Treating Arteries Instead of Risk Factors
A Paradigm Change in Management of Atherosclerosis

J. David Spence, BA, MBA, MD, FRCP, FAHA; Daniel G. Hackam, BSc, MD, PhD, FRCP

Background and Purpose—Until recently, atherosclerosis was thought to be inexorably progressive. Beginning in 2001 and implemented in our vascular prevention clinics by 2003, we have been treating arteries rather than risk factors. We studied the proportion of patients with plaque progression vs regression before and after this change in paradigm.

Methods—Carotid total plaque area was measured by ultrasound at baseline and during follow-up. Before 2003, patients were treated according to consensus guidelines. After 2003, patients with plaque progression were treated more intensively, with the explicit goal of halting plaque progression or achieving regression.

Results—Four thousand three-hundred seventy-eight patients had serial plaque measurements in a given year between 1997 and 2007; 47% were female. Mean age at time of referral was 60 (SD, 15); this increased steeply (from age 50 to 62 years over the first 5 years) as we focused on stroke prevention. The annual rate of plaque progression increased steeply as the clinic populations aged but then abruptly decreased after implementation of the new approach to therapy. Before 2003, approximately half the patients had plaque progression and ≈25% had regression; by 2005, this had reversed.

Conclusions—Treating arteries without measuring plaque would be like treating hypertension without measuring blood pressure. A clinical trial to test this approach is being designed. (Stroke. 2010;41:1193-1199.)

Key Words: atherosclerosis ■ carotid ultrasound ■ prevention

For many years, it was assumed that atherosclerosis is inexorably progressive. In the mid 1970s, it became apparent that plaques that formed in response to balloon injury in monkeys could develop and progress in several months, and also regress in several months in response to reversal of a high-cholesterol diet. In 1990, Ornish showed reduction of coronary stenosis by angiography in patients following a severely restrictive diet and intensive lifestyle program. Regression of coronary plaques, assessed by intravascular ultrasound, was regarded as a novelty when first reported. However, in recent years, we have found that regression of carotid plaque is common and becoming the norm among our patients who are treated intensively based on ultrasound assessment of atheroma burden and progression.

In 1990, we began to measure carotid total plaque area (TPA), defined as the sum of cross-sectional areas of all plaques, measured in a longitudinal view (Figure 1), in the common, internal, and external carotids on both sides. This method was first used in a study of hemodynamic effects of mental stress and progression of carotid plaque area. Since then, we have used TPA to study many putative risk factors for atherosclerosis.

In 2002, we reported that TPA is a strong predictor of stroke, death, or myocardial infarction. After adjustment in multivariable regression for age, sex, cholesterol, systolic blood pressure, pack-years of smoking, diabetes, total homocysteine, and treatment of lipids and hypertension, patients in the top quartile of TPA had a 3.4-times higher risk of stroke, death, or myocardial infarction over 5 years compared to the bottom quartile. These findings were subsequently validated in the Tromsø study, a population-based study of >6000 participants in which carotid total plaque area, but not common carotid intima-media thickness (IMT), significantly predicted coronary events.

Furthermore, in our 2002 study, 26% of patients had regression of plaque, 15% had no change in plaque area, and 59% had progression of carotid plaque area in the first year of follow-up despite treatment according to consensus guidelines. These percentages represent a correction of the error in the original article. Those with progression had twice the risk of those events, even after adjustment for the same panel of risk factors. We also found that a high Framingham risk score identified only 30% of patients who would experience events, whereas 70% of the events occurred among patients in the top quartile of TPA.

The recognition that treatment according to consensus guidelines was failing half of our patients caused us to change...
the algorithm for patient management in our vascular clinics from treating risk factors to treating arteries.7 In patients with high plaque area, and especially in those whose plaque was progressing despite achieving target levels of blood pressure, low-density lipoprotein (LDL) cholesterol, and smoking cessation, therapy was intensified with the explicit goal of halting plaque progression or achieving regression. This approach has yielded remarkable results. We recently reported11 that among 468 patients with asymptomatic carotid stenosis >60% by Doppler peak velocities, more intensive medical therapy based on plaque measurement markedly reduced the rate of carotid plaque progression during the first year of follow-up (from 69±96 mm² before 2003 to 23±86 mm²; P<0.0001), the prevalence of microemboli on transcranial Doppler (from 12.6% of patients to 3.7%; P<0.0001), and the risk of cardiovascular events. The 2-year risk of stroke declined from 8.8% to 1%, and the 2-year risk of myocardial infarction declined from 8.6% to 1% (both P=0.01). The 2-year rate of stroke, death, myocardial infarction, or endarterectomy because of new transient ischemic attack declined from 17.6% of patients to 5.2% (P<0.0001). Here we report our observations on plaque progression in all patients followed-up in our vascular prevention clinics between 1997 and 2007.

Subjects and Methods

We included in the analyses all patients who had measurement of carotid plaque in any 2 successive years, between January 1, 1997 and December 30, 2007, representing the most complete data set available.

Clinic Populations

Patients analyzed for this report were referred to the Stroke Prevention Clinic, the Atherosclerosis Prevention Clinic, or the Premature Atherosclerosis Clinic, all at University Hospital in London, Ontario, Canada. Patients originally referred to J.D.S. at the Hypertension Clinic at Victoria hospital before 1997 were transferred to the Atherosclerosis Prevention Clinic when he moved to University Hospital to focus on stroke prevention. Patients were referred to the Stroke Prevention Clinic because of a transient ischemic attack or stroke, or because of asymptomatic carotid stenosis. Patients referred to the Premature Atherosclerosis Clinic had a family history of premature vascular disease or personal history of premature or accelerated atherosclerotic disease (coronary, carotid, aortic, or peripheral arterial disease). All patients had baseline measurement of TPA, with serial follow-up measurements performed at intervals that depended on the success of their therapy. Those with low TPA for their age, or with regression of TPA, could be followed-up in our clinic less often (while continuing to be followed-up by their primary care physician); those with severe TPA or progression were seen in clinic annually unless their primary care physician referred them back sooner because of problems such as elevated blood pressure or new symptoms.

Measurement of Carotid TPA

Carotid plaque area was measured as described previously8 with a high-resolution duplex ultrasound scanner (initially an ATL Mark 9, more recently an ATL 5000 HDI; Advanced Technology Laboratories). Scanning was performed by 2 registered vascular technologists who were very experienced in this method. The technologists were aware of the patients’ blood pressure and smoking status but did not have knowledge of the medications they were using.

Plaque was defined as a local thickening of the carotid intima >1 mm in thickness. Measurements were made in magnified longitudinal views of each plaque seen in the right and left common, internal, and external carotid arteries and, when visible (usually only on the right side), the subclavian arteries. The plane in which the measurement of each plaque was made was chosen by scanning around the artery until the view showing the largest extent of that plaque was obtained. The image was then frozen and magnified, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The microprocessor in the scanner then displayed the cross-sectional area of the plaque (Figure 1). The operator then moved on to the next plaque and repeated the process until all visible plaques were measured. The sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as total plaque area. Interobserver reliability (intra-class correlation, kappa) was 0.94 for repeated measurements6, interobserver reliability was 0.85.8

As in our previous article,6 we defined progression as an increase of TPA from 1 year to the next by more than the median change of...
5 mm$^2$. Regression was defined as a decrease of TPA by >5 mm$^2$, whereas a change of <5 mm$^2$ in either direction was defined as stable plaque area.

More Intensive Therapy

Beginning in 2001, when we began to understand the implications of our findings published in 2002, we implemented in our clinic a change to treating arteries rather than simply treating risk factor levels. By 2003, this change in approach had been fully implemented; the time required to implement the change was determined by the schedule of follow-up visits. Our approach to intensive therapy for accelerated atherosclerosis has previously been described. At baseline, therapy was intensified for those with a high plaque burden. During follow-up, therapy was intensified in patients in whom plaque was progressing despite treatment aimed at consensus targets for risk factors such as blood pressure and LDL cholesterol. This included using plaque measurements to motivate patients and to inform physicians about choices of medications.

To motivate patients to adhere to smoking cessation, exercise, medications, and a Mediterranean diet initially, in patients with a high plaque burden, we showed the plaque measurements and plaque images to the patients to impress on them that their high plaque burden for their age warranted intensive therapy. Often this was expressed as their arterial age using a version of Figure 2 that is printed on our ultrasound reports. During follow-up, we showed them that their plaque was progressing.

In patients with plaque progression, we increased the dose of statin to the maximum tolerated dose, regardless of LDL levels (eg, atorvastatin 80 mg or rosuvastatin 40 mg). In patients already at their maximum tolerated dose of statin, we added ezetimibe 10 mg daily. In those already using the maximum dose of statin and ezetimibe, we added niacin for patients who were not diabetic or adding fibrates for diabetic patients or those unable to use niacin or slow-release niacin because of flushing.

We ensured that patients with vascular disease were using an angiotensin-converting enzyme inhibitor. For those not able to use angiotensin-converting enzyme inhibitors because of cough or angioedema, we ensured that they were using an angiotensin receptor blocker, unless they had contraindications to these classes of drugs. In patients not reaching blood pressure targets, we optimized blood pressure control by individualizing therapy according to the renin/aldosterone profile. In some patients with insulin resistance (defined by a high fasting insulin level with normal serum glucose), metformin or pioglitazone was added before the onset of diabetes. Virtually all the patients were using antiplatelet agents unless they were anticoagulated for such indications as atrial fibrillation. We did not use plaque measurements to adjust those therapies. Approval of the University of Western Ontario Research Ethics Board was obtained in 1977 to report anonymously the results of clinical care. Many of the patients whose results are reported here also gave consent to various research protocols approved by the University of Western Ontario Research Ethics Board over the years.

Results

We analyzed for each year the average rate of plaque progression in our patients from all 3 clinics between 1997 and 2007 and the control of risk factors over that period. In the clinic populations between January 1, 1997 and December 30, 2007, there were 4378 patients with serial plaque measurements; 47% were female. Mean age (±SE) by year of referral and TPA (mean±95% CI) by age groups and sex are shown in Figure 2.

Because stroke patients are older, the mean age at the time of referral to the clinics increased steeply after 1997 (Figure 2A). Thus, with the aging of the clinic population, we expected a steep increase in the rate of plaque progression.

Figure 2. Aging of the clinic population and plaque progression with age. A, Average baseline age of clinic patients was increasing quickly from 1997 to 2003 when we changed from a Hypertension Clinic to a Secondary Stroke Prevention Clinic. B, Steep increase of baseline total plaque area by age, in both sexes, after age 45. Because the clinic population was aging quickly, it would be expected that the rate of plaque progression would increase quickly year by year in the clinic population.

Figure 3. Rate of plaque progression by year (mean±SE) among vascular prevention clinic patients. The rate of plaque progression began to increase, but then after we began to implement the change in paradigm (to treating arteries instead of risk factors) there was an abrupt decrease in the rate of plaque progression in the clinic patients. Since 2005, the mean rate of plaque progression has been negative (ie, we now see regression of plaque on average).
Instead, after implementation of the paradigm change in our clinic (from treating risk factors to treating arteries), we saw an abrupt change in plaque progression after 2001 (Figure 3). As Figure 3 shows, the rate of plaque progression increased until 2000, and then after 2001 it abruptly began to decline. By 2006, rather than plaque progression, the mean rate of change of TPA indicated plaque regression.

Table 1 shows the baseline characteristics of the patient population. Table 2 shows the proportion of patients with plaque progression by year and the levels of LDL cholesterol in those with progression, stable plaque, or regression.

Table 1. Baseline Characteristics of the Patient Population (n=4378)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD*</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>142</td>
<td>23</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>82</td>
<td>13</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.35</td>
<td>5.39</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.32</td>
<td>6.10</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.69</td>
<td>6.09</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.48</td>
<td>6.70</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>13.68</td>
<td>19.50</td>
</tr>
<tr>
<td>Total homocysteine, μmol/L</td>
<td>12.49</td>
<td>10.68</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>94.13</td>
<td>63.95</td>
</tr>
<tr>
<td>Total plaque area, mm²</td>
<td>124</td>
<td>140</td>
</tr>
<tr>
<td>Male</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Still smoking</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Previous MI*</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Previous TIA*</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Using lipid-lowering drug</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>Using blood pressure drug</td>
<td>53%</td>
<td></td>
</tr>
</tbody>
</table>

The patients were typical high-risk vascular prevention clinic patients weighted towards stroke and transient ischemic attacks.

Instead, after implementation of the paradigm change in our clinic (from treating risk factors to treating arteries), we saw an abrupt change in plaque progression after 2001 (Figure 3). As Figure 3 shows, the rate of plaque progression increased until 2000, and then after 2001 it abruptly began to decline. By 2006, rather than plaque progression, the mean rate of change of TPA indicated plaque regression.

Table 1 shows the baseline characteristics of the patient population. Table 2 shows the proportion of patients with plaque progression by year and the levels of LDL cholesterol in those with progression, stable plaque, or regression.

Table 2. Trends in Progression/Regression of Plaque and Corresponding Levels of LDL Cholesterol by Year

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age at first visit (SD)</td>
<td>50.45 (11.34)</td>
<td>54.96 (13.24)</td>
<td>57.43 (13.09)</td>
<td>60.54 (12.37)</td>
<td>61.33 (12.37)</td>
<td>62.88 (13.05)</td>
<td>63.50 (12.74)</td>
<td>63.70 (12.51)</td>
<td>64.02 (13.13)</td>
<td>64.72 (13.50)</td>
</tr>
<tr>
<td>Progression</td>
<td>28.2%</td>
<td>33%</td>
<td>48.1%</td>
<td>61.7%</td>
<td>55.4%</td>
<td>46.1%</td>
<td>41.9%</td>
<td>40.6%</td>
<td>26.8%</td>
<td>28.4%</td>
</tr>
<tr>
<td>Stable</td>
<td>35.9%</td>
<td>28%</td>
<td>23.3%</td>
<td>18.1%</td>
<td>18.5%</td>
<td>20.4%</td>
<td>20.1%</td>
<td>25.6%</td>
<td>23.1%</td>
<td>31%</td>
</tr>
<tr>
<td>Regression</td>
<td>35.9%</td>
<td>38.7%</td>
<td>28.6%</td>
<td>19.6%</td>
<td>26.1%</td>
<td>33.4%</td>
<td>38%</td>
<td>33.9%</td>
<td>50.1%</td>
<td>40.5%</td>
</tr>
</tbody>
</table>

Table 2. Trends in Progression/Regression of Plaque and Corresponding Levels of LDL Cholesterol by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>3.61 (2.33)</td>
<td>2.45 (0.95)</td>
<td>2.29 (0.77)</td>
<td>2.43 (0.81)</td>
<td>2.35 (0.82)</td>
<td>2.34 (0.73)</td>
<td>2.32 (0.8)</td>
<td>2.22 (0.55)</td>
<td>2.14 (0.83)</td>
<td>1.84 (0.74)</td>
</tr>
<tr>
<td>Stable</td>
<td>2.93 (0.74)</td>
<td>2.61 (0.57)</td>
<td>2.21 (0.79)</td>
<td>2.58 (0.74)</td>
<td>2.41 (0.89)</td>
<td>2.51 (0.98)</td>
<td>2.34 (0.74)</td>
<td>2.35 (0.89)</td>
<td>2.12 (0.81)</td>
<td>2.25 (0.93)</td>
</tr>
<tr>
<td>Regression</td>
<td>2.63 (1.02)</td>
<td>2.20 (0.32)</td>
<td>2.18 (0.93)</td>
<td>2.37 (0.77)</td>
<td>2.38 (0.76)</td>
<td>2.42 (0.95)</td>
<td>2.25 (0.64)</td>
<td>2.01* (0.61)</td>
<td>1.94 (0.83)</td>
<td>1.87† (0.78)</td>
</tr>
</tbody>
</table>

Plaque Progression vs Regression

As shown in Table 2, the proportion of patients with regression of TPA increased as the clinic populations aged from 25% before 2002 as previously reported6 to 50% by 2005. The proportion with regression decreased between 1997 and 2001 as the average age of the clinic patients increased, and then it began to increase with more intensive therapy. Note that the proportion with progression increased as the population aged between 1997 and 2001, but it then declined after implementation of the paradigm change despite continued aging of the clinic population. The proportion of patients with progression of plaque declined from 61.7% in 2001 to 26.8% by 2006; the proportion with regression increased from 19.6% in 2001 to 50.1% by 2006.

Table 2 and Figure 4 show that the relationship between plasma LDL and regression/progression changed with the change in treatment paradigm. In the early years, as would be expected, patients with plaque progression had higher levels of LDL, whereas those with regression had lower LDL. However, by 2007, those with progression had LDL levels approximately half that of those with progression in the early years, and their LDL levels were actually lower than those in patients with regression. This shows that we were trying harder to stop plaque progression and achieve frank regression using plaque measurement to guide therapy.

**Discussion**

The consequences of atherosclerotic disease in the coronary arteries, carotid arteries, aorta, and peripheral arteries are enormous in human and economic terms. Although treatment of traditional coronary risk factors is to a great extent successful in reducing levels of those risk factors, reduction of cardiovascular events by treating risk factors has been limited. In fact, a recent report by Lee et al14 shows a substantial worsening in the risk factor burden in Canada.

Virtually all positive randomized trials of cardiovascular prevention in high-risk patients show relative risk reductions in the range of 9% to 30%; this means that 70% to 80% of events are not prevented by guideline-advocated therapies.15–19 In the STENO-2 trial, despite a long-term, intensive, multifactorial intervention in diabetic subjects, only 50% of cardiovascular events were prevented during a follow-up of...
14 years. In real-world practice, results of therapy tend to be even less effective than in clinical trials. Reasons limiting success of guidelines may include reluctance of physicians to prescribe intensive therapy and reluctance of patients to use intensive therapy. Despite widespread dissemination of consensus guidelines, targets for therapy are seldom achieved in real-world settings. Until recently, only one-third of patients with hypertension were controlled to targets, and adherence to therapy is less than many physicians would like to believe. Antihypertensive medication is prescribed in only 25% to 50% of cases of hypertension in North America and Europe, and global rates of hypertension control to <140/90 mm Hg range from 5.4% in Korea to 58% in Barbados. Long-term persistence with antihypertensive therapy is 50%. The management of LDL cholesterol remains suboptimal even in patients at high cardiovascular risk, with only 40% to 50% of patients achieving LDL cholesterol targets in the United States and Europe. Even in a well-organized and highly disciplined health maintenance organization, persistence with statins in secondary prevention was only 60%; in less structured systems, persistence with statins over the course of ≥2 years is only ≈40% in secondary prevention and 25% in primary prevention. A recent study in community-based clinical practice found that only 21% of high-risk patients achieved goals for blood pressure, LDL, and blood glucose. All of these factors suggest the need for a new paradigm for cardiovascular prevention to reduce the totality of cardiovascular risk, particularly in high-risk patients.

Despite the appeal of more intensive therapy for all patients in primary prevention, the recent results of the JUPITER study show that intensive treatment of all patients at risk (primary prevention) is not cost-effective. The development of the high-risk strategy is therefore necessary, with more intensive therapy reserved for patients identified as high-risk, either because they already have vascular disease (secondary prevention) or because they have high risk scores, for example with Framingham risk scores.

An intermediate approach is to use quantification of preclinical vascular disease to further identify high-risk patients. This is the approach exemplified in this report. We found that the proportion of patients with regression decreased between 1997 and 2001 as the average age of the clinic patients increased, and then it began to increase after the change to more intensive therapy. Despite aging of the clinic population, the proportion with regression of plaque increased from 25% before 2002, as previously reported, to 50% by 2005.

We acknowledge important limitations in this study. Our research design was observational rather than randomized.
and analyzed trend in patients accrued over the course of 10 years. Because the patients were all referred to a prevention clinic, our results would be relevant only to similar patient populations. The changes reported for each time period are group changes because there were not many patients who had serial examinations in all years. Furthermore, the changes in plaque area have not been analyzed taking into account patient characteristics. Because only 16% of the patients were still smoking at baseline, we have limited ability to assess the effects of this approach on smoking cessation in the way reported by Bovet et al (discussed below). The increase in age and risk factor burdens over time should have promoted plaque progression rather than the regression that we actually saw. By exceeding guideline-advocated treatment targets based on serial carotid plaque area measurement, we were able to reduce the proportion of patients with progression of plaque by half. This also reduced cardiovascular events. Among our patients with asymptomatic carotid stenosis, the combined outcome of stroke, death, myocardial infarction, or carotid endarterectomy (because of new cerebral symptoms on the side of the stenosis) declined from 17.6% before 2003 to 5.2% (P<0.0001) since then.11

There have been calls for improved identification of high-risk patients based on imaging methods such as carotid IMT, burden of carotid plaque, coronary calcium scores, and other methods. The rationale for this approach is that risk scores such as Framingham scores identify only a fraction of the patients who will experience events. Use of carotid ultrasound assessment of atherosclerosis burden in clinical practice was reviewed by Hurst et al.33

The hypothesis that quantification of atherosclerosis burden can improve adherence of physicians to consensus targets for vascular prevention and improve adherence of patients to prescribed regimens has been previously tested in a number of studies. Bovet et al showed that showing smokers ultrasound images of their carotid plaques significantly increased rates of cessation of tobacco smoking. Goessens et al reported that noninvasive screening for vascular disease significantly increased prescriptions for both hypertension and hyperlipidemia. Young et al found no significant improvement in outcomes among diabetic patients screened for coronary artery disease with myocardial perfusion imaging, whereas Faglia et al found the reverse.

However, recently, Korcarz et al reported that measurement of IMT in clinical practice changed both physician and patient behaviors. Doctors who found plaque in their patients were 5-times more likely to add an aspirin medication (OR, 4.84; P<0.001) and >7-times more likely to add a lipid-lowering drug (OR, 7.40; P<0.001). Patients were more likely to report increases in plans to take cholesterol-lowering medication (P=0.002) and the perceived likelihood of having heart disease or having heart disease develop (P=0.004).

However, as discussed, it is not possible to measure change in IMT within individuals over short time periods, such as 6 months or 12 months, to adjust therapy.

Furthermore, carotid plaque area is more predictive of cardiovascular risk, particularly that of myocardial infarction, than is IMT. Spence et al showed in vascular patients that carotid plaque burden assessed as TPA strongly predicted cardiovascular risk after adjusting for coronary risk factors, and that plaque progression despite treatment according to guidelines further predicted cardiovascular risk. Brook et al showed that carotid TPA was a stronger predictor of coronary stenosis than carotid IMT, coronary calcium, or C-reactive protein. In the Tromsø study, a population-based study in Norway, carotid TPA was a strong predictor of coronary events, whereas IMT as usually measured in the distal wall of the common carotid did not predict coronary events.9 It should be noted that the approach described here cannot be based on measurement of IMT because the annual change in IMT (>0.015 mm) is below the resolution of the ultrasound method (0.3 mm).41

Conclusions

Our observations support the hypothesis that measuring plaque improves therapy in cardiovascular prevention clinics. We suggest that treating atherosclerosis without measuring plaque would be like treating hypertension without measuring blood pressure.7,10 These preliminary results are intriguing and promising but cannot lead to a widespread change in practice until validated in a randomized clinical trial, which is now being designed.

Acknowledgments

Over the 10 years during which data analyzed for this report were being gathered, many people contributed to data acquisition and to data entry and clean-up. Maria DiCicco, RVT, invented measurement of carotid plaque area in our laboratory in 1990 and performed all of the earlier carotid plaque measurements and approximately half since 2001. Janine DesRoches, RVT, performed approximately half of the plaque measurements since 2001. Data entry and clean-up involved teams of summer students led for many of these years by Victoria Coates. The students included medical students Dan Hackam, Hector Li, Jonathan Klein (all from the University of Western Ontario), Chrysi Bogiatzi (from the Democritus University of Thrace, in Alexandroupolis, Greece), Laura Kuoppala (from the University of Tampere, in Tampere, Finland), and numerous other summer students, including Alexis Markham, Carly Harris, Katie Whitton, Trevor Sher, and others. In addition, the staff of the Stroke Prevention & Atherosclerosis Research Centre performed data entry on a daily basis. They included Lisa Miners, Tisha Mabb, Marsha Davis, Joan Fleming, Patricia Mills, and others. During those years the maintenance of the database was made possible by funding from the Heart & Stroke Foundation, including grant numbers T2956, T5017, NA4990, T5704, NA6018, and NA5912. It was also supported by donations to the Stroke Prevention & Atherosclerosis Research Centre.

Disclosures

None.

References


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**Treating Arteries Instead of Risk Factors**

A Paradigm Change in Management of Atherosclerosis

J. David Spence, BA, MBA, MD, FRCPC, FAHA; Daniel G. Hackam, BSc, MD, PhD, FRCPC

**背景和目的：** 之前动脉粥样硬化的进展曾被认为是不可逆的。从2001年到2003年，在血管防治门诊中，我们治疗动脉而非治疗危险因素。我们研究对比了这种模式转变前后斑块进展和消退的患者比例。

**方法：** 采用超声检测基线和随访时颈动脉斑块总体面积。2003年之前，按照共识指南进行治疗。2003年之后，按照明确的治疗目标即阻止斑块进展或消退，给予斑块进展患者更强化的治疗。

**结果：** 1997年至2007年的4378例患者有系列的斑块检测; 其中47%为女性。平均年龄为60岁（标准差，15）; 当我们把重点放在卒中预防上时，年龄大幅度的提高（在第一个5年中，从50岁提高到62岁）。随着门诊患者人群的老化, 年斑块进展率大幅度增高。在采取新的治疗后，年斑块进展率突然降低。2003年之前，大约半数患者有斑块进展，约25%患者斑块消退；到2005年，这种情况逆转了。血脂的变化显示其对斑块检测有影响，不仅仅是对所有的病人采用更强化治疗的结果，至2007年，斑块进展患者的低密度脂蛋白比斑块消退患者的更低。

**结论：** 如果治疗动脉而不检测斑块就像治疗高血压而不监测血压。正在设计一个检验这种方式的临床试验。

**关键词：** 动脉粥样硬化, 颈动脉超声, 预防

(Stroke. 2010;41:1193-1199. 何莎 译 曾进胜 校)
Spence and Hackam  Treating Arteries Instead of Risk Factors

颈动脉斑块发展的速度有所减慢 (由 2003 年前的 69 ± 96 mm² 至 23 ± 86 mm²; \( P < 0.0001 \)), 经颅多普勒 显示脑血管微栓子的发生率下降 (从 12.6% 减少至 3.7%; \( P < 0.0001 \)), 发生心血管事件的风险降低。第 二年卒中风险从 8.8% 下降至 1%, 第二年的心肌梗 死从 6% 下降至 1% (两者 \( P = 0.01 \)); 第二年发生脑卒中、死亡、心肌梗死或由于新的短暂性脑缺血发作 作行颈动脉内膜剥脱术的百分率从 17.6% 下降至 5% (\( P < 0.0001 \))。本文报告我院血管防治门诊从 1997 至 2007 接受随访的所有患者的粥样硬化斑块发展的观 察结果。

对象和方法

在分析中, 我们纳入了连续两年测量颈动脉斑 块的所有病人, 从 1997 年 1 月至 2007 年 12 月 30 日。提供可用于研究的最完整的数据

门诊病人

本研究的病人来自于加拿大安大略省伦敦市大 学医院卒中预防门诊部，动脉硬化或早期动脉硬化 预防门诊。1997 年之前维多利亚医院高血压门诊部 的病人由于该门诊部改为专注卒中预防，而转到动 脉硬化防治门诊组。短暂性脑缺血发作、脑卒中及 无症状颈动脉狭窄的病人被纳入卒中防治组。有早 发性血管疾病家族史或个人有早期血管疾病 (冠状 动脉、颈动脉、主动脉, 周围动脉) 的病人被纳入早 期动脉硬化组。所有的病人都做了 TPA 基线测量， 间隔一段时间对病人进行一系列的随访，评价治疗 是否成功。TPA 较小或 TPA 消退的病人在门诊随访 次数较少 (由他们最初的保健医生对他们在随访 继续进行随访)。有斑块面积较大或斑块进行性进展的病人每年到诊所复诊，除非他们的初级保健医生由于病人 血压升高或新的症状而要求他们回到大学医院复诊。

颈动脉TPA的测量

颈动脉斑块由高清晰双面超声波扫描仪测量 [1] ( 开始由 ATL9 号, 最近更多使用 ATL5000HDI, 先进 技术实验室)。扫描由非常有经验的 2 名注册血管扫 描技师实施。技师了解病人的血压及吸烟状况，但 不知道他们的用药情况。

斑块被定义为局部颈动脉内膜厚度 >1 mm。以 纵向视角测量于双侧颈总动脉、颈外动脉、颈动脉及 锁骨下动脉 (通常仅右侧可见) 发现的每一块斑块。选择测量每个斑块的平面取决于在测量时能 观察到斑块的最大面积。然后固定图像并放大，描 记斑块周边范围。扫描仪的图像微处理器随之显示 斑块的横截面积 (图 1)。测量员继续测量下一斑块， 重复相同的方法直到测量完所有的斑块。在锁骨至 下颌骨之间能见的斑块横截面积之和为总体斑块面 积。该项研究的可重复性为 0.94，可信性为 0.85[6]

就像我们之前的研究那样 [6]，斑块进展定义为 颈动脉 TPA 从第一年发展至第二年增长 >5 mm²，斑 块消退定义为颈动脉 TPA 减少大于 5 mm²，而 TPA 无论增长或减少只要 <5 mm² 即定义为稳定斑块。

强化治疗

从 2001 年开始，当我们的 2002 年发表的结 果其研究意义时，即开始转变治疗策略为治疗病变血管， 而不是简单停留在治疗风险因素的水平。至 2003 年， 治疗方案的改革已经全面实施，改革的时间长短取决 于随访病人的日程安排。我们强化治疗动脉硬化化的 方案已在前面描述 [23]。在治疗的基线水平, 强化治疗针 对于斑块负荷重的病人。而在随访期间，强化治疗用 于在控制血压、低密度脂蛋白胆固醇等危险因素后斑 块仍在进展的病人。包括告知病人斑块面积大小来鼓 励病人参与治疗以及告知医师注意选择药物的问题。

为了激励斑块负荷重的病人坚持戒烟、锻炼、 服药以及开始地中海食节计。我们将斑块面积和 斑块图像展示给病人看，加深他们治病的意识，病 人斑块负荷重相对于他们的年龄是需要强化治疗的。 通常这一点是使用图 2 的方法来显示他们的动脉年 龄，图 2 会附在我们的超声报告里。在随访时，我
我们会告知病人他们的斑块仍在发展。针对斑块增长的病人，无论低密度脂蛋白水平如何，我们将他汀剂量增至最大耐受量 (例如，阿托伐他汀 80 毫克或瑞舒伐他汀 40 毫克)。对于他汀已用至最大耐受量的病人，每日加用依泽替米贝 10 毫克。对于他汀及依泽替米贝均已用至最大耐受量的病人，若其已合并糖尿病则每日加用烟酸，若病人因同时患有糖尿病或因面部潮红不能使用烟酸或缓释量的烟酸，则每日加用贝特类药物。我们保证患血管疾病的病人一直服用 ACEI 类药物。对于那些因血管性水肿或咳嗽而无法耐受 ACEI 类药物的病人，予以改用ARB 类药物 [13]，除非他们有服用这类药物的禁忌症。对于没有达到降血压目标的病人，我们根据肾素/醛固酮的情况采用个体化治疗策略调控血压 [12]。对于胰岛素抵抗 (定义为随机血糖正常、空腹血糖高) 的病人使用二甲双胍或匹格列酮预防糖尿病的发生。实际上，所有的病人都应用抗血小板的药物，除外他们必须服用抗凝剂，如同时患有房颤。我们没有依据斑块面积大小来调整治疗方案。西安大略大学研究伦理委员会于 1977 年同意匿名报道临床护理结果。多年来，本研究报道的大部分病人结果也符合经西安大略省大学同意的研究协议内容。

结果

我们分析了从 1977 年至 2007 年每一年 3 个诊所的全部病人斑块进展情况以及这段时期危险因素的控制情况。从 1997 年 1 月 1 日至 2007 年 12 月 30 日的门诊病人中，有 4378 位病人存在严重的粥样硬化斑块。其中 47% 的病人为女性，图 2 显示了每一年就诊病人的平均年龄 (±SE) 以及不同年龄组和性别组的 TPA 值 (均值 ±95% CI)。由于卒中病人年龄较大，入选的门诊病人的年龄在 1997 年后急剧增加 (图 2A)，我们估计病人斑块的发展速度也会随着门诊病人的老龄化有直线下降。相反在门诊治疗策略改革实施后 (从治疗危险因素转变为治疗病变血管)，我们发现 2001 年以后斑块进展情况有了巨大变化。如图 3 显示，斑块进展的速度至 2000 年达到顶峰，接着从 2001 年起开始急剧下降。到了 2006，TPA 改变的不是斑块进展的速度而是斑块消退的速度。表 1 显示了病人基本情况。表 2 显示了每年病人斑块发展进程消退及增长各项占的比例以及斑块增长，稳定，消退病人低密度脂蛋白水平的不同情况。

斑块消退对比增长

间随着人口老龄化，斑块进展的病人比例上升。但是
在实施治疗策略模式转变后，尽管老龄化的现象仍
在存在，但斑块增长的病人所占比例却在下降，由
2001
年的
61.7%
下降至
2006
年的
26.8%
。斑块消退
的比例由
2001
年的
19.6%
增长为
2006
年的
50.1%
。

表 2 斑块消退增长的趋势以及对应年份的 LDL 胆固醇水平

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>增长</td>
<td>28.2%</td>
<td>33%</td>
<td>48.1%</td>
<td>61.7%</td>
<td>55.4%</td>
<td>46.1%</td>
<td>41.9%</td>
<td>40.6%</td>
<td>26.8%</td>
<td>28.4%</td>
</tr>
<tr>
<td>稳定</td>
<td>35.9%</td>
<td>28%</td>
<td>23.3%</td>
<td>18.1%</td>
<td>18.5%</td>
<td>20.4%</td>
<td>20.1%</td>
<td>25.6%</td>
<td>23.1%</td>
<td>31%</td>
</tr>
<tr>
<td>消退</td>
<td>35.9%</td>
<td>38.7%</td>
<td>28.6%</td>
<td>19.6%</td>
<td>26.1%</td>
<td>33.4%</td>
<td>38%</td>
<td>33.9%</td>
<td>50.1%</td>
<td>40.5%</td>
</tr>
<tr>
<td>增长</td>
<td>3.61 (2.33)</td>
<td>2.45 (0.95)</td>
<td>2.29 (0.77)</td>
<td>2.43 (0.81)</td>
<td>2.35 (0.82)</td>
<td>2.34 (0.73)</td>
<td>2.32 (0.8)</td>
<td>2.22 (0.55)</td>
<td>2.14 (0.83)</td>
<td>1.84 (0.74)</td>
</tr>
<tr>
<td>稳定</td>
<td>2.93 (0.74)</td>
<td>2.61 (0.57)</td>
<td>2.21 (0.79)</td>
<td>2.58 (0.74)</td>
<td>2.41 (0.89)</td>
<td>2.51 (0.98)</td>
<td>2.34 (0.74)</td>
<td>2.35 (0.89)</td>
<td>2.12 (0.81)</td>
<td>2.25 (0.93)</td>
</tr>
<tr>
<td>消退</td>
<td>2.63 (1.02)</td>
<td>2.20 (0.32)</td>
<td>2.18 (0.93)</td>
<td>2.37 (0.77)</td>
<td>2.38 (0.76)</td>
<td>2.42 (0.95)</td>
<td>2.25 (0.64)</td>
<td>2.01 (0.61)</td>
<td>1.94 (0.83)</td>
<td>1.871 (0.78)</td>
</tr>
</tbody>
</table>

病人来自于高风险血管预防门诊病人，主要为卒中和短暂性缺血性
发作的病人。

表 1 病人的基线特征 (n=4378)

| 年龄，年份 | 60 | 15 |
| 收缩压，mm Hg | 142 | 23 |
| 舒张压，mm Hg | 82 | 13 |
| 总胆固醇，mmol/L | 5.35 | 5.39 |
| 甘油三酯，mmol/L | 2.32 | 6.10 |
| 高密度胆固醇，mmol/L | 1.69 | 6.09 |
| 低密度胆固醇，mmol/L | 3.48 | 6.70 |
| 吸烟，包/年 | 13.68 | 19.50 |
| 同型半胱氨酸，μmol/L | 12.49 | 10.68 |
| 肌酐，mmol/L | 94.13 | 63.95 |
| 颈动脉斑块总面积，mm² | 124 | 140 |

男性 53%
糖尿病 10.4%
从未吸烟 42%
曾吸烟者 45%
仍旧吸烟者 13%
曾发病中 * 1.3%
曾发作 TIA * 22%
曾发作 TIA * 31%
使用降脂药物 42%
使用降压药物 53%

讨论

冠状动脉、颈动脉、主动脉以及外周动脉的动
脉粥样硬化疾病会对社会和经济带来巨大影响。尽
管针对冠状动脉相关危险因素的治疗策略是减
低危险因素水平的一个成功例子，但通过防治危险
因素降低心血管事件发生率的效果却是有限的。实际
上，来自加拿大 Lec 等 [14] 的研究报告表明在心血
管事件相关危险因素的负荷在不断持续恶化。

实际上，所有针对高风险患者干预其心血管事
件发生的阳性随机试验均显示相关危险因素下降范围在
9%-30%；这说明参照指南实施的治疗方案没有阻止
70% 到 80% 的事件发生 [15-19]，以 STENO-2 试验为例,
这是一个针对糖尿病患者的长程、高强度, 多因素
干预的试验项目，在长达 14 年的随访期里仅阻止了
50% 的心血管事件发生 [20]。在临床实践中，治疗结
果没有临床试验那么令人满意。限制指南成功的原
因可能包括医生不情愿开强化治疗药物以及病人不
愿接受强化治疗。尽管指南已广泛宣传，临床实践
仍然很少达到治疗目的。很多医生相信治疗的意义,
却没有坚持实施治疗 [21]。在北美和欧洲仅
25%-50%
的高血压病人服用降压药治疗 [22]，并且全世界血压
水平控制在
140/90 mmHg
以下的比例并不一致，韩
国为
5.4%
，巴巴多斯为
58% [23]。

近期一个社区临床实践研究发现只有
21%
的高风险
病人达到血压、低密度脂蛋白和血糖控制目标值
 [31]。

所有这些因素表明心血管事件的预防需要一个新的
管理模式才能达到减少心血管事件发生的整体风险,
Stroke June 2010

特别对于高风险病人群体而言更是如此。

尽管目前号召对所有病人在初级预防阶段即应实施强化的治疗方案, 但最近的 JUPITER 研究[19]指出对所有存在风险的病人进行强化治疗(即一级预防)并没有成本效益。因此发展高风险战略是很有必要的, 筛选出已经罹患心血管疾病的病人 (即实施二级预防) 及心血管事件发生危险评分很高的病人(例如 Framingham 危险评分量表), 应针对这些高风险病人实施更强化的治疗。

使用血管疾病临床前期量化的方法来进一步确定高风险的病人不失为一个折中的办法。这种方法已在此文献中阐述。我们发现在 1997 至 2001 年间, 随着门诊病人平均年龄的增加, 斑块消退的病人比例在下降。但当实施更强化的治疗后, 斑块消退的病人比例又开始上升。尽管就诊人群老龄化现象在持续, 但斑块消退的病人比例却由 2002 年的 25% 上升到 2005 年的 50%[6]。

本研究仍存在明显的不足之处, 我们是观察性的研究而非随机性试验研究, 并且分析的人群数量在十年之内累积不断增长。因为病人都参加的是预防门诊组, 所以我们研究结果只与这类病人有关。因为没有太多的病人是一年体检若干次, 每个时期报道的变化是组群的变化。此外, 分析斑块面积变化没有考虑病人的基本特征。因为纳入实验初期只有 16% 的病人依旧在抽烟, 我们对评估此方法在戒烟方面的效果能力有限, Bovet 等曾报道过此方法(讨论见下文)。年龄的增长和危险因素负荷的加重, 随着时间的推移, 会促进斑块面积的扩大而不是我们之前所见的斑块面积的缩小。通过对颈动脉超声硬化斑块面积的测量, 对病变严重的病人应给予超出指南推荐的治疗强度方案。我们能将斑块进展的病人比例降低一半。该方案同样能减少心血管事件的发生率, 在我们无症状颈动脉狭窄的病人中, 其中风、死亡, 心肌梗死或颈动脉内膜切除术的发病率由 2003 以前的 17.6% 下降至 2003 年以后的 5.2%(P<0.0001)[11]。

目前, 有学者一直呼吁[32]借助影像手段来提高鉴别高风险的病人, 例如采用测量颈动脉内膜中层厚度 (IMT)、斑块厚度、冠状动脉钙化分数以及其他方法。这种手段的提出是因为既往采用的风险评分, 如 Framingham 量表, 仅能鉴别出一部分将会遭遇卒中、心肌梗死、死亡等事件的病人。Hurst 等曾评价过临床实践中使用颈动脉超声评估斑块负担[33]。

量化动脉硬化负荷的学说可以促进医师在血管预防方面向共同目标努力, 也能提高病人对规定治疗方案的依从性, 这一点在以前的许多研究中已经得到验证。Bovet 等研究[34]显示向吸烟者展示他们颈动脉斑块的超声图像可提高戒烟率。Goessens 等[35,36]报道非侵入性的筛查血管疾病可显著地提高抗高血压和抗高血脂的处方。Young 等研究[37]发现使用心肌灌

图 4 病人每年的血脂水平: 在 1997 至 2001 年期间门诊总体病人总胆固醇和低密度脂蛋白胆固醇水平下降, 然后稳定, 接着略有上升。2003 年以后, 实施了强化治疗方案后总胆固醇和低密度脂蛋白水平再次下降。这个转折点同样显示在表 2 的斑块消退/增长中。
Spence and Hackam Treating Arteries Instead of Risk Factors


Spence JD. Point: uses of carotid plaque measurement as a predictor of cardiovascular events. Prev Cardiol. 2005;8:118 – 121.


