3D carotid ultrasound in patients with a negative exercise stress test: A practical risk stratification tool

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BACKGROUND: Exercise stress tests (EST) are frequently used to evaluate chest pain. While a negative EST is reassuring, further risk stratification for coronary artery disease (CAD) may be warranted. Three-dimensional (3D) carotid ultrasound is a non-invasive tool which can be used to identify subclinical atherosclerotic disease. We investigated the prevalence and extent of subclinical atherosclerotic lesions using 3D carotid ultrasound in patients with chest pain and a negative EST, with the aim of understanding the changes in atherosclerotic lesions with statin therapy at 1 year.

METHODS: 80 patients were prospectively enrolled and all received additional vascular assessment with 3D carotid ultrasound. If subclinical atherosclerosis was identified, high-dose statin therapy was recommended. A 3D carotid ultrasound scan was repeated at 12 months.

RESULTS: Of our cohort, 37 patients (46.3%) had carotid plaque. At baseline, median plaque volume (IQR) (left carotid, right carotid, or both) was 32.0 mm^3 (17-123). At 12-month follow-up (n=22), median plaque volume was 116.0 mm^3 (46-279) (p=0.004). Of these, only 40.9% were on high-dose statin therapy. Total plaque volume remained stable in subjects on statins (46.5 mm^3 [25-97.5] at baseline; 50 mm^3 [29-131] at 12 months, p=0.596) while it increased in those without statins (20 mm^3 [10-31] at baseline; 117 mm^3 [78-279] at 12 months, p=0.003).

CONCLUSION: In patients with chest pain and a negative EST, roughly one-half have subclinical atherosclerosis as detected with 3D carotid ultrasound. Plaque progression commonly occurs at 12 months, but is less likely with statin therapy. A further randomized study is required to confirm our findings.

Key Words: *Exercise stress test; 3D carotid ultrasound; Atherosclerosis*

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the commonest cause of morbidity and mortality worldwide. Within the western world, cardiovascular disease accounts for roughly 30% of all-cause deaths, of which one-half are due to ischemic heart disease. Coronary atherosclerotic disease spans an entire spectrum of latent asymptomatic development to the progression of fibro-fatty plaque vulnerable to rupture [1]. Moreover, more than one-half of acute coronary syndrome (ACS) events result from coronary lesions that are subclinical (i.e., not flow-limiting) [2,3]. Multiple scoring systems have been developed to help predict the risk of coronary events earlier with variable success [4-9]. More recently, other non-invasive markers of atherosclerosis have been utilized to assess cardiovascular risk [10].

We investigated the prevalence and extent of subclinical atherosclerotic lesions using three-dimensional (3D) carotid ultrasound in patients with chest pain and a negative exercise stress test (EST). In those with subclinical atherosclerosis, primary prevention strategies were encouraged and changes in atherosclerotic lesions were assessed at 1 year.

RESEARCH METHODOLOGY

Study population

Eighty healthy adult subjects without a history of coronary or peripheral arterial disease and negative exercise stress tests (EST) were prospectively enrolled. Included subjects were those referred to Chest Pain Program Clinic at the Mazankowski Alberta Heart Institute, University of Alberta Hospital with a negative EST; age 40-60 years for males, age 50-60 years for females, and agreed to participate following informed consent. Excluded subjects were those who had a history of obstructive coronary artery disease (CAD) (previous myocardial infarction, coronary revascularization procedure, angina pectoris with documented ischemia, coronary angiogram documenting obstructive CAD); history of cerebrovascular disease (previous stroke, transient ischemic attack, or carotid revascularization procedure); history of peripheral arterial disease (claudication with abnormal ankle-brachial indices or previous revascularization procedure); unstable life-threatening or severe medical conditions; refused to be involved in the study or were unable to give valid consent. The study protocol was approved by the University of Alberta Research Ethics Board. Written informed consent was obtained for all subjects.

Study protocol

After enrollment, all subjects underwent an additional vascular assessment with 3D carotid ultrasound to detect subclinical atherosclerosis. If subclinical atherosclerosis was identified, medical treatment with high-dose statin therapy and physical activity/risk factor modification (referral to a cardiac rehabilitation program) was encouraged. Given the controversial benefits of aspirin for primary prevention, this was not mandated. A letter was sent to the primary care physician informing participation in the study. The primary care physician was encouraged to promote adherence to statins and risk factor modification. A 3D carotid ultrasound scan was repeated at 12-month follow-up.

3D carotid ultrasound

Technique: Carotid scans were performed using a standard ultrasound system (Philips IU22; Philips Medical Systems) equipped with high-frequency VL 13-5 transducer. Patients were placed in a supine position with slight hyperextension and rotation of the neck in the direction opposite to the probe. The proximal, mid, and distal common carotid artery (CCA), bifurcation (BIF) of the CCA (segment between flow divider and increase in diameter of CCA), and proximal portion of the internal and external carotid arteries were systematically interrogated in long-axis and short-axis views. The mechanical single sweep 3D imaging method was used to acquire 3D volumetric data of carotid arteries. The transducer automatically moves the ultrasound beam through a pre-defined area, obtaining data that is then reconstructed into multiplanar and volume views.

Measurements

Carotid plaque was defined as a focal structure that protrudes into the arterial lumen of the carotid artery at least 0.5 mm, or a presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall, or as a focal region with carotid intima-media thickness (CIMT)

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greater than 1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary [11].

The 3D ultrasound images of plaque volumes were measured by manual planimetry method using the Q-Lab software. Plaque segmentation was performed manually by tracing the outline of the plaque contour on each slice. The vascular sonographer and or the reading cardiologist sliced the 3D image with an Interslice Distance (ISD) of 1.0 mm from one end of the plaque to the other (along with the vessel axis in the scan direction) and traced the individual plaque boundaries of the image plane by using a mouse-driven cross-hair cursor. As contours were manually outlined, the software (Q-Lab) calculates the contour area automatically. The areas measured in each slice were summed and multiplied by the ISD to calculate total plaque volume. After measuring the plaque, the experienced research reading physician reviewed the 3D image to ensure that the set of measured plaque boundaries match the plaque volume. Mismatches were adjusted by dragging the boundaries to fit the correct contour.

CIMT measurements were taken at the far wall of CCA and BIF at end-diastole using a semiautomated edge detection algorithm (QLAB version; Philips Medical Systems). A region of interest, 1cm in length, was placed parallel to the vessel wall, allowing the software to detect the luminal-intimal and medial-adventitial interfaces, enabling determination of the CIMT. When carotid plaque was verified in a segment, care was taken not to include the plaque in the CIMT measurement. The 3D carotid ultrasound was reported as: (1) normal CIMT, no plaque; (2) abnormal CIMT, no plaque; (3) abnormal CIMT, plaque present, plaque volume, degree of stenosis, degree of obstruction, and; (4) equivocal, poor image quality, non-diagnostic.

Total plaque volume was calculated as sum of left carotid artery (LCA) plaque volume if plaque was seen at left side, right carotid artery (RCA) plaque volume if plaque was seen at right side, and combined LCA plaque volume and RCA plaque volume if plaque was seen at both sides. Total maximum area of vessel reduction was calculated as sum of LCA maximum area of vessel reduction if plaque was seen at left side, RCA maximum area of vessel reduction if plaque was seen at right side, and combined LCA and RCA maximum area of vessel reduction if plaque was seen at both sides.

Data processing

The 3D carotid ultrasound measurements were performed using the Q-Lab software which is available on the IU22 scanner and the results were transferred into an Excel spreadsheet with random numbers for the patient (research coordinator). The datasets were stored in the clinical cardiovascular database (Xcelera), which guaranteed safe storage of the clinical data. All images, measurements and interpretations made for each subject were performed in a blinded fashion (unaware of current therapy) by an experienced research reading physician and confirmed by a research cardiologist (also blinded to ongoing treatment). Corrections, modifications, and reporting of incidental findings were provided to the subject's primary care physician.

STATISTICAL ANALYSIS

Participant characteristics were summarized according to the absence or presence of plaque in the carotid arteries. Participants identified with plaque at baseline were followed at 12 months. Categorical variables were reported as counts and percentages, whereas continuous variables were presented as medians with 25th and 75th percentiles. Differences between groups were tested using the χ^2 test or Fisher's exact test when cell number is less than 5 for categorical variables and using t-test or Wilcoxon rank-sum test when normality assumption is violated for continuous variables.

Mixed model for repeated measurement was used to obtain interaction between time and whether a participant is using cholesterol lowering medication by considering the participant as a random effect.

All statistical tests were two-sided with a p-value <0.05 considered as statistically significant. Statistical analyses were performed using SAS (version 9.4; Cary, NC). No correction was made for multiple comparisons.

RESULTS

In our cohort, 92 consecutive subjects with chest pain and a negative EST were reviewed. Of these, 80 subjects fulfilled the criteria and consented to participate in the study. All patients received a baseline 3D carotid ultrasound, with 37 patients (46.3%) showing evidence of carotid plaque (Figure 1).

Subject characteristics

Baseline characteristics in subjects with and without carotid plaque are outlined in Table 1. Median age was 53 years (IQR: 50-58 years) and 47.5% were female with the majority being Caucasian. As expected, the majority of subjects presented with chest pain prompting an EST. The majority of subjects had an intermediate pre-test probability of CAD (Duke Treadmill Score). Plaque positive subjects more commonly had a history of dyslipidemia (Framingham Risk Score). None of these subjects were on lipid lowering therapy prior to enrollment.
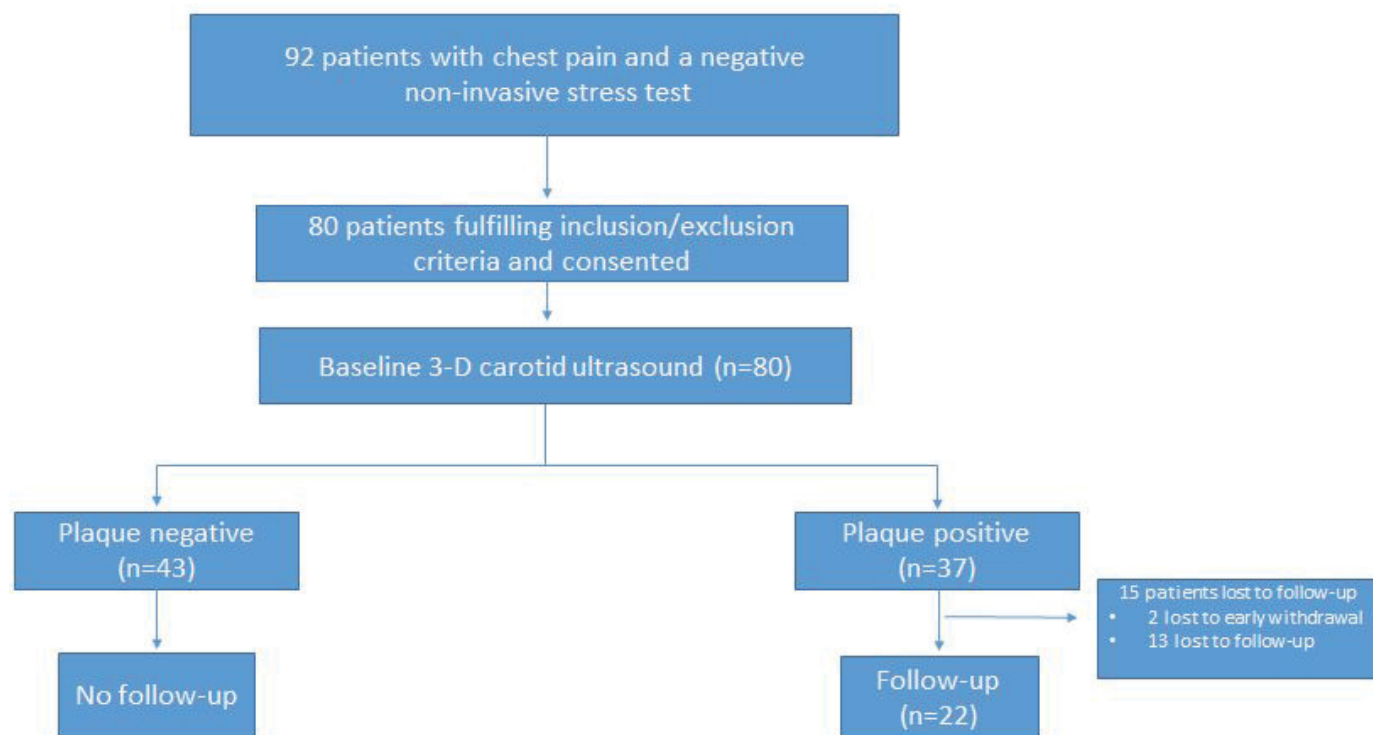

Figure 1) *Baseline 3D carotid ultrasound of patients.*

Baseline 3D carotid ultrasound

Carotid ultrasound characteristics for subjects with plaque are identified in Table 2. Median plaque volume was 32.0 mm³ (IQR: 17.0-123.0 mm³) with the majority (97.3%) being smooth in morphology. Of these plaques, 51.4% were homogeneous isoechoic and immobile. For those subjects without evidence of 3D plaque, CIMT was performed. Figures 2A and 2B shows an example of baseline 3D carotid ultrasound measurement.

12-month 3D carotid ultrasound in plaque positive subjects

Of the 37 subjects with carotid plaque identified, 22 agreed to receive a follow-up 3D carotid ultrasound at 12 months (59.5%) (Table 3). The total plaque volume significantly increased at 12 months (p=0.004) with progression in carotid stenosis (p<0.001). No difference in plaque morphology or mobility was noted at 12 months. Follow-up plaque progression can be seen in Figures 2C and 2D.

Primary prevention in plaque positive subjects at 12 months

Of the 37 plaque positive subjects, 21 participants (56.8%) agreed to be referred to cardiac rehabilitation and 12 subjects (33.3%) completed the program. As seen in Table 1, 40.9% were on statin therapy (all were suggested to start high-dose statin therapy following identification of carotid plaque). Antiplatelet therapy was used in 31.8%, angiotensin converting enzyme inhibitors in 22.7%, and beta blockers in 13.6% of subjects in follow-up.

TABLE 1

Baseline characteristics of participants, stratified by plaque.

Variables	Overall (n=80)	Plaque Negative (n=43)	Plaque Positive (n=37)	p-value
Demographics, n (%)				
Age, yrs	53 (50- 58)	55 (49- 58)	52 (50- 56)	0.442
Female	38 (47.5%)	20 (46.5%)	18 (48.6%)	0.849
Race				
Caucasian	68 (85.0%)	35 (81.4%)	33 (89.2%)	
Black or African Americans	2 (2.5%)	1 (2.3%)	1 (2.7%)	
Hispanic or Latino	3 (3.8%)	2 (4.7%)	1 (2.7%)	0.904
Asian	6 (7.5%)	4 (9.3%)	2 (5.4%)	
Other	1 (1.3%)	1 (2.3%)	0 (0.0%)	
Medical History, n (%)				
Chest pain	74 (92.5%)	41 (95.3%)	33 (89.2%)	0.407
Shortness of breath	7 (8.8%)	3 (7.0%)	4 (10.8%)	0.698
Palpitation	7 (8.8%)	3 (7.0%)	4 (10.8%)	0.698
Diabetes Type 1	2 (2.5%)	2 (4.7%)	0 (0.0%)	0.497
Diabetes Type 2	12 (15.0%)	5 (11.6%)	7 (18.9%)	0.363
Dyslipidemia	44 (55.0%)	16 (37.2%)	28 (75.7%)	<.001
Hypertension	35 (43.8%)	16 (37.2%)	19 (51.4%)	0.204
Current smoker	14 (17.5%)	5 (11.6%)	9 (24.3%)	0.136
Family history of CAD	41 (51.3%)	21 (48.8%)	20 (54.1%)	0.214
Sedentary lifestyle	45 (56.3%)	23 (53.5%)	22 (59.5%)	0.591
Obesity	39 (48.8%)	22 (51.2%)	17 (45.9%)	0.642
Overweight	27 (33.8%)	14 (32.6%)	13 (35.1%)	0.808
Pre-test probability for CAD, (Duke Treadmill Score)				
Low	2 (2.5%)	2 (4.7%)	0 (0.0%)	
Low-intermediate	2 (2.5%)	2 (4.7%)	0 (0.0%)	0.495
Intermediate	74 (92.5%)	38 (88.4%)	36 (97.3%)	
High	2 (2.5%)	1 (2.3%)	1 (2.7%)	
Physical Exam				
Systolic blood pressure, mmHg	120 (110- 131)	118 (110- 137)	120 (113- 128)	0.585
Diastolic blood pressure, mmHg	72 (70- 80)	72 (70- 80)	71 (70- 79)	0.344
BMI kg/m²	30.1 (26.7- 35.0)	30.5 (26.4- 35.0)	29.4 (27.0- 35.1)	0.901
Waist circumference, cm	101 (94- 114)	103 (94- 114)	99 (94- 112)	0.94
Lipid Lab				
Total cholesterol, mmol/L	5.1 (4.4- 5.7)	5.1 (4.4- 5.7)	5.2 (4.3- 5.8)	0.76
HDL cholesterol, mmol/L	1.3 (1.1- 1.6)	1.3 (1.1- 1.7)	1.3 (1.1- 1.6)	0.827
LDL cholesterol, mmol/L	2.9 (2.4- 3.5)	2.7 (2.6- 3.7)	3.0 (2.1- 3.3)	0.377
Triglycerides, mmol/L	1.5 (1.0- 2.1)	1.4 (0.9- 2.4)	1.6 (1.2- 1.9)	0.89

Continuous variables presented as: Median (Q1- Q3); Categorical variables presented as n (%). Paired t-test for continuous variable or Wilcoxon Signed-Rank Test when normality distribution is violated. Chi-square test or Fisher's exact test for categorical variables. CAD: Coronary Artery Disease; BMI: Body Mass Index; HDL: High-Density Lipoproteins; LDL: Low-Density Lipoproteins.

TABLE 2

Baseline 3D carotid ultrasound imaging.

Variables	Plaque Negative (n=43)	Plaque Positive (n=37)
Plaque Characteristics for Plaque Seen (n=37)		
Total plaque volume, mm^3	-	32.0 (17.0- 123.0)
Maximum area of vessel reduction, %	-	10.0 (10.0- 31.0)
Plaque surface morphology		
Smooth	-	36 (97.3%)
Irregular (defect< 2 mm)	-	1 (2.7%)
Plaque internal properties		
Homogeneous hyperechoic	-	4 (10.8%)
Homogeneous isoechoic	-	19 (51.4%)
Homogeneous hypoechoic	-	3 (8.1%)
Heterogeneous hyperechoic	-	6 (16.2%)
Heterogeneous isoechoic	-	3 (8.1%)
Heterogeneous hypoechoic	-	2 (5.4%)
Plaque mobility		
Mobile	-	1 (2.7%)
Not mobile	-	36 (97.3%)
CIMT for Plaque Not Seen (n=43)		
LCA Maximum carotid intimae media thickness, mm	0.9 (0.8- 1.0)	-
RCA Maximum carotid intimae media thickness, mm	0.9 (0.8- 1.0)	-

Continuous variables presented as: Median (Q1- Q3); Categorical variables presented as n (%). CIMT: Carotid Intima-Media Thickness; LCA: Left Carotid Artery; RCA: Right Carotid Artery.
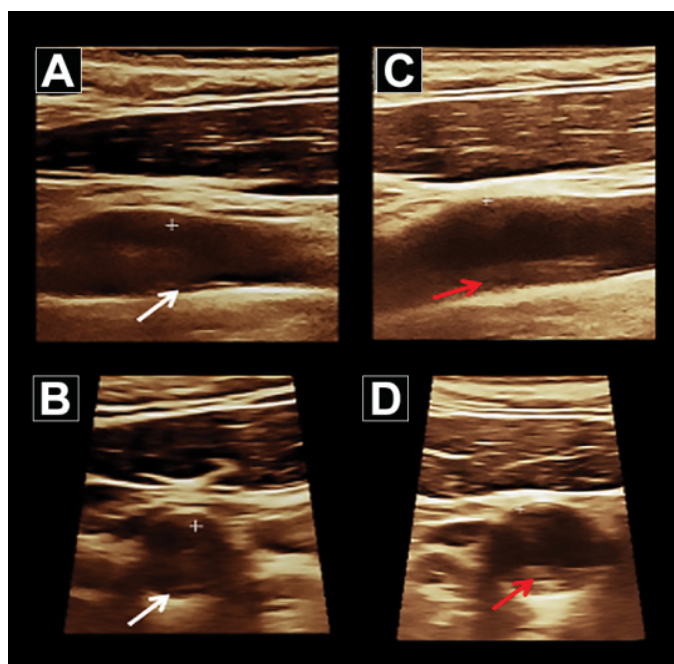

Figure 2) *3D carotid ultrasound measurement and plaque progression of patients.*

12-month 3D carotid ultrasound in plaque positive subjects stratified by use of cholesterol lowering medication

As seen in Figure 3, total plaque volume remained stable in subjects on statins (46.5 mm^3 [25-97.5 mm^3] at baseline; 50 mm^3 [29-131 mm^3] at 12 months, p=0.596), while it increased in those without statin therapy (20 mm^3 [10-31 mm^3] at baseline; 117 mm^3 [78-279 mm^3] at 12 months, p=0.003).

DISCUSSION

In a healthy middle-aged cohort of subjects without a history of ASCVD and no evidence of ischemia (negative EST), almost one-half have evidence of subclinical atherosclerosis as detected by 3D carotid ultrasound. Moreover, plaque progression commonly occurs but appears to be attenuated by statins - as observed with 3D carotid ultrasound at 1 year. Use of 3D carotid ultrasound as an additional tool for risk stratification could be considered although further investigation is warranted.

While current vascular disease prediction models are helpful in identifying high-risk individuals where primary prevention would be warranted, there appears to be a false sense of reassurance of those deemed to be intermediate (or low) risk [12,13]. In fact, a high percentage of ASCVD events still occur in this patient population [14]. Further, clinical risk models do not consider

TABLE 3

Baseline and follow-up 3D carotid ultrasound imaging in those with plaque.

Variables	Baseline 3D (n=22)	12-month 3D (n=22)	p-value
Total plaque volume, (mm³)	25.0 (13.1- 48.0)	116.0 (46.0- 279.0)	0.004
Maximum area of vessel reduction, (%)	10.0 (10.0- 30.0)	50.0 (20.0- 100.0)	<.001
Plaque surface morphology			
Smooth	22 (100.0%)	22 (100.0%)	-
Irregular (defect< 2 mm)	0 (0.0%)	0 (0.0%)	-
Plaque internal properties			
Homogeneous hyperechoic	3 (13.6%)	0 (0.0%)	
Homogeneous isoechoic	10 (45.5%)	15 (68.2%)	
Homogeneous hypoechoic	2 (9.1%)	1 (4.5%)	0.308
Heterogeneous hyperechoic	4 (18.2%)	2 (9.1%)	
Heterogeneous isoechoic	1 (4.5%)	3 (13.6%)	
Heterogeneous hypoechoic	2 (9.1%)	1 (4.5%)	
Plaque mobility			
Mobile	0 (0.0%)	0 (0.0%)	-
Not Mobile	22 (100.0%)	22 (100.0%)	-

Continuous variables presented as: Median (Q1- Q3); Categorical variables presented as n (%). Paired t-test for continuous variable or Wilcoxon Signed-Rank Test when normality distribution is violated. Chi-square test or Fisher's exact test for categorical variables.
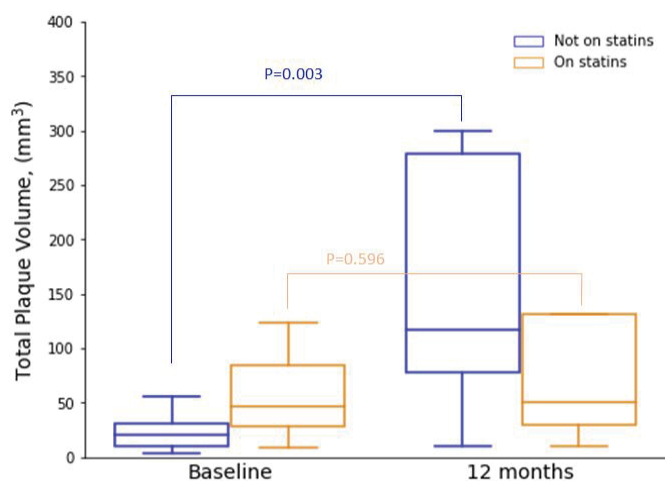

Figure 3) *Total plaque volume stability in the patients.*

lifetime risk (usually limited to 10-year risk), yet a younger population (like our study cohort) may incrementally benefit from aggressive risk factor reduction. Importantly, derivation of risk scores are based on population-based studies which do not account for ethnicity [15] or socioeconomic status [16] – now considered powerful predictors of ASCVD risk [16]. In a multi-ethnic community-based cohort, the majority of cardiovascular risk assessment scores actually overestimate ASCVD events [17]. Hence, additional risk stratification metrics are required to help mitigate outcomes in a primary prevention population.

In our cohort, a majority had an intermediate pre-test probability of CAD, yet more than one-half did not have subclinical atherosclerosis (as measured by 3D carotid ultrasound). Conversely, a minority of low-risk patients demonstrated evidence of subclinical atherosclerosis. Hence, reclassification measures may be required to help identify appropriate patients for primary prevention [18,19]. In the Multi-Ethnic Study of Atherosclerosis study evaluating additional markers of risk, a coronary calcium score of 0 was the strongest modulator of ASCVD risk and had the greatest impact on reclassification [10]. Acknowledging the importance of this risk stratification test, coronary calcium scores are not universally readily available and subject patients to the detriments of radiation exposure (albeit lower in dose with current technology). Carotid ultrasound is readily available, safe and easy to perform with no risks of radiation exposure. In addition, quantification of carotid plaque (larger plaque burden) has been associated with incremental

risk of vascular death, myocardial infarction or stroke at 5 years [20]. Our results suggest this simple and inexpensive test can be used in clinical practice and does help in the reclassification of subjects at risk.

CIMT has been proposed as a potential tool for additional risk stratification as a surrogate measurement. However, in a systematic review and meta-analysis of a one-time CIMT measurement of asymptomatic subjects, CIMT did not predict myocardial infarction or stroke (median of 10.8 years of follow-up) [21]. Similarly, in studies with serial CIMT measurements where yearly progression was measured, no association was demonstrated between CIMT progression and cardiovascular risk [22,23]. In fact, compared to CIMT, carotid plaque area is more strongly associated with traditional risk factors and more commonly predicts myocardial infarction [24,25]. As such, CIMT has not been widely adopted as a reclassification tool.

In contrast, assessment of carotid arterial plaque offers additional risk stratification given the identification of actual plaque morphology – a more meaningful reflection of atherosclerosis. Moreover, correlation exists with carotid atherosclerosis and disease burden in the coronary vascular bed [26]. Quantification of carotid plaque has now emerged as an important tool for ASCVD risk stratification, enhanced with 3D quantification [27]. With a single sweep full-vessel protocol, 3D datasets are acquired and can be serially tracked with repeated measurements that can be performed offline [28]. Additionally, the volume of all plaque lesions within the carotid can be captured and the total plaque volume measured – as has been demonstrated in our study. We have also established the feasibility of a simple test within our cohort of subjects where reclassification of cardiovascular risk becomes important in an asymptomatic population. The 2016 European Society of Cardiology guidelines on cardiovascular disease prevention now include plaque detection as a tool for refining cardiovascular risk following risk score assessment (Class IIB, LOE B) – analogous to a similar recommendation for coronary calcium scoring (Class IIB, LOE B) [29]. The 2019 American Heart Association/American College of Cardiology guidelines for primary prevention of cardiovascular disease have been silent on the use of coronary plaque imaging [30], however the 2020 American Society of Echocardiography have endorsed the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and assessment of cardiovascular risk [31]. In this context, it is interesting to note the recent findings of a prospective study showing the prognostic value of identifying subclinical carotid atherosclerosis in patients with a negative exercise echocardiogram [32].

In those subjects with established ASCVD, it is interesting to note the increase in total plaque volume and carotid stenosis at 12 months (without a change in plaque morphology) in those receiving a follow-up 3D carotid ultrasound. In a prospective observational study of 715 asymptomatic carotid disease subjects with serial carotid ultrasounds performed biannually, (mean follow-up of 3.2 years), progression of carotid disease was associated with a higher

risk of cerebrovascular events or death [33]. Data from the Asymptomatic Carotid Stenosis and Risk of Stroke study group found 20% of subjects had progression of carotid plaque and twice the risk of ipsilateral stroke [34]. The low use of cardiac rehabilitation and primary prevention recommendations despite evidence of ASCVD was disappointing, prompting further efforts in this vulnerable population.

Still, in subjects with confirmed ASCVD on 3D carotid ultrasound who decided to use statins (as per our recommendations), carotid plaques were stable in volume at 12 months. Similar findings were demonstrated in a small randomized study of high-dose statin therapy on 3D carotid plaque volume at three months [35]. Recognizing this in a small cohort of patients in the current study, it is reassuring to see the benefits of cholesterol lowering therapy in these asymptomatic carotid disease subjects. Moreover, it has been demonstrated that statin therapy in higher-risk subjects reduces coronary events and ischemic strokes long term [36].

Our results are with limitations. This is a prospective observational cohort subject to unmeasured confounders. Roughly one-half of subjects with carotid plaque at baseline had a follow-up carotid ultrasound at 12 months. While strongly encouraged, only a minority of subjects attended (and completed) cardiac rehabilitation. Similarly, a minority of subjects with plaque were on statin medication (although this did allow us to assess the treatment effect on carotid plaque volume). Finally, this was a small cohort of patients; however, to our knowledge, this is the only study assessing 3D carotid ultrasound in an asymptomatic population with a normal EST – a population that is frequently encountered for chest pain assessment.

While functional non-invasive stress tests are important for the assessment of coronary disease, many with negative tests may have evidence of ASCVD, as seen in our study. Patients are often reassured and not provided any additional tests for risk stratification. Direct assessments for atherosclerosis, such as carotid plaque imaging, may be helpful for primary prevention. Those without plaque can be reassured, whereas those with carotid plaque would benefit from primary preventative strategies. While our results are provocative, we propose a further randomized study assessing the efficacy of carotid plaque assessment in subjects with negative ESTs.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the design of the study; acquisition, analysis and interpretation of the data. All authors contributed to drafting the manuscript and provided important intellectual content.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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