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Treating arteries instead of risk factors: A paradigm change in management of atherosclerosis

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

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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. Changes in plasma lipids show that the differences were attributable to plaque measurement, not simply more intensive therapy for all patients. By 2007, patients with progression had lower levels of low-density lipoprotein than those with regression.

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.[1] 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.[2] In 1990, Ornish[3] 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.[4,5] 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.[6,7] This method was first used in a study of hemodynamic effects of mental stress and progression of carotid plaque area.[8] Since then, we have used TPA to study many putative risk factors for atherosclerosis.

In 2002, we reported[6] 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 lowest 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.[9]

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.[6] Those with progression had twice the risk of those events, even after adjustment for the same panel of risk factors.[6] 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.[10]

The recognition that treatment according to consensus guidelines was failing half of our patients caused us to change

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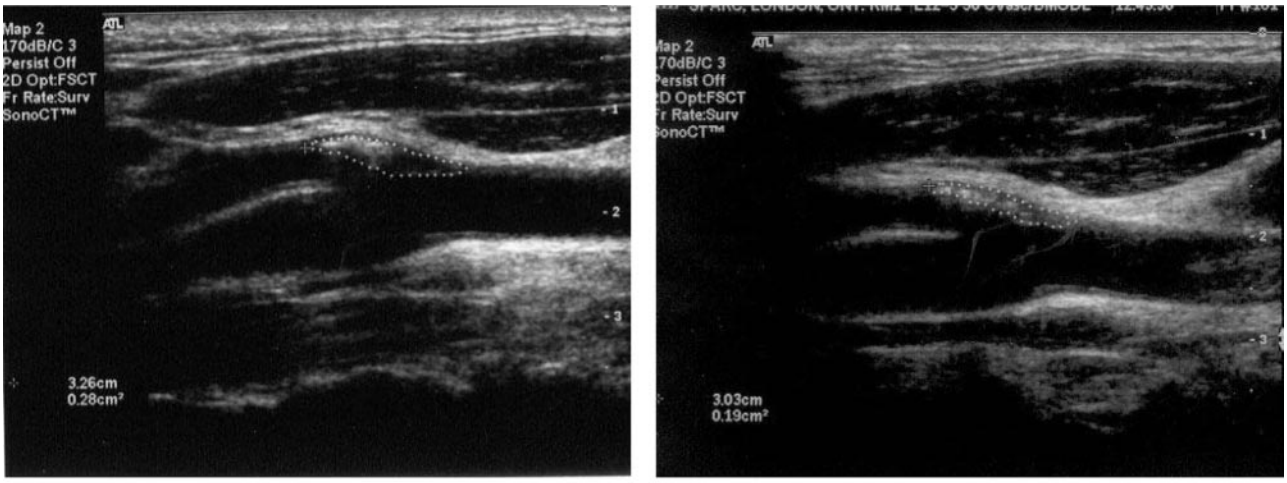

Figure 1. Plaque regression is much faster than most would expect. Left panel, A soft plaque at the origin of the left external carotid in a 64-year-old man using ezetimibe alone because of myalgias and cramps with statins. His plaque had progressed from 20 mm^2 the previous year to 28 mm^2 after stopping rosuvastatin. After restarting rosuvastatin 5 mg daily with CoQ10 200 mg daily to prevent myalgias, the plaque area regressed to 0.19 mm^2 over 3.5 months. The plaque had also become denser with regression of the soft plaque and more calcification.

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 reported[11] 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 mm^2 before 2003 to 23±86 mm^2; $P<0.0001$), 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 previously[8] 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. Intraobserver reliability (intraclass correlation, kappa) was 0.94 for repeated measurements[8]; interobserver reliability was 0.85.[6]

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

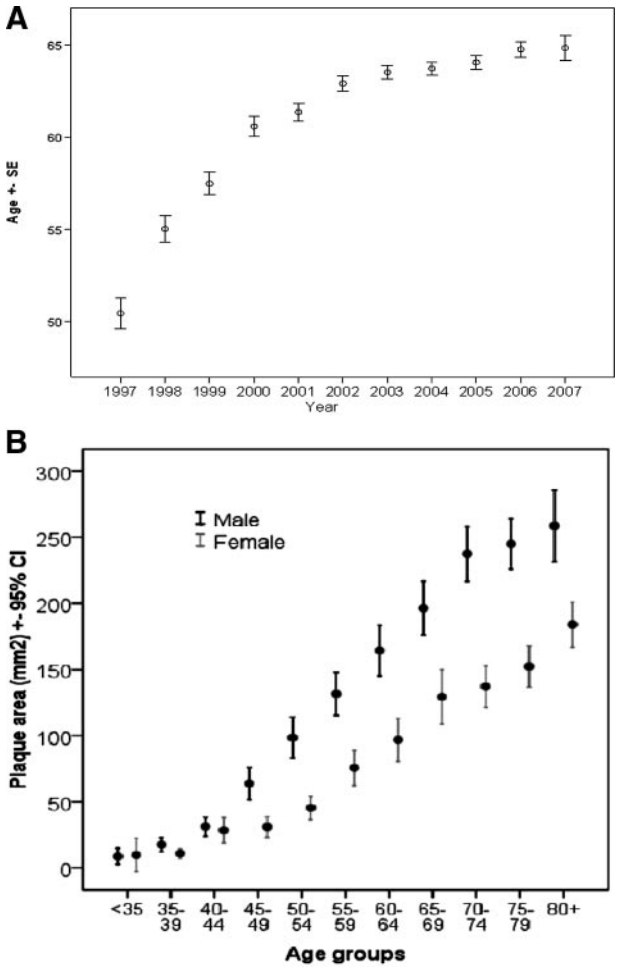

Figure 2. Aging of the clinic population and plaque progression with age. A, Average baseline age of clinic patients was increasing quickly from 1997 to 2003 when we changed from a Hypertension Clinic to a Secondary Stroke Prevention Clinic. B, Steep increase of baseline total plaque area by age, in 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.

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.[12] 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

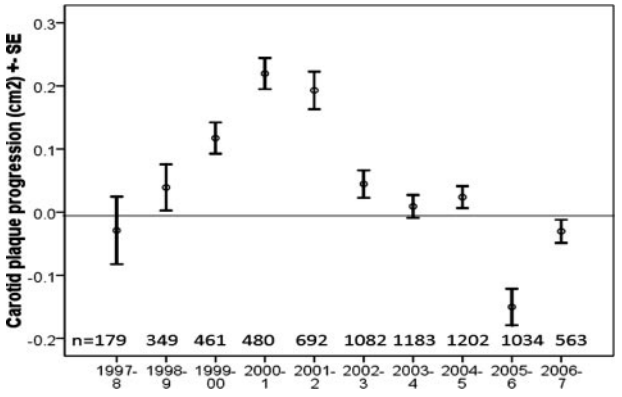

Figure 3. Rate of plaque progression by year (mean±SE) among vascular prevention clinic patients. The rate of plaque progression began to increase, but then after we began to implement the change in paradigm (to treating arteries instead of risk factors) there was an abrupt decrease in the rate of plaque 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).

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,[13] 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.[12] 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.

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

	Mean	SD*
Age, yr	60	15
Systolic pressure, mm Hg	142	23
Diastolic pressure, mm Hg	82	13
Total cholesterol, mmol/L	5.35	5.39
Triglycerides, mmol/L	2.32	6.10
HDL cholesterol, mmol/L	1.69	6.09
LDL cholesterol, mmol/L	3.48	6.70
Smoking, pack-years	13.68	19.50
Total homocysteine, μmol/L	12.49	10.68
Creatinine, mmol/L	94.13	63.95
Total plaque area, mm^2	124	140
Male	53%	
Diabetic	10.4%	
Never smoked	42%	
Former smoker	45%	
Still smoking	13%	
Previous MI*	1.3%	
Previous stroke	22%	
Previous TIA*	31%	
Using lipid-lowering drug	42%	
Using blood pressure drug	53%	

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.

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 reported[6] 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 al[14] 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

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

	1997–1998	1998–1999	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004	2004–2005	2005–2006	2006–2007
Age at first visit (SD)	50.45 (11.34)	54.96 (13.24)	57.43 (13.09)	60.54 (12.37)	61.332 (12.37)	62.88 (13.05)	63.50 (12.74)	63.70 (12.51)	64.02 (13.13)	64.72 (13.50)
Progression	28.2%	33%	48.1%	61.7%	55.4%	46.1%	41.9%	40.6%	26.8%	28.4%
Stable	35.9%	28%	23.3%	18.1%	18.5%	20.4%	20.1%	25.6%	23.1%	31%
Regression	35.9%	38.7%	28.6%	19.6%	26.1%	33.4%	38%	33.9%	50.1%	40.5%
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Progression	3.61 (2.33)	2.45 (0.95)	2.29 (0.77)	2.43 (0.81)	2.35 (0.82)	2.34 (0.73)	2.32 (0.8)	2.22 (0.55)	2.14 (0.83)	1.84 (0.74)
Stable	2.93 (0.74)	2.61 (0.57)	2.21 (0.79)	2.58 (0.74)	2.41 (0.89)	2.51 (0.98)	2.34 (0.74)	2.35 (0.89)	2.12 (0.81)	2.25 (0.93)
Regression	2.63 (1.02)	2.20 (0.32)	2.18 (0.93)	2.37 (0.77)	2.38 (0.76)	2.42 (0.95)	2.25 (0.64)	2.01* (0.61)	1.94 (0.83)	1.87† (0.78)

Trends in progression/regression of plaque.
LDL cholesterol (mmol/L [SD]) by progression groups in each year.
*$P<0.05$.
†$P<0.003$.

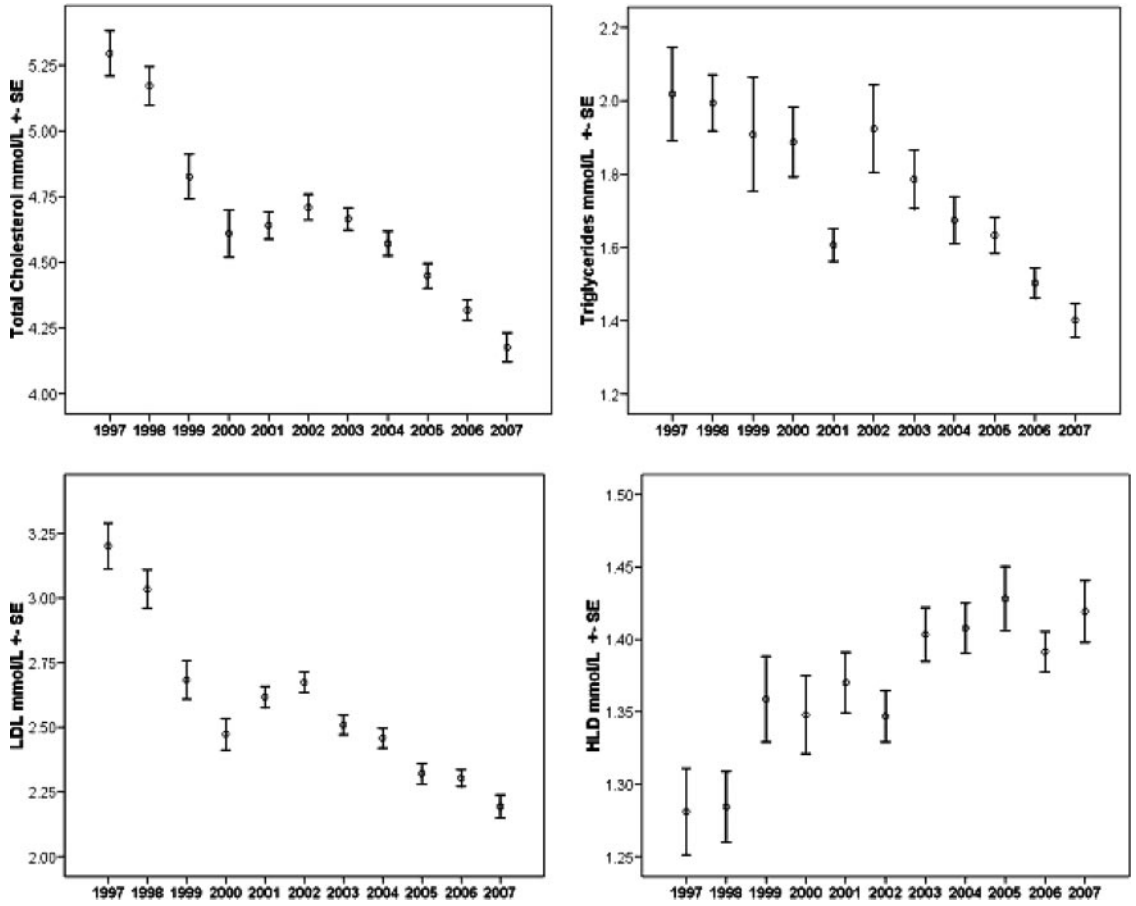

Figure 4. Plasma lipid levels by year. Levels of total cholesterol and LDL cholesterol were declining in the overall clinic population between 1997 and 2001, then leveled off, and then increased slightly. Then, after 2003, levels again declined with implementation of the strategy of treating arteries. This inflection point coincides with the change in plaque progression/regression shown in Table 2.

14 years.[20] 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,[21] 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,[22] and global rates of hypertension control to <140/90 mm Hg range from 5.4% in Korea to 58% in Barbados.[23] Long-term persistence with antihypertensive therapy is ≈50%.[24]

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[25] and Europe.[26] Even in a well-organized and highly disciplined health maintenance organization, persistence with statins in secondary prevention was only 60%;[27] in less structured systems, persistence with statins over the course of ≥2 years is only ≈40% in secondary prevention and 25% in primary prevention.[28–30] 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.[31] 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[19] 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,[6] 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[32] 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[34] showed that showing smokers ultrasound images of their carotid plaques significantly increased rates of cessation of tobacco smoking. Goessens et al[35,36] reported that noninvasive screening for vascular disease significantly increased prescriptions for both hypertension and hyperlipidemia. Young et al[37] found no significant improvement in outcomes among diabetic patients screened for coronary artery disease with myocardial perfusion imaging, whereas Faglia et al[38] found the reverse.

However, recently, Korcarz et al[39] 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 antiplatelet 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[6] 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[40] 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.

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