6-1-2017

Resistant atherosclerosis: the need for monitoring of plaque burden

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Resistant Atherosclerosis
The Need for Monitoring of Plaque Burden

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Background and Purpose—Recent studies indicate that patients with lower levels of low-density lipoprotein cholesterol (LDL-C) have greater regression of coronary plaque. In 2002, we found that carotid plaque progression doubled cardiovascular risk. In 2003, we therefore implemented a new approach, treating arteries instead of risk factors. Since then, we have seen many patients with carotid plaque progression despite very low levels of LDL-C, suggesting other causes of atherosclerosis. We studied the relationship of achieved LDL-C and change in LDL-C to progression/regression of atherosclerosis, before and after 2003.

Methods—All 4512 patients in our clinic database with at least 2 measurements of LDL-C and carotid total plaque area approximately a year apart and complete data for analyses (n=2025 before and 2487 after December 31, 2003) were included in the study.

Results—Baseline total plaque area was significantly higher after 2003 (129.56±134.32 versus 113.33±121.52 mm^2; $P<0.0001$), and plaque progression was significantly less after 2003 (2.94±37.11 versus 12.62±43.24 mm^2; $P<0.0001$). Many patients with LDL-C <1.8 mm had plaque progression (47.5%), and change in LDL-C was not correlated with plaque progression/regression. Increasing age and serum creatinine contributed to resistant atherosclerosis.

Conclusions—Many patients have Resistant Atherosclerosis, failing to achieve regression of atherosclerosis despite low levels of LDL-C. Instead of relying on LDL-C, measuring plaque burden may be a more useful way of assessing individual response to therapy, particularly in resistant atherosclerosis. **(*Stroke*. 2017;48:1624-1629. DOI: 10.1161/STROKEAHA.117.017392.)**

Key Words: arteries ■ atherosclerosis ■ blood pressure ■ creatinine ■ risk factors

In the past, consensus guidelines often focused on target levels of low-density lipoprotein cholesterol (LDL-C). For patients at high risk of cardiovascular disease, a target LDL-C <1.8 mmol/L (≈70 mg/dL) has been a common recommendation.[1]

The GLAGOV study (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound)[2] recently reported that lower levels of LDL-C were associated with greater regression of coronary plaque. Evolocumab or placebo was given in addition to statin therapy. Mean levels of LDL-C were 1.21 mmol/L with evolocumab versus 2.45 mmol/L with placebo, and plaque regression occurred in 64.3% of those on evolocumab versus 47.3% of those on placebo. A linear relationship between achieved LDL-C and regression was observed. Normalized total atheroma volume decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab ($P<0.001$). It is notable that even with mean LDL-C of 1.21 mmol/L, 45.7% of patients receiving evolocumab did not achieve plaque regression.

In 2002, our group reported[3] that carotid plaque burden, measured as total plaque area (TPA), was a strong predictor of cardiovascular risk. That finding was validated in the Tromsø study[4,5] and in the High Risk Plaque Study.[6] We also found that despite treatment according to consensus guidelines, more than half of our patients had plaque progression during the first year of follow-up, and those with progression had twice the risk of patients with stable plaque or regression.[3]

The recognition that treatment according to guidelines was failing half of our patients led us to a new approach to prevention, treating arteries instead of treating risk factors,[7] implemented in our clinic in 2003. The goal of therapy was to achieve regression of plaque, or at least stop progression of plaque, rather than to simply achieve guideline-based targets for risk factors, such as a blood pressure <140/90 mm Hg and an LDL-C <1.8 mmol/L. In 2010, we reported that among high-risk patients with asymptomatic carotid stenosis, treating arteries was associated with a reduction of the 2-year risk of stroke or myocardial infarction by >80%.[8] Efforts are under

Received February 6, 2017; final revision received April 4, 2017; accepted April 10, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.017392/-/DC1.

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way to implement a randomized controlled trial of usual care versus treating arteries.

Over the years, J.D.S. has observed that some patients required very low levels of LDL-C to achieve regression or stop progression. In this study, we explored the relationship between achieved LDL-C and change in LDL-C and progression/regression of TPA.

For reasons discussed below, we hypothesized that (1) consensus target levels of LDL-C <1.8 mmol/L would not reliably predict progression or regression of atherosclerosis; (2) there would be interindividual variability of achieved LDL-C levels among patients who achieved plaque regression; (3) there may be sex differences in the relation of LDL-C to plaque changes; and (4) that atherosclerosis may be more resistant to lowering of LDL-C with increasing age and with increasing serum creatinine.

Methods

The study is a retrospective analysis of a prospective clinic database, comparing patients assessed before and after 2003.

Data Sources

This study was conducted at the Stroke Prevention and Atherosclerosis Research Center of the Robarts Research Institute, London, Ontario, Canada. The study was approved by the Western University Health Science Research Ethics Board.

Study Population and Eligibility Criteria

Patients in the database were referred to J.D.S. for prevention of cardiovascular events. Before 1995, they were referred to the Hypertension Clinic or the Stroke Prevention Clinic at Victoria Hospital; after 1995, to the Stroke Prevention Clinic, Urgent TIA Clinic, or the Premature Atherosclerosis Clinic at University Hospital, London, Canada. Routine measurement of carotid plaque area for monitoring of therapy began at the Stroke Prevention and Atherosclerosis Research Center in 1996. A previous history of stroke, myocardial infarction, or transient ischemic attack was present in 23.7% of patients. Patients included in the study had measurements of LDL-C levels and carotid plaque at least twice, approximately a year apart. Follow-up measurements of plaque, performed to monitor success of therapy, were usually done at approximately annual intervals. We excluded those with a change in TPA per year >200 mm^2 because in our experience of >40 000 plaque measurements, greater increases in TPA would be likely to be because of occlusion, with an artifactual increase in plaque area because of inclusion of the entire branch as plaque area, and greater decreases in TPA would be because of surgical removal of plaque at the time of endarterectomy or obscuration of plaque measurement by a stent.

Lipid-Lowering Therapy

Before 2003, attempts were made to reduce LDL-C to <1.8 using diet and statins, with addition of fibrates or niacin in patients with high triglycerides and low high-density lipoprotein. After 2003, when we began to implement treating arteries, ezetimibe was commonly added in patients with plaque progression (regardless of the LDL-C).

Measurement of Serum Lipids and Carotid Plaque Burden

Fasting plasma lipids were mostly measured at local commercial laboratories, and, in some cases, plasma lipids were measured at the University Hospital Biochemistry Laboratory at the time of a clinic visit, by routine methods. As described previously,[3] carotid atherosclerosis burden was measured as TPA using a high-resolution duplex ultrasound scanner. (Details are in the online-only Data Supplement.) Figure 1 shows the tracing of a plaque.

Change in TPA per year was divided into 3 categories: regression, stable, and progression, defined as an change in TPA of 5 mm^2 per year, the median change in TPA in a previous publication from this study population,[3] in which plaque progression was shown to double the 5-year risk of stroke, myocardial infarction, or death.

Statistical Analyses

Patient characteristics were compared between those referred before and after 2003 and between those who achieved consensus target LDL-C <1.8 mmol/L and those who did not, using a 2-sample *t* test (continuous variables) or χ^2 (categorical variables). To assess the effect of achieving LDL-C <1.8 on plaque outcome, we used linear regression adjusting for confounders, including age, sex, pack-years of smoking, systolic blood pressure, high-density lipoprotein cholesterol, and diabetes mellitus. To further explore the effect of LDL-C at follow-up and LDL-C change from baseline on the change in plaque burden, we stratified patients based on quartiles of LDL-C at follow-up and quartiles of LDL-C change. We then compared the change in TPA per year as a continuous dependent variable by quartiles using 1-way ANOVA with Bonferroni correction.

Effects of age and serum creatinine on resistance of plaque to lowering of LDL-C <1.8 mmol/L were analyzed graphically.

Data were analyzed using IBM SPSS Statistics v. 23 (IBM Inc) and Stata SE v. 13 (Stata Corp). A 2-tailed *P* value <0.05 was considered statistically significant. Data were expressed as percentages (%) for categorical variables, mean±SD and median and interquartile range for normally and non-normally distributed continuous variables, respectively. For variables that did not meet assumptions for parametric analysis, the equivalent nonparametric test was performed. The results of ordinal logistic regression were presented as

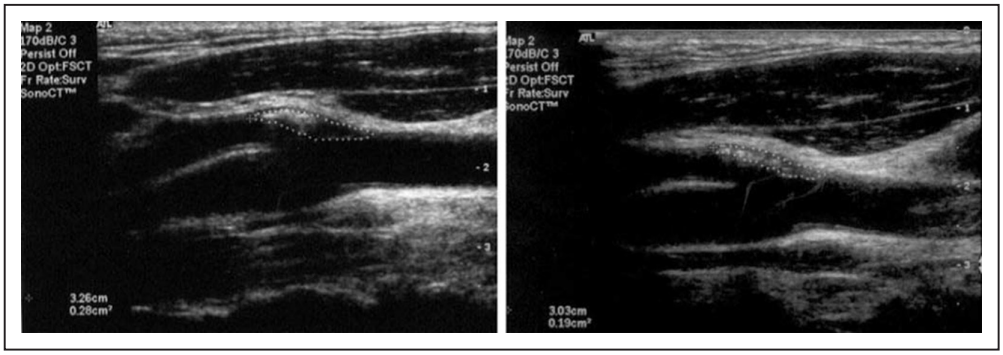

Figure 1. Change in carotid plaque area and composition over months. Plaque regression and change in composition is much faster than most would expect. **A**, Soft plaque at the origin of the left external carotid in a 64-y-old man using ezetimibe alone because of myalgias and cramps with statins. His plaque had progressed from 20 mm^2 6 mo earlier to 28 mm^2 after stopping rosuvastatin. After adding back rosuvastatin 5 mg daily, the plaque area regressed to 0.19 mm^2 over 3.5 mo (**B**). The plaque had also become denser, with regression of the soft plaque and more calcification. Reprinted from Spence and Hackam.[7]

the likelihood of being in a higher plaque category (ie, a more severe plaque outcome).

Results

The clinic database included 8539 patients. Of those patients, 4512 with complete data for analyses were included in the study; 2025 (44.9%) had their baseline plaque measurement before December 31, 2003 and 2487 (55.1%) after 2003. Table 1 compares baseline characteristics of the patients assessed after versus before 2003. A previous history of stroke, transient ischemic attack, or myocardial infarction was present in 23.7% of the patients.

During follow-up (median, 454 days and 386 days for lipid measurements and ultrasound assessments of carotid plaque, respectively), there were 1518 (33.6%) who achieved LDL-C <1.8 mmol/L and 2994 (66.4%) who did not; their baseline characteristics are described in Table I in the online-only Data Supplement. Table II in the online-only Data Supplement shows characteristics of patients included and excluded from the study.

Plaque Progression and Regression After 2003 Versus Earlier

Baseline TPA was significantly higher after 2003 (129.56±134.32 versus 113.33±121.52 mm^2; P<0.0001), and plaque progression was significantly less after 2003 (2.94±37.11 versus 12.62±43.24 mm^2; P<0.0001). After 2003, more patients achieved a target LDL-C <1.8 (43.1% versus 22%; P<0.0001), more had plaque regression (33% versus 25%; P<0.0001), and fewer had progression (39.3% versus 47.9%). Nevertheless, there were many patients with LDL-C <1.8 mmol/L who had plaque progression (44.7%), and the distribution of LDL-C among patients with progression versus regression of plaque was not different (mean LDL-C, 2.04±0.98 versus 2.03±0.96; P=0.80).

Table 1. Patient Characteristics by Era of Referral

Characteristics	After 2003 (n=2487)	Earlier (n=2025)	*P* Value
Age, y	63.59±13.41	60.95±12.65	<0.0001
Female, n (%)	1174 (47.20)	982 (48.5)	<0.02
Diabetic, n (%)	416 (16.7)	212 (10.5)	<0.0001
Pack-years of smoking	16.24±19.60	14.94±19.44	0.04
BMI, kg/m^2	27.61±5.0	27.48±6.7	0.52
Systolic BP, mm Hg	143.65±21.21	147.89±21.40	<0.0001
Diastolic BP, mm Hg	82.11±2.69	83.75±12.45	<0.0001
Plaque status, n (%)			
Regression	795 (32.0)	506 (25)	
Stable	714 (28.7)	550 (27.2)	<0.0001
Progression	978 (39.3)	969 (47.9)	
Baseline LDL-C, mmol/L	2.70±1.10	3.0±1.0	<0.0001
Follow-up LDL-C, mmol/L	2.15±1.0	2.52±0.93	<0.001

Mean±SD and n (%) are presented. Continuous variables were assessed by ANOVA and categorical variables by χ^2. BMI indicates body mass index; BP, blood pressure; and LDL-C, low-density lipoprotein cholesterol.

Target LDL-C Levels and Plaque Outcome

Neither LDL-C at follow-up nor change in LDL-C from baseline to follow-up was correlated with percent change in TPA from baseline to follow-up. There were fewer patients achieving LDL-C <1.8 mmol/L in all categories of plaque change; among patients achieving plaque regression, more patients had LDL-C >1.8 mmol/L than below that level. Although patients referred after 2003 had a higher baseline plaque burden, and on average less progression of plaque, the percentage of those with LDL-C <1.8 mmol/L who had progression of plaque was greater after 2003. While controlling for confounders, ordinal logistic regression analysis showed no association between target LDL-C levels and plaque outcome (Table III in the online-only Data Supplement).

LDL-C at Follow-Up and Plaque Regression

Mean change in plaque area±SD was 6.85±41.76 mm^2/y; the distribution of change in plaque area was normal (Figure 2). Among those with regression, 53% of patients had an LDL-C >2 mmol/L, and regression was common even among patients with LDL-C >3 mmol/L (19.5% of patients). Mean±SD LDL-C among patients with regression was 2.24±0.97 mmol/L.

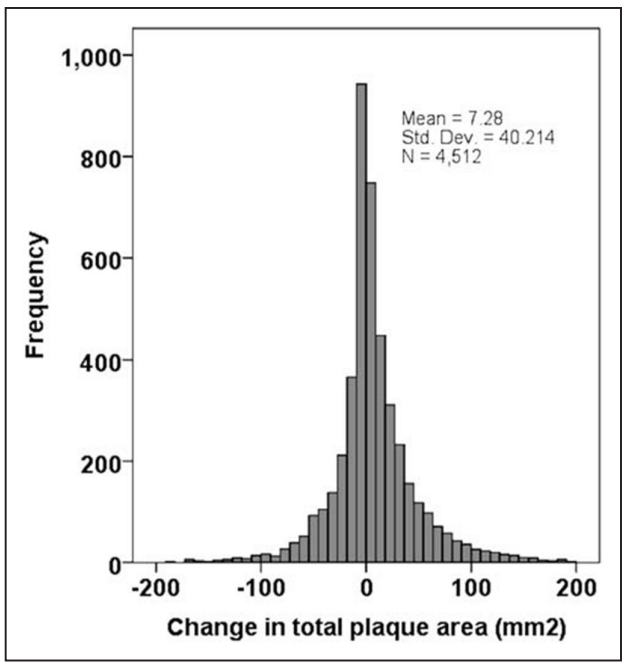

Figure 2. Distribution of change in total plaque area. Most patients had only a small change in plaque area; very large increases may have been related to intraplaque hemorrhage or plaque rupture with thrombosis and occlusion (the entire area of occluded segments is counted as plaque); large decreases may have been because of endarterectomy or stenting. (Cases with a change >200 mm^2 were excluded to limit those problems; a sensitivity analysis incases with plaque change <100 mm^2 did not give different results).

Sex Differences

In ordinal logistic regression, there was a significant interaction between female sex and LDL-C at follow-up on plaque outcome (odds ratio, 0.87; 95% confidence interval, 0.77–0.98; P=0.019; Table IV in the online-only Data Supplement). Women had a decreased likelihood of being in a more severe plaque category for every 1 mmol/L increase in LDL-C levels at follow-up, whereas men had an increased likelihood (odds ratio, 1.10; 95% confidence interval, 1.01–1.21; P=0.036; Tables V and VI in the online-only Data Supplement).

Effect of LDL-C on Baseline TPA and Effect of Change in LDL-C on Plaque Progression

In linear regression, before adding high-density lipoprotein cholesterol to the model, baseline LDL did not predict plaque burden or progression. After adding high-density lipoprotein cholesterol, the adjusted R^2 (proportion of variance explained by the variables entered) for baseline plaque area was 0.437; baseline LDL-C was then a significant predictor of baseline plaque burden, but had a lower β than age, sex, pack-years of smoking, or systolic blood pressure (Table VII in the online-only Data Supplement). The adjusted R^2 for change in plaque area was only 0.009; baseline LDL-C weakly predicted plaque change, but the change in LDL-C between baseline and follow-up was not a significant predictor of plaque progression/regression (Table VIII in the online-only Data Supplement). Table IX in the online-only Data Supplement shows ordinal logistic regression of the impact of risk factors on the odds of having plaque progression.

Effect of Age and Serum Creatinine on Resistance to Therapy

As shown in Figure 3, among patients with LDL-C <1.8 mmol/L, there was greater resistance to therapy by quartile of age and by quartile of serum creatinine. However, as shown in Table 2, treating arteries, implemented in 2003, somewhat mitigated the effects of age and renal impairment.

Discussion

Just as failure to lower blood pressure below target levels with usual therapy is called resistant hypertension, failure to achieve plaque regression with low levels of LDL might be called resistant atherosclerosis. We found that a substantial proportion of high-risk patients had plaque progression despite low levels of LDL-C.

We speculate that the reason patients referred after 2003 had higher plaque burden was that because of the new approach taken in our clinic (treating arteries), referral patterns in the community changed such that patients with more severe atherosclerosis were referred to the clinic, whereas patients with only risk factors such as hypertension were increasingly referred to other clinics. Although the subjects were referred to a highly specialized vascular prevention clinic, these observations may apply generally to treatment of atherosclerosis.

The reasons for hypothesizing that sex and age would increase resistance were that our previous studies indicated that plaque area increases steeply with age, and women have a lower mean plaque burden at any age than men.[9,10] Reasons for hypothesizing that impaired renal function may increase atherosclerosis resistance are discussed below.

An important newly recognized environmental effect (although of the internal environment) that has recently come to the fore is the interaction between diet, renal function, and the intestinal microbiome.[11] Homocysteine, thiocyanate, and asymmetrical dimethylarginine, as well as metabolic products of the intestinal microbiome, including trimethylamine n-oxide, p-cresyl sulfate, indoxyl sulfate, and indole acetic acid, all accumulate in renal failure[12] and may contribute to the very high cardiovascular risk of patients with renal failure.[12,13] Because the elderly have impaired renal function (above age 80; the mean estimated glomerular filtration rate among patients attending a vascular prevention clinic was <60),[12] such factors may contribute to resistant atherosclerosis with increasing age. In the subgroup of patients with data on total homocysteine, baseline total homocysteine (n=1319) was a significant predictor of baseline plaque burden in linear regression (Table X in the online-only Data Supplement), and change in total homocysteine from baseline to follow-up (n=576) was not excluded from the model for plaque change, P=0.086 (Table XI in the online-only Data Supplement).

In this population of high-risk vascular prevention clinic patients referred between 1996 and 2016, we found that

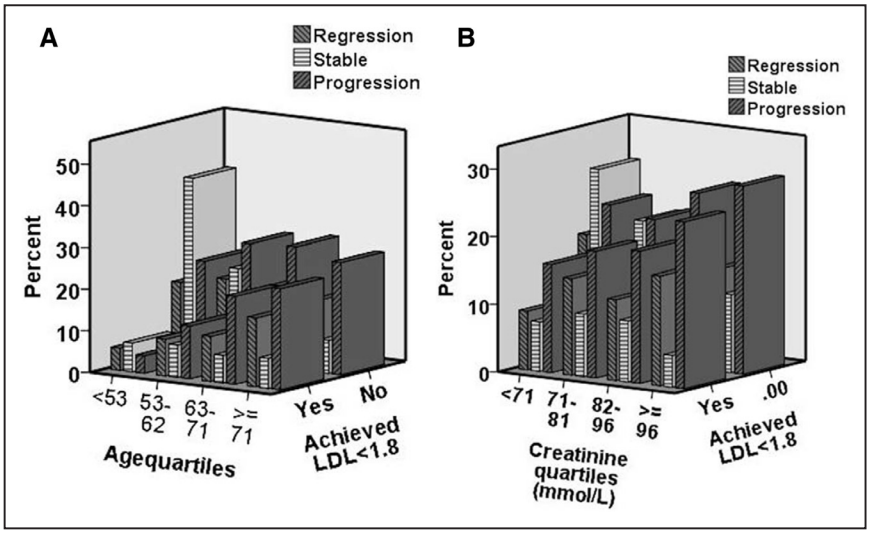

Figure 3. Effect of age and renal impairment on atherosclerosis resistance. Progression of plaque despite low-density lipoprotein cholesterol (LDL-C) <1.8 mmol/L (Resistant Atherosclerosis) was present in a higher percentage of patients by quartile of age (χ^2; P<0.0001; **A**) and by quartile of serum creatinine (χ^2; P=0.007; **B**).

Table 2. Percent of Patients With Plaque Regression/ Progression Before and After 2003, When Treating Arteries Was Implemented, by Quartiles of Age and Serum Creatinine

	Regression	Stable	Progression	*P* Value
Age quartile, y				
Earlier				0.002
<53	28.3%	40.0%	31.7%	
53–62	23.0%	24.0%	53.0%	
63–71	19.0%	19.7%	61.3%	
≥71	25.7%	16.7%	57.6%	
After 2003				<0.0001
<53	34.8%	42.9%	22.3%	
53–62	33.3%	27.5%	39.2%	
63–71	32.4%	15.7%	51.9%	
≥71	37.3%	14.4%	44.7%	
Creatinine quartile, mmol/L				
Earlier				0.017
≤71	30.2%	22.5%	47.3%	
71–81	35.8%	20.2%	43.9%	
82–96	32%	23.6%	44.4%	
≥96	38%	9.4%	52.5%	
After 2003				0.39
≤71	13.8%	24.1%	62.1%	
71–81	21.4%	32.1%	46.4%	
82–96	19%	16.7%	64.3%	
≥96	26.9%	13.5%	58.9%	

33.6% of patients achieved the target LDL-C level of <1.8 mmol/L, similar to previous reports in patients with coronary artery disease.[14]

We further observed that there was a wide range of LDL-C levels needed to achieve regression. Indeed, some patients with plaque progression had remarkably low levels: 10 had a follow-up LDL-C <0.5 mmol/L (19 mg/dL) and 6.2% had LDL-C <1 mmol/L (38 mg/dL). Among patients with LDL-C <1, 49.8% had plaque progression. (They were being treated more intensively because they had plaque progression, but despite the more intensive treatment, they remained resistant.)

Among patients with plaque regression, less than half had LDL-C <1.8, and as shown in Figure I in the online-only Data Supplement, LDL-C >1.8 mmol/L was common in patients with plaque regression. This finding is consistent with that of our previous study in 2010,[7] in which the mean of LDL-C levels in each year between 1998 and 2007 in the regression group was also higher than 1.8 mmol/L; it ranged from 1.87 to 2.63 mmol/L. This suggests that achieving target thresholds of LDL-C may not necessarily lead to the goals of atherosclerotic plaque reduction or prevention of cardiovascular events. The reason for these surprising findings is probably that, after 2003, as discussed above, therapy was intensified in patients with plaque progression, whereas in patients with plaque regression, therapy was continued unchanged.[7]

Perhaps because the baseline LDL-C levels were treated levels, change in LDL-C between baseline and follow-up did not account for a significant proportion of the change in TPA. The R^2 of only 0.437 for baseline plaque area indicates that besides LDL-C, there are other factors accounting for approximately half of atherosclerosis, such as genetic factors, total homocysteine, asymmetrical dimethylarginine, thiocyanate, impaired renal function,[12] diet, interaction of the intestinal microbiome and diet,[11] exercise, alcohol intake, air pollution, second-hand smoke, and other unrecognized influences. The observed relationship between serum creatinine and resistance to treatment supports hypotheses relating to uremic toxins. The observed relationship to age may be in part dependent on renal impairment,[12] but other factors, such as aging of the mitochondria with impaired ability to resist oxidative stress, and telomere shortening, might partially explain the apparent increased resistance to treatment with increasing age.

However, because the other factors are unknown, the principal option available at present to achieve regression (or stop progression) is to treat the LDL-C (the thing we can treat) to lower levels.

Even though the causal role of LDL-C in the pathogenesis of atherosclerosis is well established, our findings do not support relying on LDL-C levels, which is the usual approach, as a good determinant of how well a patient is responding to therapy. Khera and Kathiserin[15] reviewed recently the concept that whereas LDL cholesterol may dominate atherosclerosis in a subset of the population, a quantitative blend of causal genetic and environmental factors underlies the majority of coronary artery disease cases. Several reports have suggested that imaging of atherosclerosis may improve risk stratification and prediction. As reported in 2010,[8] doing so may have the potential to improve markedly on current approaches to vascular prevention, with residual risks of 60% to 70%.[7]

We also found a significant interaction between sex, LDL-C, and plaque progression; women seemed to have a lower likelihood of plaque progression at a given level of LDL-C, as reported previously for coronary artery disease.[16] It has been suggested that different combinations of risk factors may contribute to differences in atherosclerosis between the sexes.[17]

Limitations of the study included that the analysis was retrospective, and that there were missing data; the sample was a convenience sample from an electronic medical record. Also the duration of follow-up may be a limitation, and patients who did not have complete assessments may have had different rates of plaque progression or regression from those with complete data. Although a year may seem a short time to assess progression/regression, Figure 1 shows that plaque composition changes, and regression occurs within 3 months; this was also shown in our study of the effect of atorvastatin on regression of 3-dimensional plaque volume.[18]

The study also has several strengths, including the ability to adjust for many important variables, and the measurement of carotid plaque burden, with the advantages discussed above. The relatively large sample size compared with other studies of plaque regression supports that the findings may be robust.

As we found that in some patients, very low levels of LDL-C were required to achieve regression of plaque, and regression of plaque is associated with lower cardiovascular

risk,[3,19] our findings may have implications for intensifying therapy among patients with plaque progression, including adding ezetimibe[20] and inhibitors of plasma proprotein convertase subtilisin/kexin type 9 (PCSK9)[21] to statins. This may be particularly important in patients intolerant of statins.

An important clinical implication of our findings is that measuring LDL-C is not adequate to assess the patient's response to therapy. Many patients with a low LDL-C have high plaque burden and plaque progression and are at very high risk; to identify them, it is necessary to measure the plaque burden.

Conclusions

Achieving low levels of LDL-C did not result in consistent effects on carotid plaque burden. Many patients who attained low levels of LDL-C had Resistant Atherosclerosis, with plaque progression, and many patients who did not attain the target LDL-C level had plaque regression. Neither LDL-C at follow-up nor change in LDL-C level from baseline to follow-up was significantly associated with change in plaque burden. Measuring plaque burden may improve assessment of response to antiatherosclerotic therapy, with the objective of reducing the residual risk that remains with usual therapy based on target levels of LDL-C.

Acknowledgments

We thank the following individuals for their statistical advice and assistance in cleaning up data: Mostafa Shokoohi, Daniel Prawira, and Peter Lee. We also thank, Neil Klar, Solo's supervisor for this project conducted toward her degree in Statistics and Epidemiology. We also thank Dr Frank Veith, who assigned to Dr Spence the following lecture topic for the 2016 Veith Symposium: How low does low-density lipoprotein have to go to achieve regression of atherosclerosis? Considering this question led to the concept of Resistant Atherosclerosis.

Sources of Funding

Donations to the Stroke Prevention and Atherosclerosis Research Centre were mainly from patients.

Disclosures

In the past 2 years, Dr Spence has received modest lecture honoraria/consulting fees from Bayer and Bristol Myers Squibb, and his laboratory has performed contract research with Pfizer, Bayer, Bristol Myers Squibb, Acasti Pharma, POM Wonderful, CVRx, AGA, and Gore. He is an officer and shareholder of Vascularis Inc, which to date has generated no revenue. The other author reports no conflicts.

References

1. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis*. 2011;217:3–46. doi: 10.1016/j.recesp.2011.09.014.
2. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV Randomized Clinical Trial. *JAMA*. 2016;316:2373–2384. doi: 10.1001/jama.2016.16951.
3. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. *Stroke*. 2002;33:2916–2922.
4. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Løchen ML, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø Study. *Stroke*. 2007;38:2873–2880. doi: 10.1161/STROKEAHA.107.487264.
5. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study. *Stroke*. 2011;42:972–978. doi: 10.1161/STROKEAHA.110.589754.
6. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. *J Am Coll Cardiol*. 2015;65:1065–1074. doi: 10.1016/j.jacc.2015.01.017.
7. Spence JD, Hackam DG. Treating arteries instead of risk factors: a paradigm change in management of atherosclerosis. *Stroke*. 2010;41:1193–1199. doi: 10.1161/STROKEAHA.110.577973.
8. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186. doi: 10.1001/archneurol.2009.289.
9. Spence JD. Determinants of carotid plaque burden. *Atherosclerosis*. 2016;255:122–123. doi: 10.1016/j.atherosclerosis.2016.10.045.
10. Iemolo F, Martiniuk A, Steinman DA, Spence JD. Sex differences in carotid plaque and stenosis. *Stroke*. 2004;35:477–481. doi: 10.1161/01.STR.0000110981.96204.64.
11. Spence JD. Effects of the intestinal microbiome on constituents of red meat and egg yolks: a new window opens on nutrition and cardiovascular disease. *Can J Cardiol*. 2014;30:150–151. doi: 10.1016/j.cjca.2013.11.019.
12. Spence JD, Urquhart BL, Bang H. Effect of renal impairment on atherosclerosis: only partially mediated by homocysteine. *Nephrol Dial Transplant*. 2016;31:937–944. doi: 10.1093/ndt/gfv380.
13. Tang WH, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res*. 2015;116:448–455. doi: 10.1161/CIRCRESAHA.116.305360.
14. Karalis DG, Subramanya RD, Hessen SE, Liu L, Victor MF. Achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol*. 2011;107:886–890. doi: 10.1016/j.amjcard.2010.11.006.
15. Khera AV, Kathiresan S. Is coronary atherosclerosis one disease or many? setting realistic expectations for precision medicine. *Circulation*. 2017;135:1005–1007. doi: 10.1161/CIRCULATIONAHA.116.026479.
16. Puri R, Nissen SE, Nicholls SJ. Statin-induced coronary artery disease regression rates differ in men and women. *Curr Opin Lipidol*. 2015;26:276–281. doi: 10.1097/MOL.0000000000000195.
17. Puri R, Nissen SE, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, et al. Sex-related differences of coronary atherosclerosis regression following maximally intensive statin therapy: insights from SATURN. *JACC Cardiovasc Imaging*. 2014;7:1013–1022. doi: 10.1016/j.jcmg.2014.04.019.
18. Ainsworth CD, Blake CC, Tamayo A, Beletsky V, Fenster A, Spence JD. 3D ultrasound measurement of change in carotid plaque volume: a tool for rapid evaluation of new therapies. *Stroke*. 2005;36:1904–1909. doi: 10.1161/01.STR.0000178543.19433.20.
19. Wannarong T, Parraga G, Buchanan D, Fenster A, House AA, Hackam DG, et al. Progression of carotid plaque volume predicts cardiovascular events. *Stroke*. 2013;44:1859–1865. doi: 10.1161/STROKEAHA.113.001461.
20. Bogiatzi C, Spence JD. Ezetimibe and regression of carotid atherosclerosis: importance of measuring plaque burden. *Stroke*. 2012;43:1153–1155. doi: 10.1161/STROKEAHA.111.640789.
21. Xie W, Liu J, Wang W, Wang M, Qi Y, Zhao F, et al. Association between plasma PCSK9 levels and 10-year progression of carotid atherosclerosis beyond LDL-C: a cohort study. *Int J Cardiol*. 2016;215:293–298. doi: 10.1016/j.ijcard.2016.04.103.