Obesity has been described as “the great humbler” because so many investigators have anticipated finding an easy cure only to learn that it is stubbornly difficult to treat.1 With the exception of bariatric surgery, no major treatment breakthroughs have emerged despite decades of scientific inquiry. All this may change as a result of research that has begun to identify the humoral and behavioral forces that sustain body weight and limit the losses achievable with dietary modification.2,3 As these investigations unfold, there is reason to anticipate new therapies that safely modify appetite and eating behaviors and change how we manage obesity.

As effective treatment become feasible, obesity may constitute an important frontier for neurologists and other clinicians caring for stroke patients. This highly prevalent risk factor for stroke afflicts a large proportion of adults4 and represents a logical target for both primary and secondary prevention. In this article, we provide a narrative review of salient research that supports the optimistic view that obesity treatment will substantially reduce the burden of stroke.

Epidemiology of Obesity and Stroke
The prevalence of obesity among adults in the United States (defined as a body mass index [BMI] ≥30 kg/m²) has increased from 13% to 34% over the past half-century.4 A similar trend has been observed in other countries although the absolute prevalence of obesity varies considerably.5,6 For example, compared with the United States, current obesity rates are lower in Canada (24%), Germany (23%), and China (4%).

Over 40 published studies, between 1983 and 2011, have examined the association between obesity and cerebrovascular disease. Almost all measured obesity with the BMI; some also used measures of central obesity such as the waist-to-hip ratio or waist circumference. With few exceptions, each study reported at least one measure of adiposity to be significantly associated with increased risk for stroke. For every 1 unit increase in BMI (≈7 pounds for a human of average height), the risk for ischemic stroke increases ≈5%7–9 and the risk seems to be nearly linear starting with a still-normal BMI of ≈20 kg/m².

Four important themes emerge from research on the association between obesity and stroke risk. First, compared with BMI, measures of central obesity are better predictors of stroke in most10–15 but not every study.16 Second, the relative risk for stroke associated with obesity seems to be higher for middle-aged compared with older individuals.16,17 Third, the association is true for both ischemic and intraparenchymal hemorrhage,9,17 but it is more consistently demonstrated for the former.7,8,18

Finally, the association between obesity and increased risk for stroke is substantially explained by hypercholesterolemia, hypertension, and diabetes mellitus.7,9,10,14,16,18 Most researchers regard these as intermediate variables (ie, they are each caused by obesity and independently increase the risk of cerebrovascular disease) and, therefore, omit them from models examining the association between obesity and risk for stroke.

Obesity in Patients with Established Cerebrovascular Disease
Prevalence
The prevalence and consequences of obesity among stroke patients have not been thoroughly studied. Available estimates indicate it may be 18% to 44% as defined by total obesity (ie, BMI) and 36% as defined by central measures.19–23

Associated Conditions
Not surprisingly, obese survivors of stroke are more likely to have certain vascular risk factors, including diabetes mellitus, low high-density lipoprotein (HDL), cholesterol, hypertension, and obstructive sleep apnea.21,23–25 Obstructive sleep apnea is associated with poorer outcome and higher mortality after stroke.26

Effect on Response to Therapy
A small number of studies suggest that obesity may confer a poorer response to tissue plasminogen activator,7 lower likelihood of discharge home,19 and poorer response to rehabilitation.28 However, the effectiveness of blood pressure lowering therapy after stroke is not affected by body weight.29

Effect on Prognosis
The association between total or abdominal obesity and risk for recurrent stroke or survival has been examined in only a few studies.20,21,23,24,30 These have not demonstrated
an association between obesity and risk for recurrence.\textsuperscript{21,23} Paradoxically, poststroke mortality, as well as the composite outcome of major cardiovascular events (ie, stroke, myocardial infarction, or vascular death), may be lower among some stroke survivors who are overweight or obese compared with those of normal weight.\textsuperscript{20,21,24,30} Age seems to modify this effect such that obesity is associated with increased mortality among young stroke survivors and reduced mortality among older survivors.\textsuperscript{24}

The finding that some stroke survivors seem to be protected by obesity has been termed the “obesity paradox.”\textsuperscript{21} There are several potential explanations for the paradox. Obese stroke patients, compared with low or normal weight patients, may experience stroke subtypes associated with lower recurrence risk or receive more aggressive therapy.\textsuperscript{21} Alternatively, the paradox may simply reflect a survival bias; obese patients who have survived until their event may be somehow healthier individuals or have metabolically benign obesity (see below).

Hemiparetic stroke may exacerbate metabolic abnormalities of obesity and increase risk for weight gain, insulin resistance, and diabetes mellitus. The purported mechanisms include loss of skeletal muscle and reduced physical activity, which will combine to reduce energy intake and predispose to weight gain. Hemiparetic muscle, furthermore, may undergo tissue level changes that include intramuscular fat accumulation and a switch from slow-twitch fibers to fast myosin heavy chain fibers.\textsuperscript{31,32} Myosin heavy chain fibers rely on anaerobic metabolism, which can predispose patients to oxidative injury and inflammation that contributes to glucose intolerance. Taken together, these poststroke changes constitute a condition of sarcopenic obesity, which may contribute to the high prevalence (about 75%) of impaired glucose tolerance and diabetes mellitus in stroke survivors.\textsuperscript{33}

### Determinants of Body Weight

Body weight is determined by the balance of calories consumed in food and calories expended for maintenance of resting cellular function and physical work.\textsuperscript{35} Consumption that exceeds expenditure will, over time, result in weight gain. Factors that influence calorie consumption include genetics, social environment, food availability, knowledge, personal psychology, and several redundant neurohormonal cues that are incompletely understood.\textsuperscript{35}

For an individual who overcomes the powerful genetic and environmental factors that influence his or her eating behavior, weight loss is constrained by the dynamic nature of energy expenditure and neurochemical control of eating behavior.\textsuperscript{34,36} A fixed calorie deficit lower than that required to maintain current weight will result in nonlinear weight loss. As weight is lost, energy expenditure declines until it again matches energy intake and weight stabilizes. Further weight loss requires further reduction in intake.\textsuperscript{34} This process of metabolic adaptation explains why one-time adjustments to caloric intake are not sufficient to sustain continuing weight loss.

Persons enrolled in weight loss programs generally regain weight to baseline over months to years.\textsuperscript{37,38} The simple explanation is nonadherence to dietary modifications. Behind this simplistic explanation, however, are biological adaptations to weight loss that profoundly influence not only eating behaviors but also basal metabolic rate and, as a result, both energy intake and energy expenditure. Hormones regulating weight are derived from the gut, adipose tissue, and the adrenal gland. After weight loss, many of these hormones remain altered in patterns that stimulate appetite or decrease energy expenditure and, thereby, encourage weight regain.\textsuperscript{38}

In summary, initial weight loss results in metabolic changes that constrain continued loss and may actually promote weight regain. In this sense, metabolic changes work in the same direction as other genetic, social, and psychological factors that usually favor prevailing dietary patterns.

### Pathophysiologic Effects of Obesity

Obesity increases risk for stroke by several distinct mechanisms including diabetes mellitus, hypertension, accelerated atherosclerosis, atrial fibrillation, and obstructive sleep apnea.\textsuperscript{40-43} The end result may be progressive atherosclerosis and or or thromboembolism that may result in arterial occlusion or rupture.

To understand how obesity leads to arterial disease, it is necessary to examine the emerging science behind adipose biology and insulin resistance. Formerly thought to be a passive repository for fat, adipose tissue is now known to be a highly active both endocrinologically and immunologically. As an individual gains weight, adipose tissue undergoes hypertrophy, hyperplasia, and remodeling that includes infiltration with inflammatory cells.\textsuperscript{44} Under circumstances of unhealthy adaptation, local hypoxia and free fatty acids released by adipocytes contribute to local activation of macrophages, which, in turn, release a repertoire of immune mediators including TNF\(\alpha\), iNOS, MCP-1, and IL-6.\textsuperscript{41} Adipose tissue from obese persons also secretes less adiponectin, a protein hormone with beneficial vascular effects. Inflammation, free fatty acid release, and reduced adiponectin each significantly contribute to insulin resistance and resultant hyperglycemia in obesity.

The link between this unhealthy adaptation of fat and atherosclerosis is complex and involves several converging pathways.\textsuperscript{42,43} Hypertension, partly mediated by adipose-derived angiotensinogen and impaired nitric oxide metabolism, promotes endothelial damage. Inflammatory signaling leads to upregulation of C-reactive protein and adhesion molecules that enhance monocyte attachment to the damaged endothelium and egress into the vascular wall. Dyslipidemia related to impaired triacylglycerol trafficking and low-density lipoprotein oxidation supplies lipid substrate fat for growing atheroma. Obesity and its associated insulin-resistant state are also associated with hypercoagulability and enhanced platelet aggregation. Finally, hyperinsulinemia, the endocrine pancreas’ natural response to insulin resistance, may itself be a contributing culprit. Insulin’s accentuated activation of mitogenic pathways may promote smooth muscle cell growth and alter the behavior of the monocye/macrophage lineage that is so critical to the progression of the atherosclerotic plaque. Obesity and the insulin-resistant proinflammatory state may also stimulate factors that render mature atheroma more vulnerable to plaque rupture, the inciting event in the vascular occlusions that culminate in clinical stroke. Thus, excess body adiposity seems to contribute to each major step in the atherosclerotic process.
Not every obese patient has an adverse metabolic profile, however. Approximately 11% to 25% of obese individuals exhibit normal glucose metabolism and insulin sensitivity and are, therefore, at no increased risk for vascular disease. Research suggests that these persons with "metabolically benign obesity" have proportionately less fat in the liver, viscera, and muscles (ie, lower ratio of central obesity to peripheral obesity) compared with insulin-resistant persons. That is, they allocate fat to more metabolically quiescent sites where it is stored without significantly perturbing vascular health. For the purpose of identifying metabolic disease, therefore, obesity should be regarded as only a starting point.

**Effect of Weight Loss on Risk for Vascular Disease**

Weight loss is associated with improvement in blood pressure, glucose, triglyceride and HDL concentration, insulin sensitivity, and measures of inflammation. Not surprisingly, the magnitude of change in these cardiovascular risk factors is directly proportional to the magnitude of weight loss. With modest weight loss of 5% to 10%, for example, HbA1c falls 0.5 absolute percentage points, systolic blood pressure falls 3 to 6 mm Hg, and HDL cholesterol rises 3 mg/dL. A weight loss of 6% among overweight persons with impaired glucose tolerance has been associated with a substantive 58% reduction in the progression to diabetes mellitus. With greater weight loss achievable after bariatric surgery, HbA1c falls ≈1.4 absolute percentage points, insulin resistance improves 42% to 51%, triglycerides falls 30% to 70%, and HDL-C increases 10% to 19%.

The effects of weight loss on cholesterol and blood pressure in many contemporary studies are confounding by drug therapy and other cointerventions such as salt restriction. Research on persons who are not receiving medical therapy, however, confirm an independent effects of weight loss and research on persons who lose weight while keeping sodium intake constant confirms an independent effect on blood pressure.

Unfortunately, no trials have examined the effect of intentional weight loss on stroke risk. The first randomized clinical trial to adequately test the effectiveness of weight loss for prevention of any clinical cardiovascular events, the Look AHEAD Trial (NCT00017953), is expected to be completed in late 2014. Look AHEAD is enrolling only persons with type 2 diabetes and may leave uncertain the benefits for non-diabetic persons.

**Treatment of Obesity**

**Goals**

Epidemiological research puts the lowest risk for first stroke at a BMI of ≈22 to 25 kg/m². The risk of death from stroke or ischemic heart disease increases nearly linearly from this point for populations in western Europe, North America, and East Asia. On the basis of these data, therefore, one might argue for a BMI goal of ≈22 to 25 kg/m² if this can be achieved with acceptable risk. In practice, few overweight and obese persons are able to lose the weight required to achieve a BMI of 22 to 25 kg/m². Fortunately, even moderate BMI reduction is associated with measurable improvement in many cardiovascular risk factors. It is for this reason that many guidelines recommend an initial weight reduction goal of 5% to 10%.

Further weight loss should be encouraged for individuals who are motivated and able to continue, especially if cardiovascular risk factors remain abnormal. Blood pressure, triglyceride, HDL-C, C-reactive protein, and glucose all respond to weight loss. HbA1c falls linearly with weight and is less likely to be confounded by drug therapy than blood pressure or lipids (at least in nondiabetic persons). Epidemiological research puts the lowest risk for cardiovascular disease at an HbA1c of <5.0%, but most diabetes organizations set a threshold for lifestyle action at 5.5% to 5.7%.

In summary, any weight loss is probably beneficial. An ideal goal for patients with symptomatic cerebrovascular disease would be a BMI of 22 to 25 or an HbA1c of <5.5% to 5.7%. This goal is based on epidemiological research in healthy persons without cerebrovascular disease; similar data from cohorts of patients with stroke or transient ischemic attack is not available.

**Effective Strategies**

Patients may attempt to lose weight on their own, with the help of providers in a medical practice, or with the help of counselors in an organized program. Some will ultimately undergo bariatric surgery. Providers to overweight patients need to be aware of all options and implement them in a rational manner.

**Practice-Based Strategies**

Major guidelines recommend screening all adults for obesity and counseling to support weight reduction. The “5A” approach is probably the most well-established counseling strategy (see Figure 1). However, a single episode of advice is not effective. Repeated counseling by trained primary care providers may result in modest weight loss (ie, 2 to 3 kg) that is sustained for up to 1 year. The low rate of success for provider counseling indicates that more needs to be done.

In the primary care setting, slightly better results are obtained with intensive, team-based counseling or referral to a commercial weight loss program. Successful team-based counseling typically requires frequent visits with a lifestyle coach. Many smaller practices do not have the resources for effective team-based counseling and may achieve better results by referring patients to programs such as Weight Watchers, where a 12-month intervention has been associated with 2.77 kg weight loss (95% CI: –3.50 to –2.03) as compared with standard care.

**Comprehensive Programs**

Most comprehensive diet-based programs for weight loss involve counseling and targets for calorie intake, weight, or food selection. Counseling may include individual or group sessions and advice on physical activity. On average, these...
programs can be expected to result in a ≈6% net weight loss at 1 year (5.5 kg), half of which will be regained by 3 years. Not surprisingly, comprehensive diet-based programs that offer more intensive and frequent lifestyle counseling, including physical activity, are more successful in helping participants lose weight.64 In particular, intensive one-on-one counseling supports greater and more sustained weight loss compared with usual care. In the Look AHEAD study, for example, patients with type 2 diabetes were assigned to a usual support group or an intensive lifestyle intervention group that included in-person counseling for diet and physical activity at least once a month over 4 years.79 Weight decreased in the usual care group to a low of 1% below baseline at 4 years. In the intensive group, weight fell nearly 9% in year 1 but then rose gradually to 5% below baseline by year 4.

Structured weight loss programs that include prepared meals may be more effective than usual care (ie, consultation with a dietary professional and provision of educational reading material). When combined with counseling on physical activity and fitness, commercially available programs have been reported to help obese persons achieve up to a mean loss of 7.4 kg at 2 years.78 Interventions for weight loss maintenance have included frequent personal contact, web-based interactive programs, and personal contact combined with prepared meals. Personal contact with a trained interventionist seems to be the most effective, although most patients still regain some weight.80

### Physical Activity

The American College of Sports Medicine and the American Heart Association recommend that all adults 18–65 years of age participate in moderate intensity aerobic exercise (eg, brisk walking) for 30 minutes for 5 days each week or vigorous exercise (eg, jogging) for 20 minutes for 3 days each week.81 US federal guidelines are similar.82 Unfortunately, most community-dwelling adults do not achieve these recommendations, and hemiparetic stroke survivors are even less physically active and fit.83 Exercise, at currently recommended levels, has only a modest effect on weight in comparison with caloric restriction.66,84 The more compelling benefits of exercise may be for other specific cardiovascular risk factors.84,85 The effect on insulin resistance, for example, is almost immediate. One session of exercise effectively suppresses fatty acid-induced insulin resistance and inflammatory pathways in skeletal muscle.86 Over the longer term, 12 weeks of aerobic exercise decreases fat mass and reverses insulin resistance in obese adults87 and the beneficial effects are independent of weight or body composition.88 For individuals with chronic hemiparetic stroke, 6-month aerobic training has been shown to improve bilateral cerebral arterial vasomotor reactivity, indices of insulin sensitivity, and glucose tolerance.89 Aerobic training improves insulin resistance in adults more than resistance training, but the combination is superior to achieve simultaneous improvements in functional status.90 Regular aerobic exercise is also associated with a mean reduction in systolic blood pressure of 4 mm Hg and in diastolic blood pressure of 3 mm Hg.91

It is difficult to change human behavior; physical activity is no exception. Simple advice by healthcare providers or referral to community-based exercise programs are generally ineffective.92 Indeed, research in patients with existing vascular disease or diabetes mellitus suggests that even repeated face-to-face counseling and repeated verbal encouragement does not change physical activity.93,94 To achieve meaningful increments in physical activity, patients should be enrolled in long-term, highly structured programs that incorporate methods derived from behavior change models.95 The Diabetes Prevention Program, for example, includes frequent meetings with a case manager and supervised exercise sessions. In the original trial of this program, patients in the intervention group increased their activity after 4 years by 8

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**Figure 1.** The “5A” method for behavioral counseling.
metabolic equivalent (MET)-hours per week compared with 2 MET-hours per week in the control group.\(^\text{66}\)

### Drugs

Drugs have an adjunctive role in obesity management and are recommended for use only after dietary, exercise, and behavioral approaches have been initiated and failed.\(^\text{69}\) Only 3 drugs (orlistat, lorcaserin, and combination topiramate/phenteramine) are currently approved for long-term use in the United States. Orlistat inhibits intestinal lipases that otherwise hydrolyze triglyceride into absorbable monosaccharides and disaccharides.\(^\text{57}\) In primary care settings, orlistat 120mg TID causes a 5-kg net weight loss after 1 year of use.\(^\text{98}\) Lorcaserin is a serotonin 2C receptor agonist that was approved by the FDA in June 2012 for chronic treatment of obesity. It is not yet available.

### Bariatric Surgery

The two most common types of bariatric surgery are laparoscopic adjustable gastric banding and Roux-en-Y gastric bypass.\(^\text{59}\) Each limits the volume of food a patient may consume, but the latter also reduces nutrient absorption. There have been only a few large randomized clinical trials of bariatric surgery compared with nonsurgical treatment for weight loss. In one of these, 60 patients with new-onset diabetes mellitus and BMI between 30 and 40 kg/m\(^2\) were randomized to laparoscopic adjustable gastric banding or conventional diabetes mellitus care.\(^\text{57}\) After 2 years, patients assigned to surgery lost 21% of their body weight compared with 2% in the comparison group. Remission of diabetes mellitus was achieved in 73% of the surgery group compared with 4% of the control group. In a more recent randomized trial among 56 obese diabetic patients, diabetes mellitus remission after 2 years occurred in none of 20 patients assigned to medical therapy compared with 15/20 patients assigned to gastric bypass surgery and 19/20 assigned to biliopancreatic diversion (P<0.001 for both comparisons with medical therapy).\(^\text{100}\) In addition to weight loss and improved carbohydrate metabolism, bariatric surgery reduces blood pressure and vascular inflammation and improves quality of life.\(^\text{57,101}\) Weight loss tends to be greater with Roux-en-Y bypass compared with purely restrictive procedures such as gastric banding. Adverse events vary between the surgery types. Surgical mortality is <1% with Roux-en-Y bypass or banding, but the former may have higher rates of major perioperative complications (6.3% compared with 2.3%).\(^\text{102}\) In the long term, reoperation is more common with banding. Rarely, malabsorption with bypass surgery may result in serious deficiencies of specific nutrients.\(^\text{103}\)

### Recommendations

The US Preventive Services Task force and other major organizations in the United States and Europe recommend that physicians screen all adults for obesity at regular intervals.\(^\text{56,66,71,104}\) The American Heart Association secondary prevention guidelines recommend screening at every visit. Other guidelines call for less frequent intervals such as 2 years.\(^\text{66}\) BMI and waist circumference are the most commonly recommended screening metrics. The US National Heart Lung and Blood Institute, for example, endorses providing weight loss advice for anyone with a BMI ≥30kg/m\(^2\) or BMI 25 to 29.9 30kg/m\(^2\) with either an increased waist circumference (>102cm for men and >88 cm for women) or at least 2 additional cardiovascular risk factors.\(^\text{66}\)

Figure 2 is a proposed algorithm that represents an amalgam of older guidelines\(^\text{66,105}\) and recommendations from recent expert reviews.\(^\text{70,106}\) It borrows from American Heart Association and National Heart Lung and Blood Institute statements in recommending measurement of both BMI and waist circumference.\(^\text{104,106}\) Using country-specific criteria for elevated waist circumference.\(^\text{107}\) We incorporate the “5A” model of counseling that is broadly accepted for promoting behavioral change. Consistent with major guidelines, the algorithm reserves drug therapy and bariatric surgery for patients who do not reach goal with behaviorally oriented therapies.\(^\text{65,66,108}\)

The algorithm differs from other guidelines in explicitly recommending referral to a qualified program as a first option for all patients who are ready to lose weight. Qualified programs offer multidisciplinary counseling and intervention for behavioral change in the areas of nutrition and physical activity. They typically require frequent contact with participants for assessment, goal setting, and cognitive restructuring to build knowledge and skills in food consumption, self-monitoring, and coping with negative thoughts and behaviors. A second option, when available, is provision of weight management counseling by the patient’s personal physician. Most primary care physicians and subspecialists, however, do not have the training, time, or resources to provide the intense, sustained coaching required for success.

The plan we propose goes beyond the current guidelines for weight management in secondary prevention of stroke, which offer no specific recommendations.\(^\text{109}\) The algorithm is consistent with guidelines for primary prevention of stroke, which includes a Class IIa recommendation for weight reduction among overweight and obese persons to reduce risk of stroke.\(^\text{110}\) Clearly, how such a program can be implemented into routine clinical practice remains a major challenge.

The discovery of the obesity paradox has caused some authors to recommend caution in advocating weight loss after stroke.\(^\text{111}\) The recommendation relies partly on the observation that involuntary weight loss after stroke is associated with increased risk for death. Involuntary weight loss is usually a marker of disease first and a cause of disease only later. Proponents of caution also do not distinguish between weight and nutritional status more thoroughly defined. We believe it is important to recognize that the obesity paradox is simply an epidemiological association. It does not support a firm inference that obesity is healthy after stroke or that intentional weight loss will not improve prognosis. A vast body of evidence supports the contrary hypothesis that obesity increases risk for a first stroke and obesity treatment will reduce risk for a recurrent stroke. We agree with others, however, that the hypothesis should be put to the test.\(^\text{111}\)

### Conclusion

Several lines of evidence (ie, biological effects of obesity, biological effects of weight loss, and epidemiological evidence that obesity increases risk for first stroke) suggest that weight
loss may be an effective strategy for primary and secondary stroke prevention among overweight and obesity patients. Helping patients lose weight, however, requires a team-based, multidisciplinary approach, sustained over an indefinite period of time. Most hospital stroke programs and individual providers will need to refer their patients to qualified programs. Clinical
trials in this area will be critical to validate the most effective approaches and, ultimately, to guide policy.

For patients who present with transient ischemic attack or stroke, we believe there may be reason to intervene for obesity in the hyperacute period. Within weeks of weight loss, researchers have been able to document favorable effects on fat distribution, insulin resistance, and vascular inflammation. It is reasonable to hypothesize that such effects would result in stabilization or reversal of vascular abnormalities that predispose to early stroke recurrence. For the long term, weight loss is likely to improve measures of mobility and functional independence. While data gathers, we believe it is reasonable to implement a prudent weight reduction plan for patients before or soon after they are discharged after an acute transient ischemic attack or ischemic stroke.

Since this article was accepted for publication, the US Preventive Services Task Force updated its recommendations for screening and management of obesity in adults. Consistent with our recommendations, the Task Force also advises clinicians to refer obese adults “to intensive, multi-component, behavioral interventions.”

Disclosures
Dr Kahn: Takeda Pharmaceuticals North America provided drug, placebo tablets, and funds to support blood storage for an NIH-funded clinical trial for which I am Principal Investigator. The drug is pioglitazone and the trial is examining the effect of pioglitazone, compared with placebo, for preventing stroke, and myocardial infarction among non-diabetic patients with a recent TIA or ischemic stroke and insulin resistance.

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Obesity: A Stubbornly Obvious Target for Stroke Prevention
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