

**Diabetes, the Metabolic Syndrome and Ischemic Stroke:  
Epidemiology and Possible Mechanisms**

Ellen L. Air<sup>1</sup> M.D., Ph. D. and Brett M. Kissela<sup>2</sup> M.D.

Departments of Neurosurgery<sup>1</sup> and Neurology<sup>2</sup>,  
University of Cincinnati College of Medicine, Cincinnati, OH

Running title: Diabetes and Ischemic Stroke

Address correspondence to:  
Brett M. Kissela  
Department of Neurology  
University of Cincinnati College of Medicine  
231 Albert Sabin Way, ML 0525  
Cincinnati, OH 45267-0525  
brett.kissela@uc.edu

Received for publication 21 July 2007 and accepted in revised form 8 September 2007.

Stroke affects more than 700,000 individuals each year, is the third largest cause of death and the largest cause of adult disability in the United States. Diabetes is a major risk factor for the development of stroke, yet this risk is not realized or understood by patients with diabetes. This likely reflects a lack of understanding within the medical community of how diabetes confers this risk. We will explore the potential underlying mechanisms which lead to increased incidence of stroke among diabetic patients. Beyond diabetes itself, the metabolic syndrome and its components will also be discussed. The impact of diabetes and hyperglycemia on stroke outcomes and a discussion of current approaches to reduce stroke in this high-risk population is included. Because Type 2 diabetes affects the vast majority of those diagnosed with diabetes, it will be the primary focus of this discussion.

### **Defining the Problem**

It has been well-documented that diabetes confers a significantly increased risk of stroke, as well as increased mortality following stroke (1-7). Stroke is a preventable disease with high personal and societal cost. While great progress has been made in understanding the link between diabetes and coronary heart disease (CHD), the literature on diabetes and stroke has been less enlightening. CHD is a larger problem that accounts for 40-50% of mortality in DM. Because of the overwhelming impact of CHD, the impact of stroke has been relatively underappreciated. Thus, physicians and diabetes educators and nurses are less equipped to educate patients. We therefore review the relationship between diabetes and stroke.

Given that more than a million people are diagnosed with diabetes yearly, a figure that is expected to rise, the impact of diabetes on the incidence of stroke is of increasing importance. Diabetic patients compose

roughly 6.3% of the U.S. population but account for 15-27% of all incident strokes, based on 2002 estimates (4, 7-12). This is certainly an underestimation as most studies classify patients as having diabetes only if diagnosed prior to stroke. When considering age-adjusted incidence rates, diabetic patients are 2.9 times as likely to have a stroke as compared to non-diabetic patients, a disparity which is seen in multiple racial/geographic groups (4, 7, 9, 13-15). This is due specifically to an increase in the rate of ischemic stroke rather than hemorrhagic stroke (7, 16-18).

The heaviest burden of stroke for the general population lies with older and minority groups (4, 12, 19-22). Diabetes appears to amplify these non-modifiable risks, in part due to the increased prevalence of diabetes in these groups. (7, 23, 24) Diabetes also confers an increased risk for neurovascular disease at younger ages (25). The Greater Cincinnati-Northern Kentucky Stroke Study (GCNKSS) found that the risk for ischemic stroke in white diabetic patients is higher at every age group compared with non-diabetic patients, with highest relative risk (RR) of 5.3 found in the 45- to 54-year group. Among African-Americans, the highest risk was even greater (RR = 9.9) and was found in the 35- to 44-year group. A substantial peak in stroke risk is seen in the 45- to 64-year age group in whites and in the 35- to 54-year age-groups in African Americans. (7).

Although stroke is more common among diabetic patients, most studies report a significantly reduced rate of transient ischemic attacks (TIAs) in diabetic patients as compared to non-diabetic patients. Diabetic patients are more likely to present with cerebral infarct, indicating that ischemia in diabetic patients is less likely to be reversible (7, 26-28). This presents a unique problem for preventing stroke in this population. TIAs can serve as a warning sign, providing a

window of opportunity for medical intervention to prevent a completed stroke. The relative lack of warning in diabetic patients requires that physicians, nurses and educators be aggressive about risk factor intervention, as comprehensive programs to reduce risk can be highly successful (29). For those that do present with a TIA, aggressive treatment is equally important since diabetes has been shown to increase the risk of subsequent, completed stroke (30).

### **Cause and Effect?**

Many attempts have been made to discern the underlying mechanisms through which diabetes increases stroke risk. Such studies have largely taken cues from the cardiovascular literature in which diabetes and the associated components of the metabolic syndrome (i.e hypertension, hyperlipidemia) have been found to contribute to cardiovascular disease development (31-33). This approach has been informative, yet the relationships between diabetes, the components of the metabolic syndrome and stroke are clearly unique. Here we discuss these individual relationships, highlighting the differences between stroke and cardiac risk.

### **Diabetes vs. Hyperglycemia**

As in any discussion of diabetes and its sequelae, the fundamental question arises as to whether stroke risk is increased due to chronic hyperglycemia. Published studies provide conflicting evidence. Lehto et al. studied 1059 diabetic patients and correlated their baseline fasting glucose levels, hemoglobin A1c (HbA1c), and duration of diabetes with stroke over 7 years of follow-up. All three factors contributed significantly to increased risk of stroke, while fasting hyperglycemia (>13.4 mmol/L) remained significant after accounting for other cardiovascular risk factors (OR 2.6; 95% CI 1.5-3.8 as compared to normoglycemia) (34). The Honolulu Heart Program reported similar

results in non-diabetic patients when comparing the extremes (80<sup>th</sup> and 20<sup>th</sup> percentiles) of serum glucose levels (RR 1.4 for thromboembolic stroke; 95% CI 1.1-1.8) (16). A Finnish cohort study measured HbA1c and fasting glucose in diabetic and non-diabetic patients. In both groups they found a significant association between each measure of glucose control and stroke risk using multivariate analysis (35). More recent data from the Atherosclerosis Risk in Communities (ARIC) study reiterated this relationship finding an increased relative risk of stroke with increasing levels of HbA1c in both diabetic and non-diabetic patients (36). In contrast, the European Prospective Investigation Into Cancer (EPIC)-Norfolk study did not find a significant relationship between HbA1c and stroke risk until a threshold level was reached (37).

The only clinical trial to date that has directly evaluated the effect of tight glucose control on stroke is the United Kingdom Prevention in Diabetes Study (UKPDS). Type 2 diabetic patients in the intensive treatment group (average HbA1c 7.0%) had no significant reduction in stroke incidence ( $p=0.52$ ) as compared to those receiving traditional medical therapy (average HbA1c 7.9%), indicating that tight glucose control is not sufficient to prevent excess strokes (38, 39), though the study may not have been sufficiently powered to detect a stroke-specific relationship and/or the intensive control may not have been “intensive enough” to substantially impact stroke incidence.

To summarize, there is no clear relationship between hyperglycemia and stroke incidence. Rather, it is apparent that diabetic patients have an increased risk of stroke regardless of their level of metabolic control.

### **Insulin Resistance, The Metabolic Syndrome and Stroke**

Without substantive evidence that intensive glucose control reduces stroke risk, the focus has shifted to insulin resistance and its associated metabolic syndrome. Type 2 diabetes, characterized by an inability to produce enough insulin to overcome insulin-resistance, frequently co-exists with a constellation of cardiovascular risk factors including hypertension, obesity, and hyperlipidemia. Together, these have been termed the metabolic syndrome (a.k.a syndrome X or insulin-resistance syndrome). The role that these factors have played individually, as well as together, in the development of cardiovascular disease (40) has made them the target of studies regarding stroke as well.

#### **Insulin Resistance**

Insulin resistance, as measured by basal hyperinsulinemia (or impaired glucose tolerance, which is equated to a state of insulin resistance) has been associated with CAD and subsequent cardiovascular events (41-44). Several studies have evaluated whether an analogous relationship exists between insulin resistance and stroke. In a retrospective study, impaired glucose tolerance was not associated with stroke (45). A prospective study of Japanese men found no relationship between insulin resistance and stroke incidence (46). In contrast, the ARIC Study found an increase in RR for ischemic stroke of 1.19 for every 50 pmol/l increase in basal insulin among non-diabetic patients, supporting a role for insulin resistance (2). This was similar to results from the elderly patient population of the Finnish cohort study which included both diabetic patients and non-diabetic patients (35). As with studies of insulin resistance and cardiovascular disease, the association of insulin resistance with stroke is attenuated by the adjustment for other cardiovascular risk factors (2, 35, 43,

44). However, data from the Third National Health and Nutrition Survey (NHANES III) revealed a small, but significant, independent association between insulin resistance and stroke when other risk factors such as hypertension and level of glycemic control were taken into account (odds ratio (OR) = 1.06) (47). To summarize, a significant association between insulin resistance and stroke risk has been found, but the magnitude of this association is less than the association seen with cardiovascular disease.

#### **Hypertension**

Among the components of the metabolic syndrome, hypertension is the single most important risk factor for the development of stroke. In this respect, stroke varies significantly from cardiac disease, where hypertension is a lesser risk factor.

Evidence suggests that some of the increased risk of stroke among diabetic patients is attributable to the increased prevalence of hypertension. The GCNKSS found that the prevalence of hypertension was 79% among diabetic patients and 57% among non-diabetic patients ( $p < 0.0001$ ) (7). A significant, though smaller, difference was found in the Copenhagen Stroke Study (48% versus 30%, respectively,  $p < .0001$ ) (10). Prospectively, follow-up of diabetic patients in the UKPDS found that the occurrence of vascular complications, including stroke, were significantly associated with hypertension (48). The converse relationship has also been seen. Among hypertensive patients, diabetes is a significant predictor of ischemic stroke (OR 3.76, CI: 1.67-8.46) (49). Data from the ARIC study suggest a similar increased risk among diabetic patients with pre-hypertension, as compared to non-diabetic patients, though the number of strokes was insufficient to calculate a relative risk for stroke alone (50). No study has included statistical modeling to specifically address whether hypertension fully accounts for the

increased risk of stroke in diabetic patients. It appears that the two are synergistic in increasing stroke risk and account for up to 40% of the population attributable risk for all ischemic strokes (7). A number of studies have found anti-hypertensive treatment to reduce the incidence of cardiovascular events, including stroke, in those with diabetes (51-57), but fewer studies have focused on stroke specifically. The Systolic Hypertension in Europe Trial specifically noted a 73% decrease in stroke incidence in diabetic patients treated with anti-hypertensive medication. Stroke incidence was decreased in non-diabetic patients by 38% (58). Thus, diabetic patients appear to benefit preferentially from anti-hypertensive treatment.

#### **Hyperlipidemia**

Hyperlipidemia is one of the most important risk factors for coronary heart/artery disease, but a less important risk factor for stroke. As with hypertension, diabetic patients who have suffered a stroke are more likely to have hyperlipidemia than those without diabetes (16% vs. 8%,  $p < 0.0001$  in the GCNKSS) (7, 10). It is currently not clear to what degree the increased prevalence of hyperlipidemia accounts for the increased risk of stroke, especially as the contribution of hyperlipidemia alone to stroke incidence is controversial (59-64). Subset analysis from large placebo-controlled trials, such as the Helsinki Heart Study and Scandinavian Simvastatin Survival Study, which evaluated cholesterol reduction as primary or secondary prevention of cardiovascular disease, indicate that diabetic patients may benefit preferentially from treatment in stroke reduction. Recently reported results from the Heart Protection Study, in contrast, did not support this difference, finding that risk reduction did not vary with diabetic status (65). The Collaborative AtoRvastatin

Diabetes Study (CARDS), which expressly evaluated the contribution of hyperlipidemia to stroke risk in the diabetic population without known coronary artery disease, was halted early due to a significant, 48% reduction in the incidence of stroke among the treatment group (66). The CARDS study, taken together with the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study (67), are highly significant, in that statin treatment can now be recommended for stroke prevention even in those patients who do not have cardiovascular disease, regardless of diabetes status. However, based on the CARDS results, it seems that patients with diabetes may significantly benefit from statins, making it even more important that those with diabetes be considered for statin treatment as part of their stroke prevention regimen.

#### **Obesity**

Obesity contributes to more than 300,000 deaths per year and nearly doubles the risk of death from all causes (68-70). Given its particular association with CAD, hypertension, and diabetes (71), investigators have attempted to discern the contribution that obesity makes to stroke incidence with variable results. Many studies utilize Body Mass Index ( $BMI = \text{weight in kg/height in m}^2$ ) which provides a broad, though non-specific, estimate of obesity, is easily obtained from patient self-report or medical charts, and is commonly used in clinical practice. Both the ARIC and Northern Manhattan Stroke Study (NOMASS) studies failed to find a convincing association between BMI and risk for stroke (2, 72). An association has been noted in studies of specific subpopulations, such as middle-aged, Korean, or non-smoking Japanese men (73-75). The Nurses Health Study reported a significant association with BMI, such that subjects with BMI of 27-28.9  $\text{kg/m}^2$  had a RR of 1.8 (95% CI 1.2-2.6), subjects with BMI of

29-31.9 kg/m<sup>2</sup> had a RR of 1.9 (95% CI 1.3-2.8), and subjects with BMI  $\geq$  32 had a RR of 2.4 (95% CI 1.6-3.5) compared to those with BMI < 25 (76). A less robust, but still significant, association was found in the Women's Health Study (77). The Physician's Health Study found a relative risk of 1.95 (95% CI, 1.39-2.72) for ischemic stroke for those with a BMI > 30 as compared to those with a BMI < 23. The risk increased by 6% for each unit increase in BMI, though it was attenuated when other cardiovascular risk factors were taken into account (78).

While BMI has been commonly used in the literature as an obesity measure, many studies have shown it to poorly reflect the health impact of obesity. Rather, abdominal obesity has been more specifically associated with vascular disease and other health complications (79). Waist-to-hip ratio (WHR), while highly correlated with BMI, better represents abdominal obesity and therefore may provide additional information on stroke risk. Despite the lack of a relationship between stroke and BMI, NOMASS did find a significant relationship between WHR and risk of stroke. Analysis included 576 ischemic strokes patients and 1142 age, gender, and race-ethnicity matched controls. Compared with the first quartile, the third and fourth quartiles of WHR had an increased risk of stroke (third quartile: OR, 2.4; 95% CI, 1.5 to 3.9; fourth quartile: OR, 3.0; 95% CI, 1.8 to 4.8) after adjustment for other risk factors. These findings were consistent across both genders and all race-ethnic groups, though the effect of WHR was stronger among younger persons (72). Direct comparison of BMI vs. WHR and stroke risk in 28,643 male healthcare professionals without previous cardiovascular or cerebrovascular disease yielded similar results. Relative risk for the 1<sup>st</sup> and 5<sup>th</sup> quintiles of WHR was 2.33 (95% confidence interval 1.25-4.37) while that for 1<sup>st</sup> and 5<sup>th</sup>

quintiles of BMI was 1.29 (95% confidence interval 0.73-2.27) (80).

Taken together, these studies suggest that obesity and, in particular, abdominal obesity is a significant risk factor for ischemic stroke (81). Regardless, the impact that obesity has on the risk of DM, CAD, hypertension and hyperlipidemia will confound studies that address the risk of stroke (71). It has been estimated that the reductions in diabetes, hypertension, and hyperlipidemia associated with a 10% weight loss could lead to reduction of stroke of up to 13 per 1000 people (82).

### Microalbuminuria

The WHO definition of the metabolic syndrome also includes microalbuminuria (30-300mg/24h) as a final component. Microalbuminuria is a significant marker of cardiovascular disease and highly associated with hypertension (83, 84). It is encountered in diabetic patients more than twice as often as in non-diabetic patients (84) and may also contribute to the increased risk of stroke. The largest, population-based, prospective study to evaluate microalbuminuria and stroke risk is the EPIC-Norfolk study. Among 23,630 individuals aged 40-79 years over 7.2 years of follow up, microalbuminuria conferred a significantly increased risk of total and ischemic stroke in multivariate modeling (HR 1.49, 95% CI 1.13-2.14 and HR 2.01, 95% CI 1.29-3.31, respectively) (85). Data from the Heart Outcomes Prevention Evaluation Study implicate microalbuminuria as a factor in stroke incidence among those with diabetes (57). Treatment of non-hypertensive, diabetic patients with an angiotensin converting enzyme inhibitor (ACE-I), a class of medications known to reduce microalbuminuria (86-88), reduced stroke incidence by 32% despite minimal decrease in blood pressure (57). These data support a role for microalbuminuria in increasing the risk of ischemic stroke which may not be entirely

dependent on its direct relationship with hypertension and other well-known stroke risk factors.

### **The Metabolic Syndrome**

Each of the components of the metabolic syndrome is associated with higher stroke risk to various degrees, as described above. As has been mentioned, analysis of individual factors causes substantial adjustment of observed risk because of the interrelationship of these factors. Therefore, studying the metabolic syndrome as a whole may provide a better estimation of the true risk for ischemic stroke.

The Botnia study examined risk for cardiovascular events and stroke conferred by the metabolic syndrome in 4,483 subjects. In a multiple logistic regression analysis, the metabolic syndrome was a significant independent risk for stroke (RR 2.3,  $p < 0.001$  as compared to those without the metabolic syndrome). None of the individual components of the metabolic syndrome contributed significantly to stroke risk (89). Similar results were obtained from examination of more than 10,000 subjects in the NHANES III. In logistic regression modeling, the metabolic syndrome was associated with increased odds of stroke (OR of 2.2 95% CI 1.5-3.2 as compared to those without the metabolic syndrome). After the metabolic syndrome was in the model, each individual component was also tested. Only hypertriglyceridemia entered as an additional factor with independent significance, while hypertension and insulin resistance/diabetes trended toward significance (90). A few studies have evaluated the risk of stroke associated with the metabolic syndrome in the absence of diabetes revealing similar 2-fold increases (91, 92). In the ARIC study, both hypertension and low HDL cholesterol independently and significantly increased risk (92).

The data presented above provide evidence that the individual components of the metabolic syndrome significantly contribute to the incidence of ischemic stroke. These components are more prevalent among diabetic patients and may act synergistically to promote increased risk of stroke. In addition, several studies support a significant relationship between the collective metabolic syndrome and ischemic stroke.

The metabolic syndrome and diabetes have in common their association with insulin resistance. At a cellular and molecular level, insulin resistance confers changes that are becoming recognized as increasingly important in the pathophysiology of vascular disease, including stroke.

### **Endothelial Dysfunction and Nitric Oxide**

Both diabetic patients and those with impaired glucose tolerance have decreased endothelium-dependent vasodilation (93, 95), either due to decreased nitric oxide production or impaired nitric oxide metabolism (95). Normally, nitric oxide exerts a protective effect against platelet aggregation and plays an important role in the response to ischemic challenge (96, 97).

Only indirect evidence is available at present linking nitric oxide dysregulation and stroke. A recent study found a decreased response of cerebrovascular blood flow to nitric oxide synthase inhibition in diabetic patients as compared to non-diabetic patients, though not enough patients were enrolled to determine significance (98). In addition, parasympathetic neurons that secrete nitric oxide into the perivascular space have been documented to degenerate and eventually die in the absence of insulin signaling (99). Numerous studies have found that HMG-CoA reductase inhibitors (statins), which up-regulate nitric oxide synthesis in addition to their activity in stabilizing atherosclerotic plaques (100), significantly reduce the risk of stroke (56, 67, 101-104) The dual actions of

statins makes it difficult to distinguish which action exerts the greatest effect. However, the growing body of evidence indicates that statins exert protective effects against stroke independent of changes in cholesterol levels.

### **Hypercoagulability Conferred by Diabetes**

Defects in endothelial function may be further confounded by the hypercoagulable state of diabetic patients. Plasminogen activator inhibitor-1 (PAI-1) and antithrombin III, which inhibit fibrinolysis, as well as tissue plasminogen activator (tPA) antigen, a marker of impaired fibrinolysis, consistently have been found to be elevated in diabetic patients and those with insulin resistance (105-107). Some studies have further suggested that coagulation factors, such as factor VII, factor VIII, and von Willebrand factor also rise with degree of insulin resistance (108, 109). This up-regulation is likely secondary to a chronic inflammatory state induced by diabetes as several inflammatory markers (C-reactive protein, Lipoprotein-associated phospholipase A<sub>2</sub>) have been correlated with increased thrombotic factors as well as stroke incidence (108, 110-112). The promotion of thrombus formation likely occurs via platelet hyper-reactivity. Studies of platelets from diabetic patients have found increased aggregation in response to adenosine diphosphate (ADP) (113), a response that may be mediated by the upregulation of GPIIb-IIIa receptors that occurs in diabetic patients (114). Insulin normally acts to inhibit platelet aggregation in response to ADP; however this action is attenuated in diabetic patients (115). Thromboxane A<sub>2</sub> is also elevated in diabetic patients, possibly contributing to hyperaggregation as well (116).

The relative contribution of these mechanisms to increased ischemic stroke risk in those with diabetes has not been specifically evaluated, though several studies have implicated these pathways in the general population. In both cross-sectional and

prospective studies, increased tPA antigen and PAI-1 levels have been significantly associated with ischemic stroke (117-119). Treatment with aspirin or clopidogrel targets platelet aggregation by inhibiting thromboxane A<sub>2</sub> and ADP respectively, and are now widely used in the secondary prevention of stroke as they significantly reduce the risk of recurrent stroke (120-125). Several trials, such as the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA), Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH) studies, evaluated whether diabetic patients derived more or less benefit from anti-platelet therapy in preventing recurrent ischemic events with mixed results. As the reported end-point in these studies was a composite of all ischemic events and mortality, the specific impact of anti-platelet therapy in diabetic patients on stroke is unclear (126-128). Further investigation is required to determine the relative importance of these mechanisms in diabetic patients.

### ***Carotid Intima-media Thickness (CIMT)***

Consideration has also been given to the impact of the increased incidence of atherosclerosis among those with diabetes and stroke incidence. CIMT has been found in a number of studies to be increased with diabetes. The Insulin Resistance Atherosclerosis Study (IRAS) found a significant increase in common carotid thickness in the setting of established diabetes as compared to those with newly diagnosed diabetes (129). Though not to the same degree, impaired glucose tolerance is also associated with increased CIMT (130). Diabetic patients that have suffered a stroke have significantly greater CIMT than both those without stroke and non-diabetic patients

(131, 132). As hyperglycemia, regardless of diabetes duration, was directly related to CIMT, tight glucose control may yield benefits on carotid disease (129).

### **Surviving stroke**

Despite the uncertainties of the pathogenesis of stroke in those with diabetes, the impact of hyperglycemia and diabetes on outcomes has been more consistently defined. Hyperglycemia during the post-stroke period, regardless of diabetic status, is associated with increased morbidity and mortality. Studies have generally found increased 30-day and 1-year mortality rates among hyperglycemic patients (133-137), although increased mortality was not seen in other studies (7, 138). Morbidity, as defined by functional outcome and neurologic recovery, is also worsened in the setting of hyperglycemia and diabetes (134, 139-142). This holds true among those with only transient hyperglycemia, though such individuals fare better than those with chronically elevated glucose levels whether diagnosed pre- or post-stroke with diabetes (143, 144). In imaging studies, the initial infarct size and infarct progression are greater in hyperglycemic patients (142, 145-147). One recent study has found a decreased recanalization rate following rt-PA administration in the presence of hyperglycemia, though this was not seen in the previous NINDS rt-PA trial (139, 148). Normalization of glucose levels was associated with 4.6 times decreased risk in mortality in one retrospective study indicating the potentially large impact that can be made with aggressive medical management in these patients (149).

Diabetes is also one of the most consistent predictors of recurrent stroke or stroke after TIA (150-162). The increased risk of recurrent stroke due to diabetes ranges from 2.1 to 5.6 times that of non-diabetic patients (154, 156) and is independent of

glucose control during the inter-stroke period (163). The significance of these findings is underscored by the increased morbidity and mortality associated with recurrent stroke (164).

### **Challenges Ahead**

Diabetes significantly increases the risk of incident stroke and stroke recurrence. The magnitude of this problem will continue to expand as the prevalence of diabetes increases in the U.S., thus presenting numerous challenges for the future. Foremost among these is educating those with diabetes as to their true risk of stroke. A significant barrier appears to be the incongruence between the information the medical community believes it is imparting to patients and the actual level of knowledge demonstrated by patients. Ninety percent of physicians report discussing the risk of cardiovascular disease and the importance of prevention, though only half of patients report their physician had discussed risk factor modification (165). Recent data from the REduction of Atherothrombosis for Continued Health (REACH) registry corroborates the continued undertreatment of cardiovascular risk factors (166). Frequent and repeated patient advising regarding cardiovascular and cerebrovascular complications of diabetes and warning signs is necessary to improve upon utilization of primary and secondary prevention measures.

The potential benefit of aggressive multiple-risk reduction measures in those with diabetes has been highlighted by the Steno-2 Study. Intensive, standardized, risk factor reduction, including: a.) treatment of hyperglycemia, hypertension, dyslipidemia, and microalbuminuria; b.) secondary prevention of cardiovascular disease with aspirin; and c.) behavioral modification resulted in significant reductions in cardiovascular disease, including stroke (HR, 0.47; 95% CI, 0.24 to 0.73). This effect was

larger than that seen in studies which targeted treatment to individual risk factors (29). Though the specific mechanisms which underlie the relationship between diabetes, the metabolic syndrome, and stroke require

ongoing investigation to provide new methods for prevention and treatment, these data underscore the strides that can be made with the tools at hand.

## References

1. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, Holman RR: UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke*. 33:1776-1781, 2002.
2. 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 1077-1083.
3. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E: Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. *Stroke*. 27:210-215, 1996.
4. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB: Probability of stroke: a risk profile from the Framingham Study. *Stroke* 22:312-318, 1991.
5. Ho JE, Paultre F, Mosca L: Is diabetes mellitus a cardiovascular disease risk equivalent for fatal stroke in women? Data from the Women's Pooling Project. *Stroke*. 34:2812-2816, 2003.
6. Davis BR, Vogt T, Frost PH, Burlando A, Cohen J, Wilson A, Brass LM, Frishman W, Price T, Stamler J: Risk factors for stroke and type of stroke in persons with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *Stroke*. 29:1333-1340, 1998.
7. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP. Epidemiology of ischemic stroke in patients with diabetes: the Greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 28:355-359, 2005.
8. Centers for Disease Control. *National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2002*. 2003, Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta, GA.
9. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke W, Diener HC: Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke*. 32:2559-2566, 2001.
10. Jorgensen H, Nakayama H, Raaschou HO, Olsen TS: Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke*. 25:1977-1984, 1994.
11. Lai SM, Alter M, Friday G, Sobel E: Prognosis for survival after an initial stroke. *Stroke*. 26:2011-2015, 1995.

12. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*. 35:426-431, 2004.
13. Self-reported heart disease and stroke among adults with and without diabetes--United States, 1999-2001. *MMWR Morb Mortal Wkly Rep*. 52:1065-1070, 2003.
14. Almdal T, Scharling H, Jensen JS, Vestergaard H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med*. 164:1422-1426, 2004.
15. Ottenbacher KJ, Ostir GV, Peek MK, Markides KS: Diabetes mellitus as a risk factor for stroke incidence and mortality in Mexican American older adults. *J Gerontol A Biol Sci Med Sci*. 59:M640-645, 2004.
16. Abbott RD, Donahue RP, MacMahon SW, Reed DM, Yano K: Diabetes and the risk of stroke. The Honolulu Heart Program. *JAMA*. 257:949-952, 1987.
17. Adams HP, Jr., Putman SF, Kassell NF, Torner JC: Prevalence of diabetes mellitus among patients with subarachnoid hemorrhage. *Arch Neurol*. 41:1033-1035, 1984.
18. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G: Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology*. 62:1558-1562, 2004.
19. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke*. 27:373-380, 1996.
20. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, Paik MC, Hauser WA. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol*. 147:259-268, 1998.
21. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R: The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke*. 29:415-421, 1998.
22. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akuwumi O, Al-Wabil A, Al-Senani F, Brown DL, Moya LA: Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 160:376-383, 2004.
23. Harris MI: Diabetes in America: epidemiology and scope of the problem. *Diabetes Care*. 21 Suppl 3:C11-14, 1998.

24. Kannel WB, McGee DL: Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 241:2035-2038, 1979.
25. Booth GL, Kapral MK, Fung K, Tu JV: Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 368:29-36, 2006.
26. Fritz VU, Bilchik T, Levien LJ: Diabetes as risk factor for transient ischaemic attacks as opposed to strokes. *Eur J Vasc Surg*. 1:259-262, 1987.
27. Weinberger J, Biscarra V, Weisberg MK, Jacobson JH: Factors contributing to stroke in patients with atherosclerotic disease of the great vessels: the role of diabetes. *Stroke*. 14:709-712, 1983.
28. Lithner F, Asplund K, Eriksson S, Hagg E, Strand T, Wester PO: Clinical characteristics in diabetic stroke patients. *Diabete Metab*. 14:15-19, 1988.
29. 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*. 348:383-393, 2003.
30. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 369:283-292, 2007.
31. Mooradian AD: Cardiovascular disease in type 2 diabetes mellitus: current management guidelines. *Arch Intern Med*. 163:33-40, 2003.
32. Bloomgarden ZT: Cardiovascular disease in type 2 diabetes. *Diabetes Care*. 22:1739-1744, 1999.
33. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Jr., Sowers JR: Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 100:1134-1146, 1999.
34. Lehto S, Ronnema T, Pyorala K, Laakso M: Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke*. 27:63-68, 1996.
35. Kuusisto J, Mykkanen L, Pyorala K, Laakso M: Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke*. 25:1157-1164, 1994.
36. Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR: Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Lancet Neurol*. 4:821-826, 2005.

37. Myint PK, Sinha S, Wareham NJ, Bingham SA, Luben RN, Welch AA, Khaw KT: Glycated hemoglobin and risk of stroke in people without known diabetes in the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study: a threshold relationship? *Stroke*. 38:271-275, 2007.
38. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 352:854-865, 1998.
39. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 352:837-853, 1998.
40. Uwaifo GI, Ratner RE: The roles of insulin resistance, hyperinsulinemia, and thiazolidinediones in cardiovascular disease. *Am J Med*. 115 Suppl 8A:12S-19S, 2003.
41. Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med*. 334:952-957, 1996.
42. Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K: Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol*. 20:538-544, 2000.
43. Lakka HM, Lakka TA, Tuomilehto J, Sivenius J, Salonen JT: Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Arch Intern Med*. 160:1160-1168, 2000.
44. Bonora E, Willeit J, Kiechl S, Oberhollenzer F, Egger G, Bonadonna R, Muggeo M: U-shaped and J-shaped relationships between serum insulin and coronary heart disease in the general population. The Bruneck Study. *Diabetes Care*. 21:221-230, 1998.
45. Qureshi AI, Giles WH, Croft JB: Impaired glucose tolerance and the likelihood of nonfatal stroke and myocardial infarction: the Third National Health and Nutrition Examination Survey. *Stroke*. 29:1329-1332, 1998.
46. Adachi H, Hirai Y, Tsuruta M, Fujiura Y, Imaizumi T: Is insulin resistance or diabetes mellitus associated with stroke? An 18-year follow-up study. *Diabetes Res Clin Pract*. 51:215-223, 2001.
47. Bravata DM, Wells CK, Kernan WN, Concato J, Brass LM, Gulanski BI: Association between impaired insulin sensitivity and stroke. *Neuroepidemiology*. 25:69-74, 2005.

48. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*.j 321:412-419, 2000.
49. Khealani BA, Syed NA, Maken S, Mapari UU, Hameed B, Ali S, Qureshi R, Akhter N, Hassan A, Sonawalla AB, Baig SM, Wasay M: Predictors of ischemic versus hemorrhagic strokes in hypertensive patients. *J Coll Physicians Surg Pak*. 15:22-25, 2005.
50. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE: Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med*. 119:133-141, 2006.
51. 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*. 317:713-720, 1998.
52. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD: Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care*. 23:888-892, 2000.
53. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F: Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care*. 21:597-603, 1998.
54. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 353:611-616, 1999.
55. 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*. 338:645-652, 1998.
56. 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*. 355:253-259, 2000.
57. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, Davies R, Ostergren J, Probstfield J: Use of ramipril in preventing stroke: double blind randomised trial. *BMJ*. 324:699-702, 2002.

58. Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R: Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med.* 340:677-684, 1999.
59. Iso H, Jacobs DR, Jr., Wentworth D, Neaton JD, Cohen JD: Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med.* 320:904-910, 1989.
60. Laws A, Marcus EB, Grove JS, Curb JD: Lipids and lipoproteins as risk factors for coronary heart disease in men with abnormal glucose tolerance: the Honolulu Heart Program. *J Intern Med.* 234:471-478, 1993.
61. Kagan A, Popper JS, Rhoads GG: Factors related to stroke incidence in Hawaii Japanese men. The Honolulu Heart Study. *Stroke.* 11:14-21, 1980.
62. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR: Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke.* 34:623-631, 2003.
63. Harmsen P, Rosengren A, Tsipogianni A, Wilhelmsen L: Risk factors for stroke in middle-aged men in Goteborg, Sweden. *Stroke.* 21:223-229, 1990.
64. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet.* 346:1647-1653, 1995.
65. 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.* 361:2005-2016, 2003.
66. 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.* 364:685-696, 2004.
67. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, Silleesen H, Simunovic L, Szarek M, Welch KM, Zivin JA: High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 355:549-559, 2006.
68. The Surgeon General's 1989 Report on Reducing the Health Consequences of Smoking: 25 Years of Progress. *MMWR Morb Mortal Wkly Rep.* 38:1-32., 1989.
69. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Correction: actual causes of death in the United States, 2000. *JAMA.* 293:293-294, 2005.

70. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. *JAMA*. 291:1238-1245, 2004.
71. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB: Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 162:1867-1872, 2002.
72. Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC: Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke*. 34:1586-1592, 2003.
73. Jood K, Jern C, Wilhelmsen L, Rosengren A: Body Mass Index in Mid-Life Is Associated With a First Stroke in Men. A Prospective Population Study Over 28 Years. *Stroke*. 35: 2764-2769, 2004.
74. Song YM, Sung J, Davey Smith G, Ebrahim S: Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. *Stroke*. 35:831-836, 2004.
75. Abbott RD, Behrens GR, Sharp DS, Rodriguez BL, Burchfiel CM, Ross GW, Yano K, Curb JD: Body mass index and thromboembolic stroke in nonsmoking men in older middle age. The Honolulu Heart Program. *Stroke*. 25:2370-2376, 1994.
76. Rexrode KM, Hennekens CH, Willett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE: A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA*. 277:1539-1545, 1997.
77. Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE: Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation*. 111:1992-1998, 2005.
78. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE: Body mass index and the risk of stroke in men. *Arch Intern Med*. 162:2557-2562, 2002.
79. Megnien JL, Denarie N, Cocaul M, Simon A, Levenson J: Predictive value of waist-to-hip ratio on cardiovascular risk events. *Int J Obes Relat Metab Disord*. 23:90-97, 1999.
80. Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC: Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol*. 144:1143-1150, 1996.
81. Lu M, Ye W, Adami HO, Weiderpass E: Prospective study of body size and risk for stroke amongst women below age 60. *J Intern Med*. 260:442-450, 2006.
82. Oster G, Thompson D, Edelsberg J, Bird AP, Colditz GA: Lifetime health and economic benefits of weight loss among obese persons. *Am J Public Health*. 89:1536-1542, 1999.

83. Ravera M, Ratto E, Vettoretti S, Viazzi F, Leoncini G, Parodi D, Tomolillo C, Del Sette M, Maviglio N, Deferrari G, Pontremoli R: Microalbuminuria and subclinical cerebrovascular damage in essential hypertension. *J Nephrol.* 15:519-524, 2002.
84. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 286:421-426, 2001.
85. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ: Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *J Intern Med.* 255:247-256, 2004.
86. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Menard J: Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ.* 328:495, 2004.
87. Slowik A, Turaj W, Iskra T, Strojny J, Szczudlik A: Microalbuminuria in nondiabetic patients with acute ischemic stroke: prevalence, clinical correlates, and prognostic significance. *Cerebrovasc Dis.* 14:15-21, 2002.
88. Lasaridis AN, Sarafidis PA: Diabetic nephropathy and antihypertensive treatment: what are the lessons from clinical trials? *Am J Hypertens.* 16:689-697, 2003.
89. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 24:683-689, 2001.
90. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the third national health and nutrition examination survey. *Circulation.* 109:42-46, 2004.
91. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssonen K, Salonen JT: Metabolic syndrome and the risk of stroke in middle-aged men. *Stroke.* 37:806-811, 2006.
92. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, Ballantyne CM, Heiss G: The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *D Care.* 28:385-390, 2005.
93. Hogikyan RV, Galecki AT, Pitt B, Halter JB, Greene DA, Supiano MA: Specific impairment of endothelium-dependent vasodilation in subjects with type 2 diabetes independent of obesity. *J Clin Endocrinol Metab.* 83:1946-1952, 1998.

94. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD: Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest.* 97:2601-2610, 1996.
95. Maejima K, Nakano S, Himeno M, Tsuda S, Makiishi H, Ito T, Nakagawa A, Kigoshi T, Ishibashi T, Nishio M, Uchida K: Increased basal levels of plasma nitric oxide in Type 2 diabetic subjects. Relationship to microvascular complications. *J Diabetes Complications.* 15:135-143, 2001.
96. McCarty MF: Up-regulation of endothelial nitric oxide activity as a central strategy for prevention of ischemic stroke- just say NO to stroke! *Med Hypotheses.* 55:386-403, 2000.
97. Cosentino F, Rubattu S, Savoia C, Venturelli V, Pagannone E, Volpe M: Endothelial dysfunction and stroke. *J Cardiovasc Pharmacol.* 38 Suppl 2:S75-78, 2001.
98. Nazir FS, Alem M, Small M, Connell JM, Lees KR, Walters MR, Cleland SJ: Blunted response to systemic nitric oxide synthase inhibition in the cerebral circulation of patients with Type 2 diabetes. *Diabet Med.* 23:398-402, 2006.
99. Cellek S, Anderson PN, Foxwell NA: Nitrergic neurodegeneration in cerebral arteries of streptozotocin-induced diabetic rats: a new insight into diabetic stroke. *Diabetes.* 54:212-219, 2005.
100. Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, Liao JK: Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A.* 95:8880-8885, 1998.
101. Gil-Nunez AC, Villanueva JA: Advantages of lipid-lowering therapy in cerebral ischemia: role of HMG-CoA reductase inhibitors. *Cerebrovasc Dis.* 11 1:85-95, 2001.
102. Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Bernstein V, Cuddy TE, Moye LA, Piller LB, Rutherford J, Simpson LM, Braunwald E: Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The Care Investigators. *Circulation.* 99:216-223, 1999.
103. Blauw GJ, Lagaay AM, Smelt AH, Westendorp RG: Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke.* 28:946-950, 1997.
104. Collins R, Armitage J, Parish S, Sleight P, Peto R: Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet.* 363:757-767, 2004.
105. Aoki I, Shimoyama K, Aoki N, Homori M, Yanagisawa A, Nakahara K, Kawai Y, Kitamura SI, Ishikawa K: Platelet-dependent thrombin generation in patients with

- diabetes mellitus: effects of glycemic control on coagulability in diabetes. *J Am Coll Cardiol.* 27:560-566, 1996.
106. Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW: Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA.* 283:221-228, 2000.
  107. Davi G, Gennaro F, Spatola A, Catalano I, Averna M, Montalto G, Amato S, Notarbartolo A: Thrombin-antithrombin III complexes in type II diabetes mellitus. *J Diabetes Complications.* 6:7-11, 1992.
  108. Romano M, Guagnano MT, Pacini G, Vigneri S, Falco A, Marinopiccoli M, Manigrasso MR, Basili S, Davi G: Association of inflammation markers with impaired insulin sensitivity and coagulative activation in obese healthy women. *J Clin Endocrinol Metab.* 88:5321-5326, 2003.
  109. Mertens I, Van Gaal LF: Obesity, haemostasis and the fibrinolytic system. *Obes Rev.* 3:85-101, 2002.
  110. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Chambless LE, Myerson M, Wu KK, Sharrett AR, Boerwinkle E: Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med.* 165:2479-2484, 2005.
  111. Adeniyi A, Folsom AR, Brancati FL, Desvorieux M, Pankow JS, Taylor H: Incidence and risk factors for cardiovascular disease in African Americans with diabetes: the Atherosclerosis Risk in Communities (ARIC). *J Natl Med Assoc.* 94:1025-1035, 2002.
  112. Engstrom G, Stavenow L, Hedblad B, Lind P, Eriksson KF, Janzon L, Lindgarde F: Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke: a population-based study. *Diabetes.* 52:442-447, 2003.
  113. Mandal S, Sarode R, Dash S, Dash RJ: Hyperaggregation of platelets detected by whole blood platelet aggregometry in newly diagnosed noninsulin-dependent diabetes mellitus. *Am J Clin Pathol.* 100:103-107, 1993.
  114. Tschoepe D, Roesen P, Kaufmann L, Schauseil S, Kehrel B, Ostermann H, Gries FA: Evidence for abnormal platelet glycoprotein expression in diabetes mellitus. *Eur J Clin Invest.* 20:166-170, 1990.
  115. Trovati M, Mularoni EM, Burzacca S, Ponziani MC, Massucco P, Mattiello L, Piretto V, Cavalot F, Anfossi G: Impaired insulin-induced platelet antiaggregating effect in obesity and in obese NIDDM patients. *Diabetes.* 44:1318-1322, 1995.

116. Halushka PV, Rogers RC, Loadholt CB, Colwell JA: Increased platelet thromboxane synthesis in diabetes mellitus. *J Lab Clin Med.* 97:87-96, 1981.
117. Macko RF, Kittner SJ, Epstein A, Cox DK, Wozniak MA, Wityk RJ, Stern BJ, Sloan MA, Sherwin R, Price TR, McCarter RJ, Johnson CJ, Earley CJ, Buchholz DW, Stolley PD: Elevated tissue plasminogen activator antigen and stroke risk: The Stroke Prevention In Young Women Study. *Stroke.* 30:7-11, 1999.
118. Lindgren A, Lindoff C, Norrving B, Astedt B, Johansson BB: Tissue plasminogen activator and plasminogen activator inhibitor-1 in stroke patients. *Stroke.* 27:1066-1071, 1996.
119. Ridker PM, Hennekens CH, Stampfer MJ, Manson JE, Vaughan DE: Prospective study of endogenous tissue plasminogen activator and risk of stroke. *Lancet.* 343:940-943, 1994.
120. Teal PA: Recent clinical trial results with antiplatelet therapy: implications in stroke prevention. *Cerebrovasc Dis.* 17 Suppl 3:6-10, 2004.
121. Lalouschek W, Lang W, Mullner M: Current strategies of secondary prevention after a cerebrovascular event: the Vienna stroke registry. *Stroke.* 32:2860-2866, 2001.
122. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. *N Engl J Med.* 325:1261-1266, 1991.
123. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. *Lancet.* 338:1345-1349, 1991.
124. A randomized trial of aspirin and sulfipyrazone in threatened stroke. The Canadian Cooperative Study Group. *N Engl J Med.* 299:53-59, 1978.
125. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A: European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 143:1-13, 1996.
126. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 348:1329-1339, 1996.
127. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 354:1706-1717, 2006.

128. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ: Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 364:331-337, 2004.
129. Wagenknecht LE, D'Agostino R, Jr., Savage PJ, O'Leary DH, Saad MF, Haffner SM: Duration of diabetes and carotid wall thickness. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*. 28:999-1005, 1997.
130. Brohall G, Oden A, Fagerberg B: Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet Med*. 23:609-616, 2006.
131. Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S: Correlation between common carotid arterial wall thickness and ischemic stroke in patients with type 2 diabetes mellitus. *Metabolism*. 51:244-247, 2002.
132. Chlumsky J, Charvat J, Empana JP, Zureik M, Garipey J, Courbon D, Dartigues JF, Ritchie K, Tzourio C, Alperovitch A, Ducimetiere P, Brohall G, Oden A, Fagerberg B, Tsivgoulis G, Vemmos KN, Spengos K, Papamichael CM, Cimboneriu A, Zis V, Zakopoulos N, Mavrikakis M, Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S: Echocardiography and carotid sonography in diabetic patients after cerebrovascular attacks. *J Int Med Res*. 34:689-694, 2006.
133. 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*. 314:1303-1306, 1997.
134. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med*. 74:540-544, 1983.
135. Toni D, Sacchetti ML, Argentino C, Gentile M, Cavalletti C, Frontoni M, Fieschi C: Does hyperglycaemia play a role on the outcome of acute ischaemic stroke patients? *J Neurol*. 239:382-386, 1992.
136. Moulin T, Tatu L, Crepin-Leblond T, Chavot D, Berges S, Rumbach T: The Besancon Stroke Registry: an acute stroke registry of 2,500 consecutive patients. *Eur Neurol*. 38:10-20, 1997.
137. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR: Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 59:67-71, 2002.

138. Kronmal RA, Barzilay JI, Smith NL, Psaty BM, Kuller LH, et al. Mortality in Pharmacologically Treated Older Adults with Diabetes: The Cardiovascular Health Study, 1989–2001. *PLoS Medicine* Vol. 3, No. 10, e400 (doi:10.1371/journal.pmed.0030400).
139. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE: Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 59:669-674, 2002.
140. Bruno A, Biller J, Adams HP, Jr., Clarke WR, Woolson RF, Williams LS, Hansen MD: Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurology*. 52:280-284, 1999.
141. 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*. 55:263-270, 1992.
142. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM: Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 52:20-28, 2002.
143. Szczudlik A, Slowik A, Turaj W, Wyrwicz-Petkow U, Pera J, Dziedzic T, Trabka-Janik E, Iskra T: Transient hyperglycemia in ischemic stroke patients. *J Neurol Sci*. 189:105-111, 2001.
144. Topic E, Pavlicek I, Brinar V, Korsic M: Glycosylated haemoglobin in clarification of the origin of hyperglycaemia in acute cerebrovascular accident. *Diabet Med*. 6:12-15, 1989.
145. de Falco FA, Sepe Visconti O, Fucci G, Caruso G: Correlation between hyperglycemia and cerebral infarct size in patients with stroke. A clinical and X-ray computed tomography study in 104 patients. *Schweiz Arch Neurol Psychiatr*. 144:233-239, 1993.
146. Kushner M, Nencini P, Reivich M, Rango M, Jamieson D, Fazekas F, Zimmerman R, Chawluk J, Alavi A, Alves W: Relation of hyperglycemia early in ischemic brain infarction to cerebral anatomy, metabolism, and clinical outcome. *Ann Neurol*. 28:129-135, 1990.
147. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM: Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 34:2208-2214, 2003.
148. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, Quintana M, Alvarez-Sabin J: Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke*. 36:1705-1709, 2005.

149. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J: Decreased mortality by normalizing blood glucose after acute ischemic stroke. *Acad Emerg Med.* 13:174-180, 2006.
150. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD: Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke.* 34:1457-1463, 2003.
151. Johnston SC, Sidney S, Bernstein AL, Gress DR: A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. *Neurology.* 60:280-285, 2003.
152. Staaf G, Lindgren A, Norrving B: Pure motor stroke from presumed lacunar infarct: long-term prognosis for survival and risk of recurrent stroke. *Stroke.* 32:2592-2596, 2001.
153. Eriksson SE, Olsson JE: Survival and recurrent strokes in patients with different subtypes of stroke: a fourteen-year follow-up study. *Cerebrovasc Dis.* 12:171-180, 2001.
154. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, Stewart-Wynne EG: Long-term risk of first recurrent stroke in the Perth Community Stroke Study. *Stroke.* 29:2491-2500, 1998.
155. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology.* 50:208-216, 1998.
156. Alter M, Sobel E, McCoy RL, Francis ME, Davanipour Z, Shofer F, Levitt LP, Meehan EF: Stroke in Lehigh Valley: risk factors for recurrent stroke. *Neuro.* 37:503-507, 1987.
157. Hier DB, Foulkes MA, Swiontoniowski M, Sacco RL, Gorelick PB, Mohr JP, Price TR, Wolf PA: Stroke recurrence within 2 years after ischemic infarction. *Stroke.* 22:155-161, 1991.
158. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR: Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. *Stroke.* 20:983-989, 1989.
159. Sacco RL, Shi T, Zamanillo MC, Kargman DE: Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology.* 44:626-634, 1994.
160. Soda T, Nakayasu H, Maeda M, Kusumi M, Kowa H, Awaki E, Saito J, Nakashima K: Stroke recurrence within the first year following cerebral infarction - Tottori University Lacunar Infarction Prognosis Study (TULIPS). *Acta Neurol Scand.* 110:343-349, 2004.
161. Lee AH, Somerford PJ, Yau KK: Risk factors for ischaemic stroke recurrence after hospitalisation. *Med J Aust.* 181:244-246, 2004.

162. Berthet K, Neal BC, Chalmers JP, MacMahon SW, Bousser MG, Colman SA, Woodward M: Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial. *Blood Press.* 13:7-13, 2004.
163. Alter M, Lai SM, Friday G, Singh V, Kumar VM, Sobel E: Stroke recurrence in diabetics. Does control of blood glucose reduce risk? *Stroke.* 28:1153-1157, 1997.
164. Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS: Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. *Neurology.* 48:891-895, 1997.
165. American Diabetes Association/American College of Cardiology. *The diabetes-heart disease link: surveying attitudes, knowledge and risk.* 2003, American Diabetes Association/American Academy of Cardiology. p. 1-4.
166. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liao CS, Richard AJ, Rother J, Wilson PW: International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA.* 295:180-189, 2006.