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

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Running title: Diabetes and Ischemic Stroke

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Received for publication 21 July 2007 and accepted in revised form 8 September 2007.
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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\(^{th}\) and 20\(^{th}\) 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 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 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 and stroke incidence (46). 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 = weight in kg/height in m²) 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 kg/m² had a RR of 1.8 (95% CI 1.2-2.6), subjects with BMI of
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29-31.9 kg/m² had a RR of 1.9 (95% CI 1.3-2.8), and subjects with BMI ≥ 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 1st and 5th quintiles of WHR was 2.33 (95% confidence interval 1.25-4.37) while that for 1st and 5th 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
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Statins makes it difficult 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.

**Hypercoaguability 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 A2) 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 A2 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 A2 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.
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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


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