/nonfatal MI or sudden death. Secondary outcomes, for patients free of primary outcomes, included stroke. Mean follow-up was 6.2 years.	0.9 % and 1.4% of patients in the treatment and placebo conditions, respectively, had a history of previous stroke. For the primary study endpoint, treatment with bezafibrate was associated with a 9.4% reduction in risk (p=0.26). For stroke, there was no significant between group differences reported either for total stroke (p=0.66) or ischemic stroke (p=0.36).
VA-HIT Study Group Robins et al.	Men with a history of coronary heart disease and having low levels of HDL (mean = 0.83 mmol/L) and low	With gemfibrozil, levels of HDL were increased in the treatment group compared to placebo (p<0.001),

2001 USA 9 (RCT)	levels of LDL (mean = 2.88 mmol/L) were randomly allocated to receive either gemfibrozil 1200 mg/day (n=1264) or matching placebo (n=1267).	triglycerides were lowered (p<0.001) while LDL concentrations remained the same. CHD events were reduced by 11% in the treatment condition for every 0.13 mmol/L increase in HDL cholesterol (p=0.02). However, lipid concentrations achieved within the gemfibrozil group could account for only 23% of the treatment benefit.
FIELD Study Investigators (2005) International 9 (RCT)	9795 patients between the ages of 50 – 75 years with type 2 diabetes and an initial plasma total cholesterol of 3.0 – 6.5 mmol/L plus total cholesterol to HDL ratio of 4.0 or more or plasma triglyceride concentration of 1.0 mmol/L to 5.0 mmol/L participated in a 16-week study run-in (4 weeks dietary modification, 6 weeks single blind placebo and 6 weeks single blind fenofibrate therapy). After the run-in phase, participants were randomly assigned to receive either micronised fenofibrate (200 mg/day) or matching placebo. Primary study outcome was coronary events. Secondary outcomes included stroke. Study duration was 5 years.	4% and 3% of patients allocated to treatment and control conditions, respectively, had a history of prior stroke. Relative to placebo, treatment with fenofibrate was associated with 11% reduction in total-cholesterol concentration, 12% for LDL cholesterol – triglyceride concentration increased by 29% and HDL by 5% by 4 months. Differences were maintained for total cholesterol, LDL and triglycerides over the course of the study. Treatment was associated with a nonsignificant reduction in risk for the primary study outcome (HR = 0.89 95% CI 0.75 – 1.05). 175 strokes were recorded in the treatment group and 158 in the placebo group. This represented a non-significant reduction in risk for stroke associated with treatment (HR = 0.90 95% CI 0.73 – 1.12).

Discussion

In the VA-HIT trial, use of gemfibrozil was not associated with any major adverse effects and was generally well tolerated. The most common complaint reported by participants was that of abdominal discomfort. Within a population of patients with low levels of HDL cholesterol, the magnitude of benefit derived from gemfibrozil therapy appears similar to that reported for pravastatin therapy in populations with average to moderately high levels of LDL cholesterol (Rubins et al. 1999). While 5 year numbers needed to treat are provided for myocardial infarctions and

deaths from CHD and are, indeed, similar to those provided for pravastatin (Rubins et al. 1999), no analysis is provided for the secondary outcomes of stroke and/or TIA. It should be noted that, in the VA-HIT study, benefits of treatment were not apparent until approximately 2 years after commencement of the trial and, although the reduction in stroke events associated with treatment appears large, it did not reach statistical significance. However, studies examining the effectiveness of treatment with fibrates have not considered stroke events among their primary study outcomes. To this point, studies may not have been

adequately powered to adequately detect change in these event rates.

Unlike the VA-HIT trial, the more recent FIELD trial recruited only patients with Type 2 DM. No significant benefit associated with treatment was reported for either the primary study outcome or for stroke events. However, during the study, 36% of patients in the placebo group began treatment with non-study lipid lowering therapies (vs. 19% in the treatment group). When the analysis was adjusted for this factor, treatment was associated with a 15% reduction in risk for cardiovascular events (p=0.004) (FIELD Study Investigators 2005). No results of this revised analysis were provided for stroke events alone.

Table 8.16. Studies Included in the Meta-Analysis of Fibrates for Prevention of CVD (Allmann et al. 2006)

Primary Prevention: Cullen et al. (1974) Helsinki et al. (1987) DIS, 1991 SENDCAP, 1998 FIELD, 2005 (mixed pop., 78% primary prevention)	Secondary Prevention: VA-HIT, 1999 BIP, 2000 DAIS, 2001 FIELD (22%, secondary prevention)
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A meta-analysis examining the use of fibrates in patients with Type 2 DM (Alleman et al. 2006) included 8 trials (Table 8.16), four of which were considered secondary prevention trials, in that they recruited patients with known coronary heart disease. Pooled analysis demonstrated a non-significant reduction in stroke associated with fibrate treatment (Incidence Rate Ratio = 0.87, 95% CI 0.73-1.05). Similar to statin trials, the four secondary prevention trials of fenofibrate included relatively few

individuals with both diabetes and history of previous stroke, ranging from none (Bezafibrate Infarction Prevention Study, 2000) to 12% of diabetic patients in the VA-HIT trial (Rubins et al. 2002). In the VA-HIT trial, treatment with gemfibrozil was associated with a non-significant reduction in risk for stroke among participants with diabetes (HR=0.60, p=0.46).

A more recent meta-analysis (Saha and Arora 2009) confirmed the results reported by Allmann et al. (2006). Based on data from the DAIS, BIP, VA-HIT and FIELD studies, longer term (> 1year) use of fibrates was associated with a non-significant reduction in the risk for stroke (RR = 0.88, 95% CI 0.73 – 1.05). However, fibrate therapy was associated with a significant reduction in the risk for nonfatal myocardial infarction (RR=0.79, 95% CI 0.67-0.93, p=0.006). The authors suggest that statins should be considered first line therapy for dyslipidemia in individuals with Type 2 DM, although fibrates may be of use for treatment of individuals who are unable to achieve desired lipid levels via statin therapy.

Conclusions Regarding Diabetes and the Treatment of Dyslipidemia

There is conflicting evidence with regard to the impact of treatment with statins on the risk for stroke in individuals with Type 2 diabetes mellitus.

There is strong (Level 1a) evidence that treatment with fibrates is associated with increased HDL cholesterol and lower triglyceride concentrations.

There is strong (Level 1a) evidence that among individuals with Type 2 diabetes, treatment with fenofibrate is not

associated with a reduction in risk for stroke.

Neither statin nor fibrate trials have included many patients with both diabetes and a history of stroke or TIA. Therefore, further study within this group of patients is required.

Although use of statins may prevent recurrent coronary events in individuals with diabetes, it is not clear whether the use of statins is associated with reduced risk for recurrent stroke.

8.4.5 Treatment Recommendations

Treatment of hypertension and hyperlipidemia in patients with

diabetes reduces the incidence of macrovascular complications such as stroke. Early screening for diabetes in individuals with hypertension and/or hyperlipidemia together with prompt intervention to reduce cardiovascular risk has been recommended (Brown et al. 2004, Feig et al. 2005). The Heart and Stroke Foundation recommendations include tight glycemic control and the use of ACE inhibitors (such as Ramipril) to control hypertension. The recent recommendations for the secondary prevention of stroke from the American Heart Association/American Stroke Association (AHA/ASA) Council on Stroke (Sacco et al. 2006) are presented in Table 8.17.

Table 8.17 AHA/ASA Treatment Recommendations for Diabetes

- More rigorous control of blood pressure and lipids should be considered in patients with diabetes
- Although all major classes of antihypertensives are suitable for the control of BP, most patients will require >1 agent. ACE inhibitors and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with diabetes mellitus.
- Glucose control is recommended to near normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications
- The goal for Hb A_{1c} should be ≤7%

Summary

- 1.** *There is evidence, based on a systematic review and 2 meta-analyses, that improved glycemic control is associated with reduced risk for macrovascular complications in both Type 1 and Type 2 diabetes. However, benefit in terms of reduced risk for stroke is less clear.*
- 2.** *There is also evidence from a recent meta-analysis that, while intensive treatment has cardiovascular benefits, it is not more effective than standard therapy in reducing risk for stroke in individuals with Type 2 diabetes.*
- 3.** *There is strong (Level 1a) evidence that intensive glucose-lowering therapy is not more effective than standard therapy in reducing risk for macrovascular events in individuals with previous macrovascular disease.*
- 4.** *There is moderate (Level 1b) evidence, based on subgroup analysis from a single RCT that the addition of pioglitazone to the treatment regimen of individuals with Type 2 diabetes and a history of previous stroke is associated with reduced risk for recurrent stroke*
- 5.** *There is strong (Level 1a) evidence that intensive glucose-lowering therapy is associated with increased episodes of hypoglycaemia.*
- 6.** *There is strong (Level 1a) evidence that treatment of hypertension in diabetic patients reduces the risk of stroke.*
- 7.** *There is strong evidence (Level 1a) that calcium-channel blocker and ACE-inhibitor-based regimens provide no additional benefit over conventional therapies in terms of both blood pressure control and prevention of macrovascular events including stroke in individuals with Type 2 diabetes.*
- 8.** *There is conflicting evidence with regard to the impact of treatment with statins on the risk for stroke in individuals with Type 2 diabetes mellitus.*
- 9.** *There is strong (Level 1a) evidence that treatment with fibrates is associated with increased HDL cholesterol and lower triglyceride concentrations.*
- 10.** *There is strong (Level 1a) evidence that among individuals with Type 2 diabetes, treatment with fenofibrate is not associated with a reduction in risk for stroke.*
- 11.** *Neither statin nor fibrate trials have included many patients with both diabetes and a history of stroke or TIA. Therefore, further study within this group of patients is required.*

References

- Allemann S, Diem P, Egger M, Christ ER, Stettler C. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *Curr Med Res Opin* 2006;22:617-623.
- Athyros VG, Papageorgiou AA, Symeonidis AN, Didangelos TP, Pehlivanidis AN, Bouloukos VI, Mikhailidis DP. Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology* 2003 Nov;54(6):679-90.
- Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? *Am J Epidemiol* 1988;128(1):116-23.
- Boden-Albala B, Cammack S, Chong J, et al. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care* 2008;31:1132-1137
- Brown LC, Johnson JA, Majumdar SR, Tsuyuki RT, McAlister FA. Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis. *CMAJ* 2004;171:1189-1192.
- Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA Reductase Inhibitors on Stroke. A meta-analysis of randomized, controlled trials. *Ann Intern Med.* 1998; 128: 89-95.
- Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care* 2004;27:1647-1653
- Collins R, Armitage J, Parish S, Sleight 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.
- Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
- Davis TM, Millns H, Stratton IM, Holman RR, Turner RC, for the UK Prospective Diabetes Study Group. Risk factors for stroke in Type 2 Diabetes Mellitus. *Archives of Internal Medicine* 1999;159:1097-1103.
- Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-1289.
- 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 Jan;360(2):129-39.
- Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253-259.
- Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998;317:713-720.
- Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998 Mar;338(10):645-52.

- Feig DS, Palda VA, Lipscombe L, Canadian Task Force on Preventive Health Care. Screening for type 2 diabetes mellitus to prevent vascular complications: updated recommendations from the Canadian Task Force on preventative health care. *CMAJ* 2005;172:177-179.
- Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008 Jun;358(24):2545-59.
- Goldberg RB, Mellies MJ, Sacks FM, et al. 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
- Heart and Stroke Foundation of Ontario. Best Practice Guidelines for Stroke Care: A resource for implementing optimal stroke care, 2003.
- Ho JE, Paulre F, Mosca L. Is Diabetes Mellitus a cardiovascular disease risk equivalent for fatal stroke in women? Data from the Women's Pooling Project. *Stroke* 2003;34:2812-2816.
- Kaarisalo MM, Raiha I, Sivenius J, et al. Diabetes worsens the outcome of acute ischemic stroke. *Diabetes Res Clin Pract* 2005;69:293-298.
- Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117-125
- Keach A, Simes RJ, Barter P, et al. 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.
- Keach A, Colquhoun D, Best J, et al. 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
- Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478-1485.
- Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care* 2004;27:1496-1504.
- Kuller LH, Dorman JS, Wolf PA. Cerebrovascular diseases and diabetes. In: National Diabetes Data Group, Department of Health and Human Service, National Institutes of Health, ed. *Diabetes in America: Diabetes Data Compiled for 1984*, Bethesda MD, National Institutes of Health 1985: 1-18.
- Sacco RL. Stroke Risk Factors. In: Norris JW, Hachinski V, eds. *Stroke Prevention*. New York: Oxford University Press, 2001.
- Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke* 1996;27:63-68.
- Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180-1188.
- Lindholm LH, Hansson L, Ekblom T, Dahlof B, Lanke J, Linjer E, Schersten B, Wester PO, Hedner T, de FU. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000 Nov;18(11):1671-5.
- Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000;283:1967-1975.
- Otiniano ME, Du XL, Ottenbacher K, Markides KS. The effect of diabetes combined with stroke on disability, self-rated health, and mortality in older Mexican Americans: results from the Hispanic EPESE. *Arch Phys Med Rehabil* 2003; 84(5): 725-30.

- 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 Jun;358(24):2560-72.
- Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-840.
- Pyorala 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.
- Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009 May;373(9677):1765-72.
- Ringleb PA, European Stroke Organization Executive Committee. Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008. *Cerebrovasc Dis* 2008;25:457-507
- Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001;285:1585-1591.
- Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-418.
- Sacco RL, Prabhakaran S, Thompson JL, et al. Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death: subgroup analyses from the Warfarin-Aspirin Recurrent Stroke Study. *Cerebrovasc Dis* 2006;22:4-12.
- Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus - A pooled meta-analysis of randomized placebo-controlled clinical trials. *Int J Cardiol* 2009 Feb.
- Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease--a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J* 2007;154:943-953.
- Sander D, Kearney MT. Reducing the risk of stroke in type 2 diabetes: pathophysiological and therapeutic perspectives. *J Neurol* 2009 Apr.
- Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients With Coronary Artery Disease: The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000;102:21-27.
- Sever PS, Poulter NR, Dahlof B, Wedel H. Different time course for prevention of coronary and stroke events by Atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA). *Am J Cardiol* 2005;96[suppl]:39F-44F.
- Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-1630.
- Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350:757-764.
- Stern MP. The effect of glycemic control on the incidence of macrovascular complications of Type 2 Diabetes. *Archives of Family Medicine* 1998;7:155-162.
- Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am Heart J* 2006;152:27-38.
- Tanne D, Koren-Morag N, Goldbourt U. Fasting Plasma Glucose and Risk of Incident Ischaemic Stroke or Transient Ischaemic Attacks: A Prospective Cohort Study. *Stroke* 2004;35:2351-2355.

- The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329(14):977-86.
- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus*. Follow-up Report on the Diagnosis of Diabetes Mellitus. *Diabetes Care* 2003;26:3160-3167.
- Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-713.
- Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999;340:677-684.
- Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;165:1410-1419.
- Vinik A, Flemmer M. Diabetes and macrovascular disease. *Journal of Diabetes and its Complications* 2002;16:235-245.
- White HD, Simes J, Anderson NE, Hankey GJ, et al. Pravastatin therapy and the risk of stroke. *N Engl J Med* 2000;343:317-326.
- Wilcox R, Bousser MG, Betteridge DJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;38:865-873.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22(3):312-8.