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## REPORT

## A New Paradigm for Stroke Prevention

By William Davis, MD, FACC

*Stroke is the third leading cause of death in the US. Fortunately, diagnostic imaging for stroke risk and stroke-prevention strategies have advanced greatly in recent years. It is now possible to reduce the artery-clogging plaque that leads to stroke, offering hope that this debilitating condition can be prevented.*

If you have ever witnessed a stroke victim, you understand the humbling nature of this disease, which can reduce the mightiest human being to an immobile, helpless creature. Stroke can destroy or impair crucial functions such as speech, swallowing, walking, and bowel and bladder control. Even the perpetually youthful television personality Dick Clark was struck down by stroke at the age of 75, despite his outward appearance of perfect health. Clark's stroke resulted in a six-week hospital stay and, judging from fragmentary reports, significant disability.



The disease process that underlies stroke requires decades—30 or 40 years—to develop. With that much lead time, why are we not better able to detect or stop this crippling disease? The truth is that we are able to predict many, if not most, strokes. Advances in imaging technology allow detection of the atherosclerotic plaque that causes stroke years before it becomes a threat. Similar progress has been made in deciphering the causes of stroke.

Unfortunately, most physicians still focus on diagnosing the crisis rather than averting it. With stroke as with heart disease, most physicians prefer to deal with catastrophe once it occurs and are only minimally interested in prevention. The medical community focuses on procedures such as carotid surgery or stents instead of preventive diagnostics and care. Even when a person is forewarned by a “mini-stroke,” or transient ischemic attack, little is done once it has been determined that surgery is not immediately necessary—even though this person has a high risk for future stroke. For someone recovering from a transient ischemic attack, the risk for recurrent stroke, heart attack, or death approaches 50% over 10 years.<sup>1</sup>

A more powerful approach to **stroke prevention** would use screening and diagnostic procedures to assess risk, and would implement nutritional strategies and lifestyle changes to reverse plaques. Surgical procedures such as carotid endarterectomy (to remove a buildup of plaque from the carotid artery) would be used only after exhausting preventive care options. The need for invasive procedures represents a failure of preventive medicine.

### ORIGINS OF THE MODERN THEORY OF STROKE

“The first person to investigate the pathological signs of [stroke] was Johann Jacob Wepfer. Born in Schaffhausen, Switzerland, in 1620, Wepfer studied medicine and was the first to identify postmortem signs of bleeding in the brains of patients who died of [stroke]. From autopsy studies, he gained knowledge of the carotid and vertebral arteries that supply the brain with blood. He also was the first person to suggest that [stroke], in addition to being caused by bleeding in the brain, could be caused by a blockage of one of the main arteries supplying blood to the brain; thus stroke became known as a cerebrovascular disease (“cerebro” refers to a part of the brain; “vascular” refers to the blood vessels and arteries).”

— National Institute of

### HOW STROKE OCCURS

Stroke develops when some portion of the brain is deprived of blood and thus oxygen. This usually results when a tiny bit of debris dislodges from an atherosclerotic plaque within an artery wall and blocks a blood vessel to the brain. The same sort of plaque accumulates in coronary arteries to cause heart attack. The sources of debris have been a subject of controversy for decades, but new imaging technologies have settled the question: essentially, any blood vessel that leads from the heart to the brain can be a source of the debris that causes stroke. The two carotid arteries that lie on both sides of your neck are a frequent source, as these arteries are very prone to develop plaque.

In the last decade, medical researchers have recognized the aorta as another source of stroke. The aorta is the body's main artery, with branches that emerge from the heart and lead to the head, arms, and legs. New imaging devices such as transesophageal echocardiography (ultrasound performed with a probe in the esophagus) allow imaging of the aorta, an eight-inch vessel that is a common site for plaque.<sup>2</sup>

Atherosclerotic plaque is a live tissue that, given a chance through poor diet, inactivity, high cholesterol, or excess weight, can grow and become progressively unstable. At some point, the plaque can fragment. Little bits

and pieces break away, traveling to the brain. Fractured plaque also exposes its deeper structures to flowing blood, triggering blood-clot formation, which in turn can also fragment and travel to the brain. Atherosclerotic plaque is thus a prerequisite of risk for the most common causes of stroke.

If most strokes are caused by plaque, why not measure plaque to determine whether you are at risk for stroke? How can we easily, safely, and accurately quantify plaque in the areas that present stroke risk, such as the carotid arteries and aorta? And if plaque can be measured, can it be shrunk or inactivated to reduce or eliminate the risk of stroke? These compelling questions will form the basis of this article.

## HOW CAN PLAQUE BE MEASURED?

New imaging technologies are becoming more accurate and accessible. Just 20 years ago, the only practical way to identify plaque in the carotids or aorta was by angiography, which requires the insertion of catheters into the body to inject x-ray dye. Angiography was not practical as a broad screening measure and was not a good test of the health of the arterial wall.

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are emerging as exciting methods of imaging both the carotid arteries and the aorta. Unfortunately, most imaging centers and physicians are much more focused on the diagnostic use of these technologies for people who have already suffered a stroke or other catastrophe. The application of these devices for preventive uses is still evolving. One exception is when aortic calcification or aortic enlargement is incidentally noted on the increasingly popular CT heart scans; this is an important finding that can signal the presence of aortic plaque that increases stroke risk.

The one test that is widely available and can be performed in just about any center is carotid ultrasound. Simple, painless, and precise, this procedure is useful for assessing two indicators of stroke risk:

### 1. *Plaque detection.*

Atherosclerotic plaque that has potential for fragmentation and thus for stroke risk can be clearly visualized. If plaque blocks more than 70% of the diameter of the vessel, or if there are “soft” (unstable) elements in the plaque, then stroke risk may be high enough to justify surgery or stents. Even if there are plaques that are less severe, substantial risk for stroke may still exist, which can be reduced with preventive measures.<sup>3</sup>

### 2. *Carotid intima-media thickness.*

This is a measure of the carotid artery lining in areas that do not yet contain plaque but that often precede the development of more mature plaque. Carotid intima-media thickness also provides an index of body-wide potential for atherosclerotic plaque that can place you at risk for stroke. The aorta, for instance, cannot be imaged by surface ultrasound but can still be a source for stroke. Increased carotid intima-media thickness and carotid plaque are closely associated with the likelihood of aortic plaque. The Rotterdam Study of 4,000 participants demonstrated that if carotid intima-media thickness is greater than normal (1.0 mm), then you can be at risk for stroke (and heart attack), even if no plaques are detected.<sup>4</sup>

Carotid ultrasound is the one test you should consider that provides the most information with the least effort. Ultrasound is virtually harmless, painless, and can be obtained just about anywhere. Even if your doctor disagrees with your request for a carotid ultrasound, an increasing number of mobile services nationwide make this test available for around \$100. One important caveat: many scanners and interpreters will report only whether plaque is present or not. While this is important information, you should request that your carotid intima-media thickness be measured as well. Not all centers can perform this simple measure, but it does not hurt to ask. Any amount of carotid plaque is cause for concern about stroke risk and reason to follow a preventive program, even if the plaque is insufficient to justify surgery.

## CAN PLAQUE BE REDUCED?

Can we shrink plaque in the carotid arteries and aorta, thereby reducing or perhaps eliminating these sources of stroke?

Study after study has documented that plaque and stroke risk can be reduced. A 10–20% reduction in plaque size is possible

### STROKE FACTS

- 700,000 new strokes occur each year in the US
  - Women with new strokes outnumber men by 40,000 annually
  - Stroke is the third leading cause of death in the US
  - Someone dies of stroke every three minutes
  - 22% of men and 25% of women who have a first stroke die within a year
  - In 2004, the direct and indirect costs of stroke in the US were \$53.6 billion.
- American Heart Association, 2004 Update

within a year or two. The following important influences on carotid and aortic plaque growth need to be considered in any plaque-reduction program. (If you smoke, you need to concentrate on quitting, as the adverse influences of smoking will overwhelm any treatment you follow.)

- **Hypertension.** Considerable re-search documents the power of lowering elevated blood pressure in helping to prevent stroke.<sup>6</sup> The most recently updated guideline for blood pressure, released by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, recommends a blood pressure no higher than 140/90, and defines normal as 120/80. The commission also emphasizes that the risks of stroke and heart attack begin to escalate at a blood pressure of 115/75.<sup>7</sup>

Just how low should your blood pressure be? The best evidence comes from the recent CAMELOT trial, conducted by the Cleveland Clinic's Steven Nissen, MD. Nearly 2,000 participants with coronary artery disease with starting blood pressure in the normal range of 129/78 had blood pressure further reduced to 124/76 using the drugs amlodipine (Norvasc®) or lisinopril (Prinivil®). In just two years, this blood-pressure reduction produced a modest but significant reduction in future risk of heart attack and stroke.<sup>8</sup> This bolsters the argument that the previously acceptable blood pressure of 140/90 may not protect you from stroke and that further reduction is needed.

- **Diabetes, Metabolic Syndrome, and Hyperinsulinemia.** Just being overweight substantially increases risk of future stroke. A Swedish study of 7,400 men with body mass indexes above 30 (considered "obese") had double the risk of stroke compared to non-obese men.<sup>9</sup> Increased body weight frequently leads to diabetes and its closely related conditions of metabolic syndrome and hyperinsulinemia (increased insulin levels), which play an overwhelmingly important role in increasing stroke risk in the US. Of people who suffer strokes, a shocking 70% will have one of these diagnoses. When diabetes is present, risk for stroke can be as much as sixfold greater.<sup>10</sup>



Metabolic syndrome and insulin resistance, which are predecessors of diabetes, are far more common than full-blown diabetes and can accompany even modest quantities of excess weight. Metabolic syndrome consists of excessive abdominal fat, high blood pressure, low HDL (high-density lipoprotein), high triglycerides, and resistance to insulin, which results in increased blood insulin levels. Metabolic syndrome is rampant in the US, afflicting as many as one in three adults as a result of sedentary lifestyles, processed foods, and other factors that lead to being overweight or obese.<sup>11</sup> High insulin levels and resistance to insulin are powerful drivers of plaque accumulation, causing carotid plaque to grow at a faster rate.<sup>12,13</sup> The rapidly escalating prevalence of metabolic syndrome and diabetes in the US population virtually guarantees a future epidemic of stroke.

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• **Small LDL, IDL, LDL Particle Number, and Lipoprotein(a).** Even more than high cholesterol, various lipoprotein abnormalities carry a greater risk for carotid and aortic plaque growth and consequent stroke. Lipoproteins are fat-carrying proteins in the blood that cause plaque to grow. Powerful instigators of plaque growth and stroke include:

1. Small LDL (low-density lipoprotein) particles encourage carotid plaque growth more so than large LDL particles. This important abnormality also triples heart attack risk. Small LDL often occurs as part of metabolic syndrome.<sup>14</sup>
2. IDL (intermediate-density lipoprotein) particles, which are triglyceride-rich but can be present even when triglycerides are low, are a measure of how well fat is cleared from the blood after a meal. This lipoprotein fraction is among the most potent drivers of carotid plaque growth.<sup>15</sup> Increased IDL also creates plaque high in soft, unstable fat that makes it more prone to rupture.<sup>16</sup>
3. LDL particle number, also measured as apolipoprotein B, is the actual count of LDL particles (per milliliter of blood, for instance). This measure is superior to LDL or total cholesterol as a predictor of heart disease and stroke. Dr. Howard Hodis of the University of Southern California has shown that increased LDL particle number is associated with greater carotid plaque growth, and is a better predictive factor than LDL.<sup>17,18</sup>
4. Lipoprotein(a) is a crucial yet underappreciated factor that is clearly associated with heightened risk of stroke and heart attack. Lipoprotein(a) promotes blood clotting and constricted arteries, and increases the dangers of cholesterol. Carotid ultrasound studies have shown that lipoprotein(a) causes accelerated plaque growth.<sup>19,20</sup>

• **Fibrinogen.** This blood-clotting protein not only promotes carotid plaque growth, but also contributes to the formation of unstable plaques. These volatile plaques have more inflammatory cells (called macrophages) and a thinner tissue covering, making them more prone to rupture. A pooled analysis from Oxford University with more than 5,000 participants confirmed the role of fibrinogen in increasing stroke risk.<sup>21</sup> Fibrinogen levels exceeding 407 mg/dL heighten stroke risk sixfold.<sup>22</sup>



• **C-reactive protein (CRP).** This measure of inflammation is proving to be a useful marker for identifying people at higher risk for stroke. Increased risk begins at levels above 0.5 mg/L.<sup>23</sup> High CRP also predicts more rapidly growing carotid plaque.<sup>24</sup>

• **Homocysteine.** Homocysteine is an important marker for increased likelihood of both carotid and aortic plaque, as well as stroke.<sup>25,26</sup> In 1997, the European Concerted Action Project reported more than a doubling of stroke when homocysteine levels exceed 12 umol/L.<sup>27</sup> As homocysteine increases to 20 umol/L, risk for stroke and heart attack increases an amazing fivefold over that at a level of 9 umol/L.<sup>28</sup>

• **Cholesterol/LDL.** While total cholesterol and LDL clearly contribute to heart disease risk, their role in stroke is less clear. Pooled data suggest that lowering cholesterol with statin drugs does, however, slow carotid plaque growth and reduces stroke risk by approximately 21%.<sup>29</sup> In an interesting study from the Cardiovascular Institute at the Mt. Sinai School of Medicine in New York, magnetic resonance imaging (MRI) of the carotids and thoracic aorta showed an impressive 20% regression in plaque area when simvastatin (Zocor®) was taken for two years.<sup>30</sup>

Although treatment guidelines recommend reducing LDL to 100 mg/dL in high-risk individuals, a report from the Walter Reed Army Medical Center in Washington, DC, showed that carotid plaque was more effectively reduced when LDL was lowered to 70 mg/dL or less using statin drugs.<sup>31</sup>

#### TREATMENT STRATEGIES TO REDUCE PLAQUE

The essential question is how do we reduce carotid and aortic plaque, and thus the risk for stroke? If you have carotid or aortic plaque detected during a screening such as a carotid ultrasound, or aortic calcification as indicated by a CT heart scan, you are at increased risk for stroke. You also have a baseline for future comparison to gauge whether your stroke-prevention program is working.

“Carotid intima-media thickness and aortic calcifications were related most strongly to the risk of stroke.”<sup>4</sup>

“. . . carotid plaques are associated with increased risk of stroke, irrespective of their location. It is likely that carotid plaques in neurologically asymptomatic subjects are both

Because most people have not one but several causes of carotid and aortic plaque, no single treatment effectively eliminates risk for stroke. Instead, most people require a comprehensive program of healthy diet, exercise, supplements, and medication when indicated. The following nutritional supplements can be critical components of your plaque-reduction and stroke-prevention program.

markers of generalized atherosclerosis and sources of thromboemboli [debris].”<sup>5</sup>

— M. Hollander, MD  
The Rotterdam Study

- **Fish Oil.** Fish oil is a cornerstone of any stroke-prevention program. Epidemiological observations suggest a strong relationship between fish intake and reduced stroke risk.<sup>32</sup> Carotid ultrasound studies have demonstrated that less carotid plaque is present in those with the greatest intake of omega-3 fatty acids from fish.<sup>33</sup>

One cleverly designed study made the fascinating discovery that fish oil actually transforms the structure of carotid plaque. In this trial, 150 people with severe carotid plaque scheduled for carotid endarterectomy (surgical removal of the plaque) were given either fish oil, sunflower oil, or no treatment over several months while waiting for their procedures. Plaque was then removed surgically and examined microscopically. Participants who took fish oil had reduced inflammation in plaque and thicker tissue covering the fatty core, two markers of more stable plaque. Those taking sunflower oil or no treatment had unstable plaques with greater inflammation and thinner, less sturdy covering tissue. This suggests that consuming fish oil for just a few months substantially stabilizes carotid plaque, making it less likely to rupture and fragment.<sup>34</sup>

A standard fish oil capsule (containing 300 mg of EPA plus DHA) contains the same amount of omega-3 fatty acids as a three-ounce serving of cod or halibut; three capsules (containing 900 mg of DHA plus EPA) contain the equivalent of a serving of salmon. A daily dose of four capsules (1200 mg of EPA plus DHA) seems to provide the greatest benefits, including protection from stroke, lowering of triglycerides, and modest anti-coagulation effects, including reduction of fibrinogen (More concentrated fish oil capsules provide 2400 mg of EPA plus DHA per four capsules).<sup>35</sup>

- **Coenzyme Q10 (CoQ10).** Although no studies to date have addressed whether coenzyme Q10 reduces plaque, CoQ10 is a marvelously effective way to reduce blood pressure, a crucial factor contributing to carotid and aortic plaque growth. A pooled analysis of eight studies showed that, on average, CoQ10 in daily doses of 50–200 mg reduced systolic blood pressure by 16 mmHg and diastolic pressure by 10 mmHg.<sup>36</sup> Other data suggest that CoQ10 can reverse abnormal heart muscle thickening (hypertrophy), another manifestation of high blood pressure. This strongly suggests that CoQ10 has benefits that go beyond reducing blood pressure.<sup>37,38</sup>

## SUPPLEMENTS TO CORRECT METABOLIC SYNDROME

Weight loss is, without question, the most immediate and direct way to correct metabolic syndrome. Weight loss of as few as 10–20 pounds can yield improvements across the board: increased sensitivity to insulin, increased HDL, and reductions in triglycerides, blood pressure, CRP, fibrinogen, and small LDL particles.<sup>39,40</sup> Diet and exercise are fundamental components of any weight-loss program. Low-carbohydrate or reduced-glycemic diets (such as the South Beach and Mediterranean diets) that are rich in fibers are clearly effective.<sup>41</sup> Several supplements can amplify these weight-reduction efforts and be useful adjuncts to your lifestyle program. They include:

- **White bean extract** blocks intestinal absorption of carbohydrates by up to 66%. Taking 1500 mg twice a day with meals results in, on average, three to seven pounds of weight loss in the first month of use. The only side effect of white bean extract is excessive gas, due to unabsorbed starches. Of course, because the blocking effect is partial, resist the urge to overeat carbohydrates.<sup>42</sup>

- **Glucomannan** is a unique viscous fiber that, when taken before meals, absorbs many times its weight in water and thereby fills the stomach, causing most people to eat less. Most people lose about four pounds a month by consuming 1500 mg of glucomannan before each meal.<sup>43</sup> PGX™ combines glucomannan with xanthan and alginate to enhance the satiety effect. Interestingly, glucomannan also blunts the rise in blood sugar after meals, an effect that itself may lead to weight loss.<sup>44</sup> Be sure to drink plenty of water when using fiber supplements.

- **DHEA** is an adrenal hormone that is essential to maintaining physical stamina, mood, muscle mass in men, and libido in women.<sup>45</sup> A recent randomized, placebo-controlled study at Washington University found that 56 subjects taking 50 mg of DHEA daily experienced significant declines in abdominal fat associated with insulin resistance. The participants also demonstrated improved glucose control and lower insulin levels.<sup>46</sup> DHEA supports physical and mental well-being, and improves insulin resistance, a risk factor for stroke.

- **Pectin and beta-glucan** are wonderful fibers that provide feelings of fullness while lowering cholesterol and slowing the release of sugars. Both can play a role in weight reduction. Pectin is the soluble fiber in citrus rinds, green vegetables, and apples, and is available as a supplement. Beta-glucan is the soluble fiber of oats and is also available as a supplement. A University of Southern California study in 573 subjects showed that higher intake of healthy fibers like pectin and beta-glucan is associated

with less carotid plaque growth, as measured by ultrasound. Interestingly, the highest fiber intake among participants was 25 grams a day, a number you can easily achieve or exceed with attention to fiber intake.<sup>47</sup>

### **FOLIC ACID AND VITAMINS B6 AND B12**

A study conducted by Dr. Daniel Hackam at the Stroke Prevention and Atherosclerosis Research Centre in Ontario, Canada, used carotid ultrasound to measure plaque reduction. Daily treatment with folic acid (2500 mcg), vitamin B6 (25 mg), and vitamin B12 (250 mcg) resulted in modest plaque reduction in 101 participants. This was especially true in participants whose homocysteine levels exceeded 14 umol/L at the start of the trial when compared to untreated participants who experienced substantial plaque growth. Curiously, even participants with homocysteine levels of less than 14 umol/L saw reductions in plaque when taking the vitamin regimen, though the effect was about half of that in participants with homocysteine greater than 14 umol/L.<sup>48</sup>



A National Institutes of Health-sponsored study of stroke prevention sought to clarify the role of homocysteine treatment. In this study, 3,680 participants with a prior history of stroke were given either a “low-dose” vitamin regimen (20 mcg of folic acid, 0.2 mg of vitamin B6, and 6 mcg of vitamin B12) or a “high-dose” regimen (2500 mcg of folic acid, 25 mg of B6, and 400 mcg of B12). Although homocysteine levels at the start of the trial showed a graded association with stroke risk—with higher homocysteine levels predicting greater stroke risk—the high-dose treatment group experienced, on average, only a 2-umol/L drop in homocysteine levels, and both groups showed no reduction in stroke risk over two years. The study investigators, as well as critics of the study, have suggested that the study failed to show benefit due to an insufficient treatment period or because the vitamin doses used were too low to be of benefit, even in the “high-dose” group.<sup>49</sup> (The doses used in the plaque-reduction program at my clinic are 2500-5000 mcg of folic acid, 50 mg of vitamin B6, and 1000 mcg of vitamin B12.)

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#### CONCLUSION

Reducing stroke risk by reversing carotid and aortic plaque is becoming an everyday reality, as more and better tools become available to us. To determine your own stroke risk, the best and most widely available imaging tool is carotid ultrasound, which aims to identify carotid plaque or intima-media thickness of more than 1.0 mm. Any degree of calcification of the aorta, such as that indicated by a CT heart scan, is another useful measure of risk. A prior transient ischemic attack, or "mini-stroke," also puts you at heightened risk for future stroke.

Treatment to reduce risk is multifaceted and should examine all sources of risk, such as metabolic syndrome and levels of small LDL, lipoprotein(a), and C-reactive protein. Fish oil is the one crucial ingredient in any stroke-prevention program. Other supplements can be used in a targeted fashion, depending on the sources of carotid or aortic plaque. Ideally, repeat scanning of the carotids should be performed some years after beginning your treatment program to assess whether you have successfully reversed plaque growth.

"You know that medicines when well used restore health to the sick: they will be well used when the doctor, together with his understanding of their nature, shall understand also what man is, what life is, and what constitution and health are. Know these well and you will know their opposites; and when this is the case, you will know well how to devise a remedy."

—Leonardo da Vinci

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