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"ΤΡΙΣΔΙΑΣΤΑΤΗ ΥΠΕΡΗΧΟΓΡΑΦΙΚΗ ΑΠΕΙΚΟΝΙΣΗ ΤΟΥ ΚΑΡΩΤΙΔΙΚΟΥ ΔΙΧΑΣΜΟΥ"

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ΤΡΙΑΝΤΑΦΥΛΛΟΥ Γ. ΓΙΑΝΝΑΚΟΠΟΥΛΟΥ

Αγγειοχειρουργού

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διακρατικού Μεταπτυχιακού Διπλώματος Ειδίκευσης

«Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»

Λάρισα, 2016

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ΕΥΧΑΡΙΣΤΙΕΣ

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Την οικογένειά μου που υποστηρίζει τις προσπάθειές μου

Τριαντάφυλλος Γ. Γιαννακόπουλος

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Περίληψη

Υπό το πρίσμα της διαρκούς βελτίωσης της αποτελεσματικότητας της βέλτιστης φαρμακευτικής αντιμετώπισης (BMT) στη μείωση του κινδύνου εγκεφαλικού επεισοδίου που σχετίζεται με την ασυμπτωματική καρωτιδική στένωση, οι πιο πρόσφατες κατευθυντήριες οδηγίες της American Heart Association αναφέρουν ότι η αποτελεσματικότητα της παρέμβασης σε σύγκριση με τη BMT για την ασυμπτωματική καρωτιδική στένωση δεν έχει εδραιωθεί ικανοποιητικά. Η ανίχνευση της ευάλωτης αθηρωματικής πλάκας είναι το «ιερό δισκοπότηρο» στην αναζήτηση των ασθενών που ωφελούνται περισσότερο από την παρέμβαση. Ο στόχος αυτής της συστηματικής ανασκόπησης της βιβλιογραφίας ήταν η σύνοψη των δημοσιευμένων στοιχείων για τις κλινικές εφαρμογές της τρισδιάστατης υπερηχογραφίας του καρωτιδικού διχασμού (3DUS) με απώτερο σκοπό την ανίχνευση του δυναμικού αυτής της εξελισσόμενης απεικονιστικής μεθόδου στην αναγνώριση του ευάλωτου καρωτιδικού αθηρώματος. Τα δημοσιευμένα στοιχεία δείχνουν ότι η τρισδιάστατη ογκομετρία της ασυμπτωματικής καρωτιδικής πλάκας αποτελεί μια αξιόπιστη, επαναλήψιμη και αναπαραγώγιμη, μη-επεμβατική μέθοδο της παρακολούθησης της βραχυπρόθεσμης προόδου ή υποστροφής της καρωτιδικής αθηρωμάτωσης σαν απάντηση στην εντατικοποίηση της BMT όταν τίθεται η ένδειξη παρέμβασης με βάση το βαθμό στένωσης. Ειδικά σχεδιασμένες τυχαιοποιημένες μελέτες απαιτούνται για να ελεγχθεί αν η μεταβολή του όγκου της αθηρωματικής πλάκας όπως μετράται από τη 3DUS μπορεί να βελτιώσει την ανίχνευση των ασυμπτωματικών ασθενών που ωφελούνται από την καρωτιδική παρέμβαση.

Abstract

In light of the improved efficacy of best medical therapy (BMT) in reducing stroke risk associated with asymptomatic carotid disease the most recent American Heart Association guidelines stated that the effectiveness of intervention for asymptomatic carotid disease compared to BMT is not well established. Detecting the vulnerability of the carotid atherosclerotic plaque is the "holy grail" to the quest of identifying the asymptomatic patients that benefit from intervention. The aim of this systematic review of the literature was to summarize published evidence on the clinically relevant applications of three dimensional ultrasound (3DUS) in order to detect the potential of this evolving imaging field in spotting the vulnerable carotid plaque. Published evidence show that 3DUS plaque volumetry is a reliable, repeatable and reproducible, non-invasive technique for monitoring the short-term progression or regression of asymptomatic carotid atherosclerosis in response to best medical treatment enhancement when a stenosis indication for intervention is set. Specially designed randomized trials are in order to test whether 3DUS plaque volume change can improve identification of patients that benefit the most from asymptomatic carotid intervention.

Contents

Introduction

Stroke is a leading cause of death in developed countries. Although the number of deaths from stroke is decreasing, it remains a public health problem in the United States, with billions of U.S. dollars in direct cost and indirect cost of stroke.[1] Carotid artery stenosis represents an important risk factor for ischemic stroke, which accounts for nearly 90 percent of all strokes among U.S. men and women. It is increasingly prevalent from the fifth decade of life onward[2] and patients with vascular disease and multiple risk factors (e.g., diabetes, hypertension, hyperlipidemia, and smoking) have a higher probability of having asymptomatic carotid stenosis. Since carotid artery atherosclerosis can proceed silently and affect approximately 7 percent of women and over 12 percent of men, older than 70 years of age[3], the first manifestation can be a debilitating or fatal stroke.

The importance of intervention for symptomatic carotid disease has been established[4,5] and has been firmly incorporated in guidelines documents[6] regardless of the carotid endarterectomy (CEA) versus carotid artery stenting (CAS) debate.[7] On the other hand, asymptomatic carotid stenosis patients have been reported by natural history studies[8,9] to be at an increased risk of ipsilateral carotid territory ischemic events and this was supported by the 5-year risk of stroke (including perioperative stroke/death) in patients randomized to CEA or best medical therapy (BMT) in the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST).[10–12] Consequently, the rationale behind asymptomatic carotid intervention incorporation in consensus documents has been the outcome of the "battle" between the stroke risk assumed by the stenosis grade versus peri-interventional risk.

In light of the decreasing risk of stroke for asymptomatic carotid disease patients [13,14] and the effectiveness of evolving BMT[15] it has become clear that even if CEA/CAS periprocedural risk was reduced to 0% the majority (93%) of interventions on ACAS/ACST randomized patients would still be

unnecessary in 5 and 10 years respectively.[16] Finally, the 2014 American Heart Association (AHA) Guidelines recommended that "1. Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted (Class I; Level of Evidence C). 2. In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated (Class I; Level of Evidence C). 3. It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, myocardial infarction (MI), and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established (Class IIa; Level of Evidence A). 4. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50% (Class IIa; Level of Evidence C). 5. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (Class IIb; Level of Evidence B). 6. In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established (Class IIb; Level of Evidence B)".[17]

Identification of the vulnerable carotid plaque seems to be the key to asymptomatic carotid intervention in terms of decision to intervene and type of intervention. Preoperative plaque vulnerability and subsequent perioperative embolic potential[18] depend on a panel[19] of clinical, imaging, technical and biological markers. The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS)[20] study is in the process of investigating the effectiveness of panels of markers to detect the patients that benefit the most from intervention after reaching the % stenosis threshold. They recently reported that the clinical value

of screening for stenosis grade progression simply for selecting patients for carotid procedures is limited because of the low frequency of progression and its relatively low associated stroke rate.[21]

Imaging of the carotid plaque in vivo has the leading role amidst the panel of vulnerability markers. Various imaging phenotypes have been found to predict long-term carotid events and thus reflect plaque vulnerability (Intima Media Thickness – IMT[22], Gray Scale Median - GSM[23], Juxtaluminal Black Areas - JBA[24], Discrete White Areas – DWA[20], Intraplaque Hemorrhage – IPH – on Magnetic Resonance Imaging – MRI[25–27], fluoro-2-deoxyglucose – FDG - positron emission tomography/computed tomography - PET/CT uptake)[28]. However, these phenotypes' value as tools for evaluating short-term plaque progression is limited[22,29]. Besides being a vulnerability marker, short-term plaque progression can also serve as a means of testing the effect of BMT optimization directly on the plaque.

Aim / Objectives

Even though atherosclerotic plaque is a three dimensional (3D) pathophysiological entity, all of the aforementioned Ultrasound (U/S) imaging phenotypes are confined to studying two-dimensional (2D) plaque slices. Three dimensional ultrasound (3DUS) has been technically around since 1983 (phantom apparatus)[30] and was first reported to be used in vivo in 1991 by Hennerici et al.[31] Subsequent technological advances and computer power exponential growth have made it increasingly available for research and clinical applications in carotid bifurcation. It's volumetric and surface reconstruction potential seem promising in unmasking previously unavailable features of the vulnerable carotid plaque by moving from 2 to 3 dimensional imaging. According their 3D Registration type the main 3DUS systems' realizations are (a) *Freehand*, where a linear U/S probe is translated manually along or across the carotid to produce a series of images; it can be tracked (movement is registered in space by a mechanical arm, an electromagnetic sensor[32] or other similar application) or untracked (spatial

registration is unavailable since probe movement is dependent on operator), (b) *Mechanical assemblies,* where the U/S probe is translated by a linear[33]/rotational[34] stage/motor of given speed and distance/angle in order to provide spatial registration and (c) *3D-Real-Time*, where the 3rd dimension is provided in real-time by an array of perpendicular probes (2D-array[35]) or relevant technology (UltraFast[36] probes).

The aim of this study was to summarize published evidence on the clinically relevant application of 3DUS in order to detect the potential of this evolving imaging field in elucidating the elusive vulnerable carotid plaque. By qualitative analysis of caveats, superiority aspects, limitations and research gaps of the technique the author will try to point out whether 3DUS can become the "holy grail" of asymptomatic carotid intervention.

Methods

The PubMed Database was queried with the search term "carotid[All Fields] AND ("3-d"[All Fields] OR "3d"[All Fields] OR "three dimensional"[All Fields] OR "3-dimensional"[All Fields] OR "three-dimensional"[All Fields] OR "three dimension"[All Fields] OR "three-dimension"[All Fields] OR "three dimensions"[All Fields]) AND ("ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonics"[All Fields])" in order to detect publications relevant to 3D carotid ultrasonography. Publications in English language referring to clinical applications of 3D carotid ultrasonography and publications reporting 3D plaque volume measurement repeatability and/or reproducibility were retrieved as full text while review publications were excluded. Retrieved publications' reference lists and abstracts were screened and additional relevant full text papers were also retrieved.

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Results

The query returned 512 records that were entered into the Abstract Screening flow chart in order to exclude irrelevant publications to the scope of this study **(Figure 1)**. In total, 191 records were deemed as relevant to 3D carotid ultrasonography and their count per publication year was cross-tabulated by type of relevance **(Figure 2)** and by 3D imaging phenotype studied **(Figure 3)**. It is clear that there is a growing publication interest during the past 15 years that focuses on imaging details research and specifically on volumetric measurements. Clinical applications of 3D ultrasonography also demonstrated an increase but to a lesser extent. Notably, computational fluid dynamics (CFD) applications based solely on 3DUS acquired volumes are commencing to be reported in the literature with results comparable with CFD based on Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) acquired volumes.[37–41]

a. Clinical Relevance Studies

Studies that investigated clinically relevant parameters of 3DUS and were able to be retrieved as full text were 54 and were used for qualitative analysis. They were subsequently grouped by the plaque parameter they reported on as follows:

(1) **Volume** of the atherosclerotic plaque was the focus of interest of 32 studies, 18 of which investigated *risk prediction* potential of plaque volume **(Table 1)**. Identification of atherosclerosis related genes was linked to plaque volume.[42,43] Progression of different expressions of plaque volume (Total Plaque Volume – TPV, Vessel Wall Volume – VWV with or without the plaque) and plaque burden (Carotid Plaque Burden – CPB) were found to be predicted by diastolic blood pressure[44], diabetes mellitus[44–47], the male gender[48] and absence of hormone replacement therapy in women[49]. In many cases[46–48] IMT was deemed inferior compared to plaque volume with regards to risk prediction. Plaque volume phenotypes also had a predictive value on both the absence[50] and severity of coronary

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artery disease (CAD)[51,52] and this effect was not detected for either IMT or maximum plaque thickness.[50] Furthermore, cardiovascular events rates were predicted by plaque volume[53,54] and burden[55] progression and not by neither IMT nor Total Plaque Area (TPA). Finally, ex-smokers with non-clinical atherosclerosis were found to be carriers of larger (VWVs and TPVs) plaques compared to non-smokers.[56,57]

The remaining 14 studies employed plaque volume measurements to test *treatment effects* (**Table 2**). The concept of hypercholesterolemia effect on atherosclerosis was intuitively shown by Hennerici et al.[31] in the first report of in-vivo TPV measurement by 3DUS. The authors demonstrated that TPV was reduced by extracorporeal plasmapheresis of hypercholesterolemic patients. After that, statin treatment effect was demonstrated in 6 more studies where authors proved that both TPV[58,59] and VWV[60–62] were reduced after statin treatment. Additionally, systolic blood pressure (SBP),[63] olmesatrtan[64] and cilostazol[65] were associated with plaque volume reduction while VWV rate of change was shown to be affected by Vitamin D supplement in patients with nephropathy.[66]

(2) **Stenosis degree** measurement or categorization using 3DUS versus various different modalities was employed in 11 studies with multiple comparisons in many occasions (**Table 3**). *DSA* was used as the reference method in 5 studies where inter-method correlation (Spearman's *r*) ranged from 0.57[67] (p=0.01) to 0.82.[34] The correlation was better when the area (vs diameter) method was used[34] while it was noted that DSA underestimated medium grade (40-70%) stenoses.[68] In 5 studies the reference method was *2DUS* and the inter-method correlation (Spearman's *r*) ranged from 0.83 (p<0.001)[69] to 0.998[70]. The correlation was found to be even better when Peak Systolic Velocity (PSV) was used (vs PSV Ratio)[69] and when Power Doppler implementation was undertaken.[70] When MRA was used as a reference method an IntraClass Correlation Coefficient (ICC) value of 0.79 +/- 0.17 was reported for grading ICA stenosis.[71] Finally, Pfister et al.[72] have elegantly compared surgical evaluation of carotid stenosis with a variety of modalities and demonstrated that MRA achieved an r=0.94 followed by 3D B-flow with contrast medium enhancement with an r=0.93.

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(3) **Surface** features was the point of interest for 5 papers **(Table 4)** and the majority studied atherosclerotic plaque ulcers in terms of number and their change over time[73,74], ability of detection[75,76] and ulcer volume.[77] One publication reported that mobile plaque components were more readily identified by 3DUS compared to 2DUS.[76] The main finds of the two largest cohorts were that (A)[77] ulcer volume >5mm^3 and (B)[74] presence of >3 ulcers/plaque together with detection of emboli on Trans Cranial Doppler (TCD) predicted cardiovascular events and revascularization procedures.

(4) **Texture** of atherosclerotic plaques in three dimensions was analyzed in 7 studies **(Table 5)**. As a 3D GSM projection, Mean Gray Value (MGV) was calculated by Heliopoulos et al. and it was found to correlate with increased Vascular Endothelial Growth Factor (VEGF)[78] serum levels as well as with symptomaticity[79] of patients with carotid stenosis. Koyama et al.[80] demonstrated that echogenic plaque areas without acoustic shadow corresponded to histology of macrophage infiltration and thus inflammatory activity (vulnerability) while the use of Integrated Back Scattering (IBS) in 3D associated increased lipid and blood plaque content with early symptomatic plaques.[81] More recently, Awad et al.[62] and Engelen et al.[54] developed models that accurately predicted vascular events and plaque response to aggressive statin therapy by incorporating changes in TPV together with changes in textural characteristics.

b. Repeatability (IntraObserver Variability) and Reproducibility (InterObserver Variability) reporting Studies

Studies that reported repeatability and reproducibility of 3DUS for plaque volume measurements that were able to be retrieved as full text were 33 and were used for comparative analysis since evaluation statistics varied significantly **(Table 6)**. *Mechanical Linear (ML) assemblies along with Manual Segmentation* were used in more than half of the studies (n=17) and yielded an intraobserver variability that ranged from a coefficient of variance (COV)=3%[44] to COV=23.9%[82] and from

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ICC=0.91[47] to ICC=0.95[83] while interobserver variability varied from COV=4%[44] to COV=46.6%[82] and from ICC=0.82[83] to ICC=0.93[42,43,46]. *Mechanical Rotation (MR) transducers results in conjunction with Manual Segmentation* were reported in 6 studies. This combination gave an intraobserver variability that started from COV=3.1%[84] and reached COV=4%[85] and from ICC=0.91[86] up to ICC=0.987.[64] The respective interobserver variability reported was COV=6.4 +/- 4.1%[85] and ranged from ICC=0.87[86] to ICC=0.964.[84]

Real Time (RT) 3DUS was utilized in 6 more recent studies and Manual Segmentation was also used for identifying anatomic features of the atherosclerotic plaque. In this case the intraobserver variability was as high as ICC=0.94[52] to ICC=0.99[65,87] while interobserver ICC was reported to be 0.93.[52] As far as *registration* is concerned, Graebe et al.[86] compared ICCs for Untracked freehand (UFH) 3D Registration with those of an MR transducer and found that both intraobserver and interobserver variability were better for the MR system (0.91 vs 0.74 and 0.87 vs 0.6 respectively). Although semi-automated *segmentation* solutions were reported to significantly reduce the required time to complete the process, intraobserver variability was not improved.[48,88]

Finally, 28 out of 33 studies used the TPV *plaque phenotype to study volume measurement* technique and progression. However, since 2007 Egger et al.[82,83] introduced VWV (including plaque volume) and compared it with TPV reporting improved intraobserver (ICC=0.95 vs ICC=0.85) and interobserver (ICC=0.85 vs ICC=0.82) variability.

Discussion

Even though 3D carotid ultrasound has been around for the past 20 years and researchers are increasingly trying to prove that it can evolve carotid artery imaging, it is clear that its use has not been widely spread among clinicians. In order for two-dimensional carotid bifurcation images to be converted into reliable 3D information they have to be (A) Registered in space (3D Registration) and (B) Vessel,

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lumen and plaque anatomic boundaries have to be recognized and properly marked for each and every 2D image and then propagated into the 3rd dimension (Segmentation). The first researchers employed complicated and bulky linear stages[31] and relevant software to complete image synthesis while more and more advanced technolohy has offered Real-Time 3D systems with either Mechanically rotated transducers or 2D-Arrays. Despite modern realizations being more practical, the cost remains a major limitation in widespread penetration of carotid 3DUS and the majority of researchers still use mechanical assemblies. Overall cumbersome registration and segmentation sequences involved with carotid 3DUS have rendered it unattractive to clinicians.

This study demonstrates that plaque volume is the most valuable carotid atherosclerosis phenotype that 3DUS is offering to the clinician who is trying to prevent stroke and stabilize the atheromatous lesion. TPV dominates the literature and has been proven to be associated with atherosclerosis risk factors (arterial hypertension[31], diabetes[45], male gender[48], smoking[56]) and to be adequately potent in predicting CAD phenotypes.[50,52] More importantly, in contrast to IMT – a significant plaque phenotype used in large cross sectional studies for cardiovascular risk prediction – TPV change (regression or progression in 1 year) detection and measurement was recently found to be able to predict clinical cardiovascular events for the next 5 years.[53,54]

Furthermore, Ainsworth et al.[59] have proved that the regression effect of aggressive statin therapy on the volume of the atherosclerotic plaque as measured by TPV is so powerful that can be statistically detected even in small sample studies (20 patients) and in short time periods (3 months). A possibly important use of plaque volume measurements is in the clinical setting of monitoring an individual's carotid plaque response to therapy. In this case, the minimum volume change that can be confidently detected beyond measurement variability depends on the desired confidence level and the operator variability.[89] Landry et al.[90,91] have published evidence on the effect of plaque size on TPV intraobserver and interobserver variability and noted that the volumetric change that must be observed to establish with 95% confidence that a plaque has undergone change was ≈20% to 35% for plaques <100

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mm^3 and $\approx$10% to 20% for plaques >100 mm^3. Plaque volume measurement precision was unchanged for Inter Slide Distances (ISD) <3.0 mm, whereas plaque volume measurement variability increased with ISD. They demonstrated that both repeatability and reproducibility is increased for larger plaques making the method ideal for asymptomatic carotid disease fulfilling intervention criteria in terms of stenosis degree.[17] For smaller plaques, the variability can be kept relatively low by lowering ISD as reported by Landry et al.[56]

Variability has also been shown to decrease[82,83] by the use of VWV which is a measure that contains both the plaque and a three dimensional representation of the IMT. When texture features are added to the algorithm[62] along with surface characteristics like ulcer number[74] and volume[77], VWV can even more accurately detect plaque response to intervention (change) as well as predict cardiovascular events. Intuitively, the findings of ACSRS[20] on Discrete White Areas without acoustic shadow are in accordance with Koyama et al.[80] who related them with histology of macrophage plaque infiltration after 3DUS.

Real-time 3D systems are accompanied by excellent variability but are often hampered by increased costs while semi-automated segmentation realizations offer time saving but do not increase repeatability of reproducibility. Conceptually, a mechanical assembly kit that converts regular 2DUS systems into 3DUS realizations might be the solution to a more rapid and widespread adoption of 3DUS. Electrocardiogram (ECG) Gated 3DUS[71] was employed to minimize the effect of pulsation artefacts but it was not found to have significant effect for the study of atherosclerotic patients due to arterial rigidity. Carotid calcification has been shown to affect 3DUS due to acoustic shadowing but the use of multiple angle acquisitions (windows), contrast medium and b-Flow techniques can minimize this limitation.[72] Finally, although 3DUS value in stenosis[72] degree determination comes close to that of MRA when both compared to surgical evaluation, the method lacks the dynamic data of arch and cerebral circulation provided by DSA and MRA.

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Conclusion

In light of the improved efficacy of best medical therapy in reducing stroke risk associated with asymptomatic carotid disease the most recent AHA guidelines stated that the effectiveness of intervention for asymptomatic carotid disease compared to BMT is not well established. The present study has shown that 3DUS plaque volumetry is a repeatable and reproducible, non-invasive technique for monitoring the short-term progression or regression of asymptomatic carotid atherosclerosis in response to best medical treatment enhancement when a stenosis indication for intervention is set. Specially designed RCTs are in order to test whether 3DUS can improve identification of patients that benefit the most from asymptomatic carotid intervention.

Appendix A: Figures

Figure 1: Literature Review flowchart

PubMed Search

carotid[All Fields]
AND
("3-d"[All Fields] OR "3d"[All Fields] OR "three dimensional"[All
Fields] OR "3-dimensional"[All Fields] OR "three-dimensional"[All
Fields] OR "three dimension"[All Fields] OR "three-dimension"[All
Fields] OR "three dimensions"[All Fields])
AND
("ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR
"ultrasonics"[All Fields])

512 Records Retrieved

Screening → **31** Excluded due to Irrelevance

Abstract Review → **290** Excluded due to
- 40   2DUS - IMT
- 14   CFD
- 30   CTA – 3DCTA
- 67   MRA – 3D4DMRA
- 10   IVUS – 3DIVUS
- 16   3DTCD
- 7   DSA – 3DDSA
- 20   Animal
- 33   Other Anatomy
- 36   Case Report
- 8   Reviews - LTEs
- 9   Non English LNG

191 Records for Carotid 3DUS

Abstract Review

57 Clinical Relevance

107 Imaging Relevance

27 Review Papers

53 Full Text Retrieved

Abstract Review

33 Reporting Plaque Volume Variability

+1 Added from Reference List Review

54 Clinically Relevant Retrieved

33 Variability Measure Retrieved

3DUS=3D Ultrasonography, **2DUS**=2D Color Ultrasonography, **CFD**=Computational Fluid Dynamics, **CTA**=Computed Tomography Angiography, **3DCTA**=3D Computed Tomography Angiography, **MRA**=Magnetic Resonance Angiography, **3D4DMRA**= 3D/4D Magnetic Resonance Angiography, **IVUS**=Intra Vascular Ultrasound, **3DIVUS**=3D Intra Vascular Ultrasound, **3DTCD**=3D Trans Cranial Doppler, **DSA**=Digital Subtraction Angiography, **3DDSA**=Rotational Digital Subtraction Angiography, **LTE**=Letter to the Editor, **LNG**=Language
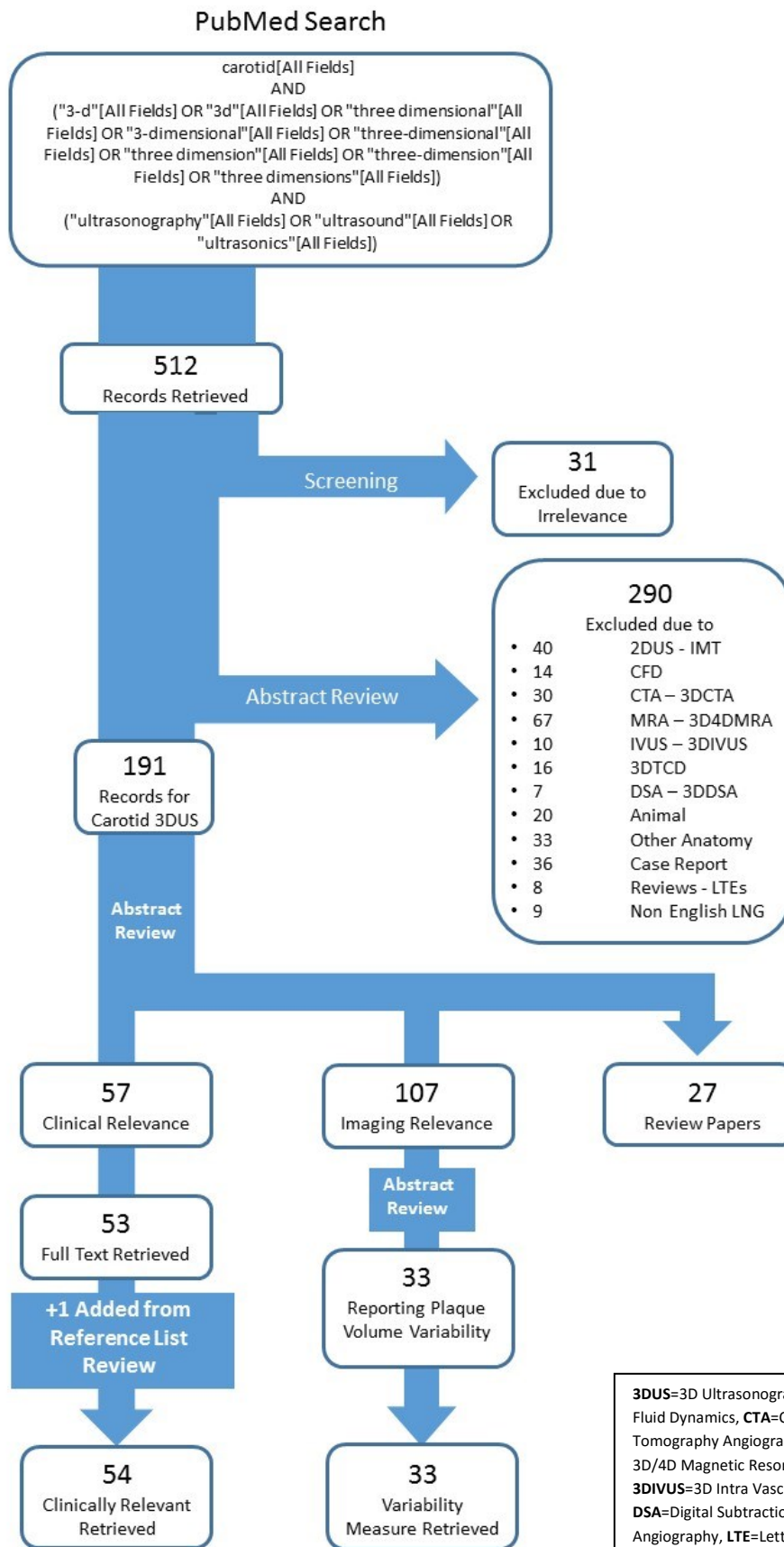
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Figure 2: Stack chart of studies and their count per publication year is shown by type of relevance to 3D ultrasonography
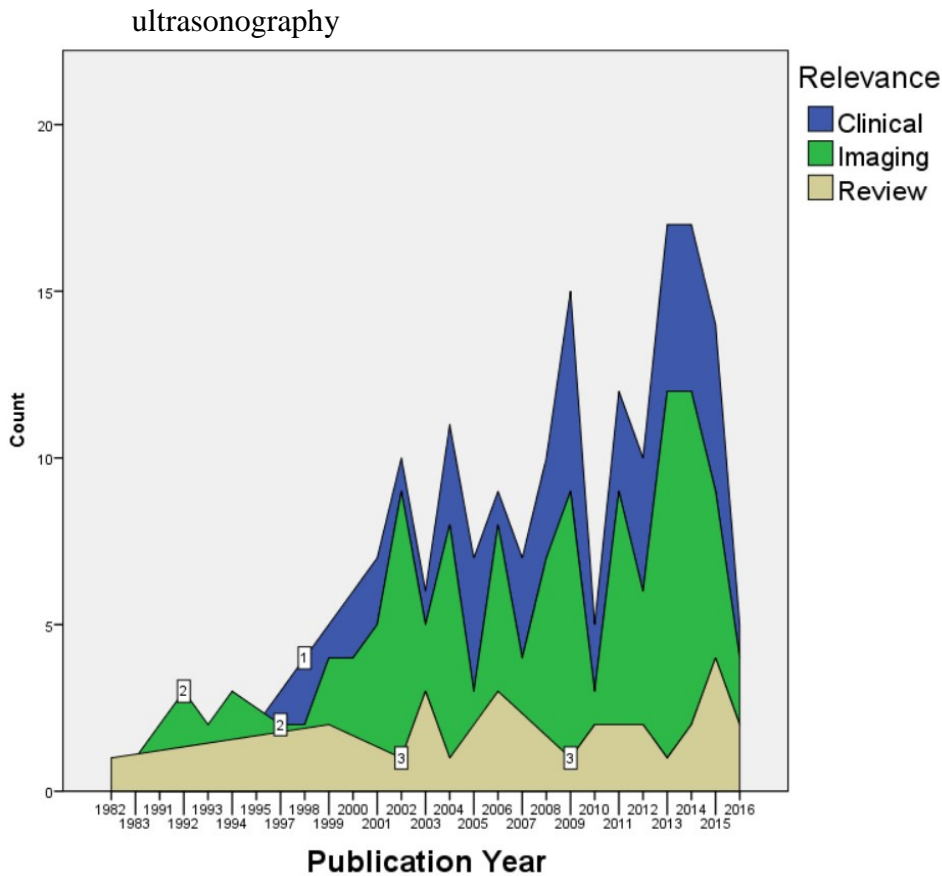
Figure 3: Stack chart of studies and their count per publication year is shown by plaque type phenotype investigated. (**CFD**=Cumputational Fluid Dynamics)
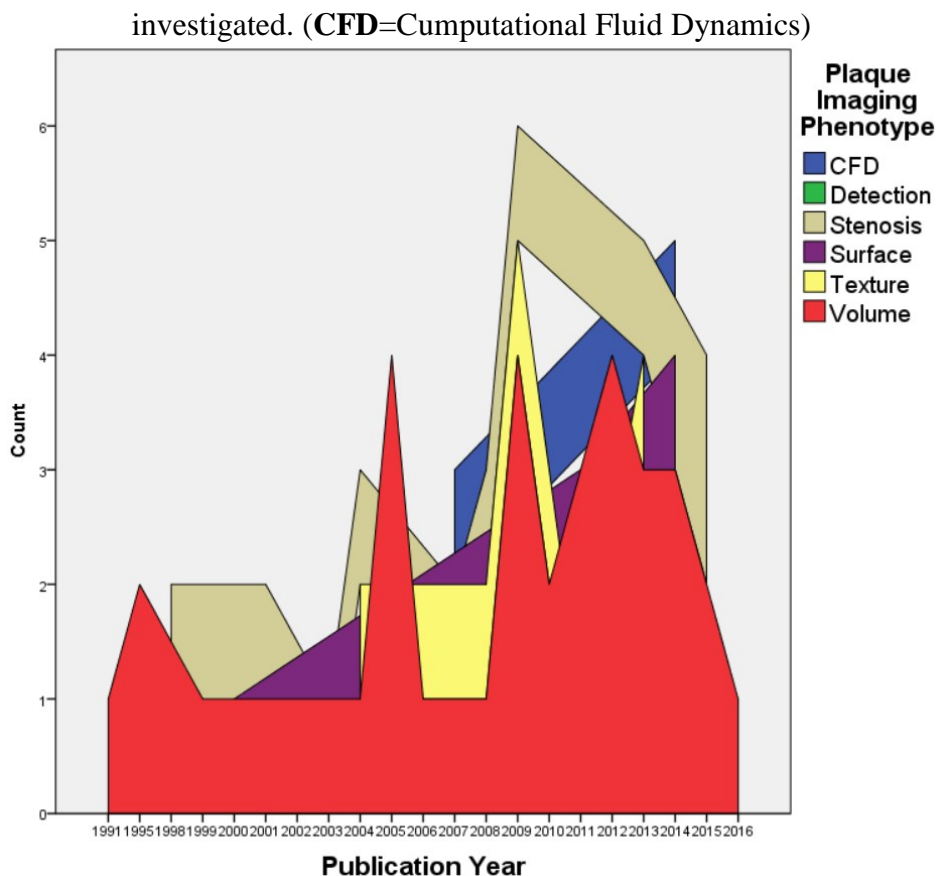
Appendix B: Tables

Table 1 Clinical effect studied by 3D ultrasonography volumetry of the carotid bifurcation.

	Author	Year	Std Type	Pts (n)	Sx (%)	Std Dur. (wk)	3D Reg	Conclusion
1	Delcker et al.[44]	1995	CSS	54	0	12	ML, ECG	**Diastolic blood pressure** (p<.01) and **Diabetes** (p<.03) independently predicted **TPV** progression
2	Griewing et al.[49]	1999	CCS	90	6	18	ML, ECG	**TPV progression greater** in **women without HRT** versus with HRT. No significant changes in IMT
3	*Al-Shali et al.[42]	2004	PC	161	n/r	n/a	ML	Atherosclerosis linked gene **PPARG c.1431T allele** had greater TPV than others. Different allele associated with increased IMT
4	*Hegele et al.[43]	2005	PC	150	n/r	n/a	ML	Gluconeogenesis linked gene **PCK1-232G/G genotype** had more carotid IMT but **less TPV** versus other genotypes
5	*Al-Shali et al.[45]	2005	PC	168	n/r	n/a	ML	Different ultrasound traits showed different correlations with risk factors. (IMT to hypertension, TPA to smoking/cholesterol, **TPV to diabetes)**
6	*Pollex et al.[46]	2005	CCS	98	n/r	84	ML	**TPV** measurements **(p=0.037), but not IMT, were higher in diabetics** compared to the normoglycemic controls.
7	Riccio et al.[47]	2006	PC	170	0	n/a	ML	only **TPV** (not IMT) was associated with **diabetes** and **ulcerations** in a diabetic population
8	Zhang et al.[92]	2009	PC	104	55,7	n/a	RT, ECG	**VCR** and **Systolic blood pressure** were associated with ICEs independently.
9	Buchanan et al.[48]	2012	PC	316	0	n/a	TFH	**TPV, VWV, IMT** associated with **age** in **males**. Only IMT associated in females.
10	Sillesen et al.[51]	2012	PC	6101	0	n/a	UFH	**CPB** correlated stronger with **CACS** than IMT (Bioimage)
11	Johri et al.[50]	2013	PC	70	0	n/a	RT	**TPV predicted the absence of CAD** better than max plaque thickness

12	Kim et al.[52]	2013	PC	107	0	n/a	RT	**TPA and TPV** showed correlation with **CAD severity** (not IMT)
13	Wannarong et al.[53]	2013	PC	349	33,3	72	TFH	**TPV progression predicted cardiovascular events/death** (not IMT, not TPA)
14	Bedi et al.[2]	2014	PC	1422	0	n/a	TFH	**Automatic Ultrasound increases** subclinical Carotid disease **detection** rates. **IMV** included in **FUN score**
15	v. Engelen et al.[54]	2014	PC	298	51,3	12	TFH	**Changes** in plaque **texture** and **TPV predict** vascular events
16	**Pike et al.[56]	2015	PC	61	0	n/a	TFH	**Ex-smokers** had significantly greater HeVDP and **carotid TPV** than never-smokers
17	Baber et al.[55]	2015	PC	5808	0	36	UFH	**MACE rates** increased with increasing **CPB** and **CAC** tertile (Bioimage)
18	**Cheng et al.[57]	2016	PC	61	n/r	n/a	TFH	**Ex-smokers** had significantly greater HeVDP and **carotid VWV (and not VWV without plaque)** than never-smokers

Std: Study, **Pts**: Patients, **Sx**=Symptomatic, **Dur**=Duration, **Reg**=Registration, **CSS**=Cross Sectional Study, **ML**=Mechanical Linear Assembly, **ECG**=Electrocardiogram Gated, **PC**=Prospective Cohort, **TPV**=Total Plaque Volume, **CCS**=Case,Control Study, **HRT**=Hormone Replacement Therapy, **IMT**=Intima Media Thickness, **n/r**=Not reported, **n/a**=Not applicable, **PPARG**= Peroxisome proliferator-activated receptor gamma, **PCK1**= phosphoenolpyruvate carboxykinase 1, **TPA**=Total Plaque Area, **RT**=3D-RealTime, **VCR**=Volume Compression Ratio, **ICE**=Ischemic Cardiovascular event, **TFH=**Tracked FreeHand, **VWV**=Vessel Wall Volume, **UFH**=Untracked FreeHand, **CPB**=Carotid Plaque Burden, **CACS**=Coronary Artery Calcium Score, **CAD**=Coronary Artery Disease, **IMV**=Intima Media Volume, **FUN**=Fuster-Narula Score, **HeVDP**= (3)He ventilation defect percent, **MACE**=Major adverse cardiovascular events, **CAC**=Coronary Artery Calcification, ***** and ** Indicate substudies of the same patient cohort

Table 2: Clinical effect studied by 3D ultrasonography volumetry of the carotid bifurcation.

	Author	Year	Std Type	Pts (n)	Sx (%)	Std Dur (wk)	3D Reg	Outcome
1	Hennerici et al.[31]	1991	PC	21	14,2	17	ML	**TPV** reduced in hypercholesterolemia by extracorporeal **plasmapheresis**
2	Yao et al.[34]	1998	PC	20	100	n/a	MR	**Vessel Volume increased after Patch** CEA vs Primary closure
3	Schminke et al.[58]	2002	RT	31	69,5	21	ML	**TPV reduced** by **statin** for **echolucent** plaques & **dyslipidemic** patients
4	*Ainsworth et al.[59]	2005	RCT	38	0	3	ML	**TPV reduced** by **aggressive statin** in **3 months** – **Small sample adequate**
5	Stumpe et al.[64]	2007	RCT	165	0	24	ML	**TPV + IMT reduced by Olmesartan** and not Atenolol (only IMT)
6	*Egger et al.[60]	2008	RCT	8	0	3	ML	**VWV reduced by aggressive statin**
7	Mallett et al.[66]	2009	RCT	71	n/r	53	TFH	**VWV(cca+ica) rate of change** affected by **Vitamin B** supplement in **nephropathy** (not TPA nor IMT)
8	*Krasinski et al.[61]	2009	RCT	35	0	3	ML	**VWV reduced** by **aggressive statin**
9	Yamada et al.[93]	2009	RCT	40	0	6	MR 3DIBS	**Plaque Lipid volume** decreased by **statin** vs lipid diet – Not volume
10	Shai et al.[63]	2010	RCT	140	n/r	24	TFH	Weight loss induced **SBP reduction** leads to **decrease in VWV & IMT**
11	*Awad et al.[62]	2010	RCT	38	0	3	ML	**Texture features improve VWV sensitivity** to **detect** plaque **change after aggressive statin**
12	Yamaguchi et al.[65]	2012	PC	16	38,9	6	RT	**Cilostazol** associated with **decreased TPV & increased GSM** - **MRI** reduced lipid components
13	Lindenmaier et al.[94]	2013	RCT	39	100	6	ML	Cardiac rehabilitation after TIA/Stroke does not alter IMT, TPV, VWV, TPA
14	Yamaguchi Oura et al.[87]	2014	PC	16	61	12	RT	**Cilostazol** associated **ONLY** with **MRI** reduced lipid components in long term

Std: Study, **Pts**: Patients, **Sx**=Symptomatic, **Dur**=Duration, **Reg**=Registration, **PC**=Prospective Cohort, **ML**=Mechanical Linear Assembly, **TPV**=Total Plaque Volume, **MR=**Mechanical Rotation Transducer, **n/a**=Not applicable, **CEA**=Carotid Endarterectomy, **RT**=Randomized Trial, **RCT**=Randomized Controlled Trial,

IMT=Intima Media Thickness, **VWV**=Vessel Wall Volume, **TFH=**Tracked FreeHand, **n/r**=Not reported, **CCA**=Common Carotid Artery, **ICA**=Internal Carotid Artery, **TPA**=Total Plaque Area, **3DIBS**=3D Integrated Back Scattering, **RT**=3D-RealTime, **GSM**=Gray Scale Median, **MRI**=Magnetic Resonance Imaging, **TIA**=Transient Ischemic Attack, ***** Indicates substudies of the same patient cohort

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Table 3: Stenosis degree studied by 3D ultrasonography of the carotid bifurcation compared to other

modalities

	Author	Year	Pts (n)	Sx %	3D Reg	Ref	Inter-Method Evaluation	Comment
1	Yao et al.[34]	1998	20	100	UFH	DSA	r=0.82, MD=1.8±0.5%	**Area** method is **better** than diameter.
2	Bendick et al.[95]	1998	32	50	ML	DSA	Accuracy of 87%.	**Categorization** of stenosis degree
3	Keberle et al.[70]	2000	75	48	UFH PD	2DUS	r=0.982-0.998; p<0.01	**Power Doppler** segmentation
4	Kozàkovà et al.[68]	2001	46	69,5	RT MR	DSA	r = 0.79, p<0.01; MD=7.8±15.5%	For **40%-70%, 2DUS indicate a higher** stenosis than DSA
5	Bucek et al.[67]	2003	48	n/r	TFH ECG	2DUS	r=0.85; P<0.001	Excellent correlation with 2DUS
						DSA	r=0.57; P=0.01	
6	Wessels et al.[96]	2004	62	57,1	TFH PD	2DUS	r=0.86; P<0.001	3DUS tended to underestimate high-grade stenoses
						DSA	r=0.74; P<0.001	
7	Forsberg et al.[69]	2008	59	n/r	RT 3DF	PSV EDV	ICC=0.83, p<0.0001	**PSV** was better than **PSV Ratio**
						PSVR	ICC=0.65	
8	Pfister et al.[72]	2009	25	100	RT MR	SUR	MRA r=0.94	**3D BFlow (+/- CM)** compares with **Surgical** evaluation for Stenosis
							3DBF+CM r=0.93	
							3DBF r=0.91	
							3DCCDS r=0.90	3D BFlow (+/- CM) better for **Calcification**
							CTA r=0.85	
							3DPD r=0.84	
							3DUS r=0.77	

Std	Study	Year	Pts	Sx	Reg	Ref		Result	Comments
9	He et al.[52]	2013	66	0	RT FTU	MRA		n/r	Increased sensitivity to detect plaques reported
10	Pelz et al.[71]	2015	73	16	TFH	MRA		CCA ICC 0.67±0.19	Not all plaques visualized due to calcification
								ICA ICC 0.79±0.17	
						2DUS		ICC=0.8 p<0.001	
11	Igase et al.[76]	2015	58	18,9	RT	MRA		n/r	Mild stenoses not detected by MRA

Std: Study, **Pts**: Patients, **Sx**=Symptomatic, **Reg**=Registration, **Ref**=Reference Method, **UFH**=Untracked FreeHand, **DSA**=Digital Subtraction Angiography, **ML**=Mechanical Linear Assembly, **PD**=Power Doppler, **2DUS**=2D Color Ultrasonography, **r**=Spearman's Correlation Coefficient, **RT**=3D-RealTime, **MR**=Mechanical Rotation Transducer, **n/r**=Not reported, **TFH**=Tracked FreeHand, **ECG**=Electrocardiogram Gated, **3DUS**=3D Ultrasonography , **3DF**=3D Flow, **PSV**=Peak Systolic Velocity, **EDV**=End Diastolic Velocity, **PSVR**=Peak Systolic Velocity Ratio, **ICC**=Intraclass Correlation Coefficient, **SUR**=Surgery, **MRA**=Magnetic Resonance Angiography, **3DBF**=3D B-Flow, **CM**=Contrast Medium, **3DCCDS**=3D Color Coded Duplex Sonography, **CTA**=Computed Tomography Angiography, **3DPD**=3D Power Doppler, **FTU**=Fly Through Ultrasound, **CCA**=Common Carotid Artery, **ICA**=Internal Carotid Artery

Table 4: Plaque Texture properties studied by 3D ultrasonography of the carotid bifurcation

	Author	Year	Study Type	Pts (n)	Sx (%)	Study Duration (wk)	3D Reg	Outcome
1	Heliopoulos et al.[78]	2004	PC	28	71,4	n/a	UFH	**VEGF** correlated to Plaque **MGV** (neovascularization)
2	Heliopoulos et al.[79]	2008	PC	214	51,4	n/a	UFH	**MGV lower** in **symptomatic** patients with carotid stenosis
3	Faggioli et al.[97]	2009	PC	68	0	n/a	RT	Detection of CAS **stent intimal coverage** associated with **hypertension**
4	Awad et al.[62]	2010	RCT	38	n/r	3	ML	**Texture features improve VWV sensitivity** to **detect** plaque **change after aggressive statin**
5	Yamada et al.[81]	2011	RC	95	47,3	n/a	RT 3DIBS	**3D-IBS** %Lipid & %Blood Plaque identified **Early Symptomatic plaques**
6	Koyama et al.[80]	2013	PC	18	n/r	n/a	RT	**Macrophage** infiltration associated with **echogenic without acoustic shadow**
7	Engelen et al.[54]	2014	PC	298	51,3	12	TFH	**Changes** in plaque **texture** and **TPV predict** vascular events

Pts: Patients, **Sx**=Symptomatic, **wk=**weeks, **Reg**=Registration, **PC**=Prospective Cohort, **n/a**=Not applicable, **UFH**=Untracked FreeHand, **VEGF**=Vascular Endothelial Growth Factor, **MGV**=Mean Gray Value, **RT**=3D-RealTime, **CAS**=Carotid Artery Stenting, **RCT**=Randomized Controlled Trial, **ML**=Mechanical Linear Assembly, **n/r**=Not reported, **VWV**=Vessel Wall Volume, **3DIBS**=3D Integrated Back Scattering, **TFH=**Tracked FreeHand, **TPV**=Total Plaque Volume.

Table 5: Plaque Surface properties studied by 3D ultrasonography of the carotid bifurcation

	Author	Year	Study Type	Pts (n)	Sx (%)	Study Duration (wk)	3D Reg	Outcome
1	Schminke et al.[73]	2000	PC	17	75	24	ML	**Regression > Progression** was observed for **ulcers**
2	Madani et al.[74]	2011	PC	253	0	36	ML	**>3 Ulcers/plaque** & TCD **Emboli (+)** had more events
3	Heliopoulos et al.[75]	2011	PC	62	100	n/a	UFH	**Ulcer Detection** 3DUS > 2DUS
4	Kuk et al.[77]	2014	PC	313	66,8	60	RT	**Ulcer Volume >5mm** predicts **CVE & Revascularization**
5	Igase et al.[76]	2015	PC	58	18,9	n/a	RT	**Moving plaques & Ulcers** detected only by 3DUS

Pts: Patients, **Sx**=Symptomatic, **wk**=weeks, **Reg**=Registration, **PC**=Prospective Cohort, **ML**=Mechanical Linear Assembly, **TCD**=Trans Cranial Doppler, **UFH**=Untracked FreeHand, **3DUS**=3D Ultrasonography, **2DUS**=2D Color Ultrasonography, **RT**=3D-RealTime, **CVE**=Cardiovascular Events.

Table 6: Repeatability (IntraObserver Variability) and Reproducibility (InterObserver Variability) reporting Studies

	Author	Year	Std Type	Pts or Plq (n)	Phen	3D Reg	Seg	ECG	Intra-Observer Evaluation	Inter-Observer Evaluation
1	Hennerici et al. [31]	1991	PC	21	TPV	ML	MAN	No	COV 6%	COV 18%
2	Delcker et al.[44]	1995	PC	54	TPV	ML	MAN	Yes	COV 3%	COV 4%
3	Griewing et al.[98]	1997	PC	21	TPV	ML	MAN	Yes	COV 4.16%	COV 5.7%
4	Yao et al.[34]	1998	PC	20	VV	MR	MAN	No	SEE 42,9mm^3 r=0.99 N=20	SEE 54,4mm^3 r=0.99 N=20
5	Delcker et al.[99]	1998	PC	25	TPV	TFH	MAN	Yes	COV 4.6%	COV 4.5%
								No	COV 13.3%	COV 16.7%
6	Palombo et al.[85]	1998	PC	33	TPV	MR	MAN	Yes	COV 4+/- 2.7%	COV 6.4+/- 4.1%
7	Griewing et al.[49]	1999	CCS	101	TPV	ML	MAN	Yes	ICC>0.85	MEAN DIF <5%
8	Al-Shali et al.[42]	2004	PC	161	TPV	ML	MAN	No	ICC=0.94	ICC=0.93
9	Landry et al.[90]	2004	PC	40	TPV	ML	MAN	No	COV 19.2-1.9% SEM=6.5%	COV 24.1-2.2% SEM=6.9%
10	Ainsworth et al.[59]	2005	RCT	38	TPV	ML	MAN	No	53 mm^3	n/r
11	Hegele et al.[43]	2005	PC	150	TPV	ML	MAN	No	ICC=0.94	ICC=0.93
12	Pollex et al.[46]	2005	CCS	98	TPV	ML	MAN	No	ICC=0.94	ICC=0.93

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13	Landry et al.[91]	2005	PC	<u>48</u>	TPV	ML	MAN	No	90.8-3.9% RMSD=4.2%	70.2-3.1% RMSD=5.7%
14	Riccio et al.[47]	2006	PC	170	TPV	ML	MAN	No	ICC=0.91	n/r
15	Stumpe et al.[64]	2007	RCT	165	TPV	MR	MAN	No	ICC=0.987	ICC=0.964
16	Egger et al.[83]	2007	PC	10	VWV	ML	MAN	No	4.6% ICC=0.95	5.7% ICC=0.85
					TPV	ML	MAN	No	22.7% ICC=0.85	31.1% ICC=0.82
17	Landry et al.[89]	2007	PC	<u>15</u>	TPV	ML	MAN	No	RMSD=3.2%	n/r
18	Ludwig et al.[84]	2008	PC	<u>105</u>	TPV	MR	MAN	No	3.1-3.4%	ICC=0.964
19	Egger et al.[82]	2008	PC	10	VWV	ML	MAN	No	COV 4.7%	COV 13.5%
					TPV	ML	MAN	No	COV 23.9%	COV 46.6%
20	Mallett et al.[66]	2009	RCT	71	VWV	TFH	MAN	No	COV 10%	n/r
21	Zhang et al.[92]	2009	PC	104	TPV	RT	MAN	Yes	7.5%	8.3%
22	*Ukwatta et al.[88]	2011	PC	21	VWV	ML	SEMI	No	5.1%	n/r
							MAN	No	3.9%	n/r
23	Yamaguchi et al.[65]	2012	PC	16	TPV	RT	MAN	No	ICC=0.99	n/r
24	*Buchanan et al.[48]	2012	PC	316	VWV	TFH	SEMI	No	5.1%	n/r
							MAN	No	3.9%	n/r
25	Sillesen et al.[51]	2012	PC	6101	TPV	UFH	SEMI	No	ICC=0.823	k=0.55
26	Kim et al.[52]	2013	PC	107	TPV	RT	MAN	No	ICC=0.94	ICC=0.93
27	Johri et al.[50]	2013	PC	70	TPV	RT	MAN	No	RMSE 7 mm^3	k=0.912

28	Cheng et al.[100]	2013	PC	34	TPV	ML	MAN	No	COV 5.6-7.85%	n/r
							AUTO	No	n/r	r=0.992-0.993
29	Yamaguchi Oura et al.[87]	2014	PC	16	TPV	RT	MAN	No	ICC=0.99	n/r
30	Græbe et al.[86]	2014	PC	62	TPV	MR	SEMI	No	ICC=0.91	ICC=0.87
						UFH	SEMI	No	ICC 0.74	ICC 0.60
31	Bar et al.[101]	2014	PC	20	TPV	ML	MAN	Yes	n/r	r=0.808
32	Kalashyan et al.[102]	2014	PC	82	TPV	RT	MAN	No	n/r	COV 5.6+/-6%
33	AlMuhanna et al.[103]	2015	PC	10	VWV	MR	MAN	No	ICC=0.95 SEM=1.9%	ICC=0.87 SEM=4.7%

Std: Study, **Pts**: Patients, **Plq**=Plaques, **Phen**=Imaging Phenotype, **Dur**=Duration, **Reg**=Registration, **Seg**=Segmentation, **ECG**=Electrocardiogram Gated, **PC**=Prospective Cohort, **TPV**=Total Plaque Volume, **ML**=Mechanical Linear Assembly, **MAN**=Manual, **COV**=Coefficient of variance**, ICC**=IntraClass Correlation Coefficient, **VV**=Vessel Volume, **MR**=Mechanical Rotation Transducer, **SEE**=Standard Error of estimate, **r**=Spearman's Correlation Coefficient, **TFH=**Tracked FreeHand, **CCS**=Case Control Study, **SEM**=Standard Error of Measurement, **RCT**=Randomized Controlled Trial, **n/r**=Not reported, **RMSD**=Root Mean Squared Difference, **VWV**=Vessel Wall Volume, **RT**=3D-RealTime, **SEMI**=Semi Automated, **k**=Cohen's Kappa statistic, **UFH**=Untracked FreeHand, **RMSE**=Root Mean squared Error

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012 Jan 3;125(1):e2–220.

2. Bedi R, Nagra A, Fukumoto T, Lynum S, Sengupta P, Aw J, et al. Detection of subclinical atherosclerosis in peripheral arterial beds with B-mode ultrasound: a proposal for guiding the decision for medical intervention and an artifact-corrected volumetric scoring index. Glob Heart. 2014 Dec;9(4):367–78.

3. de Weerd M, Greving JP, de Jong AWF, Buskens E, Bots ML. Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. Stroke J Cereb Circ. 2009 Apr;40(4):1105–13.

4. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. Stroke J Cereb Circ. 1999 Sep;30(9):1751–8.

5. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998 May 9;351(9113):1379–87.

6. Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2009 Apr;37(4 Suppl):1–19.

7. Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD. The European Society for Vascular Surgery Guidelines for Carotid Intervention: An Updated Independent Assessment and Literature Review. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg [Internet]. 2012 May 31 [cited 2012 Jun 9]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22658616

8. Kartchner MM, McRae LP. Noninvasive evaluation and management of the "asymptomatic" carotid bruit. Surgery. 1977 Dec;82(6):840–7.

9. Thompson JE, Patman RD, Talkington CM. Asymptomatic carotid bruit: long term outcome of patients having endarterectomy compared with unoperated controls. Ann Surg. 1978 Sep;188(3):308–16.

10. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA J Am Med Assoc. 1995 May 10;273(18):1421–8.

11. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet Lond Engl. 2004 May 8;363(9420):1491–502.

12. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet Lond Engl. 2010 Sep 25;376(9746):1074–84.

13. Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2009 Jun;37(6):625–32.

14. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. Nat Rev Cardiol. 2012 Feb;9(2):116–24.

15. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke J Cereb Circ. 2009 Oct;40(10):e573–83.

16. Naylor AR, Schroeder TV, Sillesen H. Clinical and imaging features associated with an increased risk of late stroke in patients with asymptomatic carotid disease. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2014 Dec;48(6):633–40.

17. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke J Cereb Circ. 2014 Dec;45(12):3754–832.

18. Giannakopoulos TG, Moulakakis K, Sfyroeras GS, Avgerinos ED, Antonopoulos CN, Kakisis JD, et al. Association between Plaque Echogenicity and Embolic Material Captured in Filter during Protected Carotid Angioplasty and Stenting. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2012 Jun;43(6):627–31.

19. Giannakopoulos TG, Antonopoulos CN, Moulakakis K, Sfyroeras GS, Kakisis JD, Brountzos EN, et al. Embolic material captured by filters during protected carotid artery stenting reflects plaque echogenicity: Implications for carotid stenting. Ital J Vasc Endovasc Surg. 2013;20(4):197–211.

20. Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. J Vasc Surg. 2010 Dec;52(6):1486–96.e1–5.

21. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg. 2014 Apr;59(4):956–67.e1.

22. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen T-P, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet Lond Engl. 2012 Jun 2;379(9831):2053–62.

23. Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. Circulation. 2004 Aug 10;110(6):756–62.

24. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T, et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. J Vasc Surg. 2013 Mar;57(3):609–18.e1; discussion 617–8.

25. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. Radiology. 2009 Aug;252(2):502–8.

26. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke J Cereb Circ. 2006 Mar;37(3):818–23.

27. Underhill HR, Yuan C, Yarnykh VL, Chu B, Oikawa M, Dong L, et al. Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. AJNR Am J Neuroradiol. 2010 Mar;31(3):487–93.

28. Moon SH, Cho YS, Noh TS, Choi JY, Kim B-T, Lee K-H. Carotid FDG Uptake Improves Prediction of Future Cardiovascular Events in Asymptomatic Individuals. JACC Cardiovasc Imaging. 2015 Aug;8(8):949–56.

29. Spence JD, Hegele RA. Noninvasive phenotypes of atherosclerosis: similar windows but different views. Stroke J Cereb Circ. 2004 Mar;35(3):649–53.

30. Blankenhorn DH, Chin HP, Strikwerda S, Bamberger J, Hestenes JD. Work in progress: common carotid artery contours reconstructed in three dimensions from parallel ultrasonic images. Radiology. 1983 Aug;148(2):533–7.

31. Hennerici M, Kleophas W, Gries FA. Regression of carotid plaques during low density lipoprotein cholesterol elimination. Stroke J Cereb Circ. 1991 Aug;22(8):989–92.

32. Carvalho DDB, Klein S, Akkus Z, ten Kate GL, Schinkel AFL, Bosch JG, et al. Estimating 3D lumen centerlines of carotid arteries in free-hand acquisition ultrasound. Int J Comput Assist Radiol Surg. 2012 Mar;7(2):207–15.

33. Toonkum P, Suwanwela NC, Chinrungrueng C. Reconstruction of 3D ultrasound images based on Cyclic Regularized Savitzky-Golay filters. Ultrasonics. 2011 Feb;51(2):136–47.

34. Yao J, van Sambeek MR, Dall'Agata A, van Dijk LC, Kozakova M, Koudstaal PJ, et al. Three-dimensional ultrasound study of carotid arteries before and after endarterectomy; analysis of stenotic lesions and surgical impact on the vessel. Stroke J Cereb Circ. 1998 Oct;29(10):2026–31.

35. Chen Y, Nguyen M, Yen JT. 7.5 MHz dual-layer transducer array for 3-D rectilinear imaging. Ultrason Imaging. 2011 Jul;33(3):205–16.

36. Provost J, Papadacci C, Demene C, Gennisson J-L, Tanter M, Pernot M. 3-D ultrafast Doppler imaging applied to the noninvasive mapping of blood vessels in vivo. IEEE Trans Ultrason Ferroelectr Freq Control. 2015 Aug;62(8):1467–72.

37. Glor FP, Ariff B, Hughes AD, Crowe LA, Verdonck PR, Barratt DC, et al. Image-based carotid flow reconstruction: a comparison between MRI and ultrasound. Physiol Meas. 2004 Dec;25(6):1495–509.

38. Glor FP, Ariff B, Hughes AD, Crowe LA, Verdonck PR, Barratt DC, et al. The integration of medical imaging and computational fluid dynamics for measuring wall shear stress in carotid arteries. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2004;2:1415–8.

39. Hammer S, Jeays A, Allan PL, Hose R, Barber D, Easson WJ, et al. Acquisition of 3-D arterial geometries and integration with computational fluid dynamics. Ultrasound Med Biol. 2009 Dec;35(12):2069–83.

40. Harrison GJ, How TV, Poole RJ, Brennan JA, Naik JB, Vallabhaneni SR, et al. Closure technique after carotid endarterectomy influences local hemodynamics. J Vasc Surg. 2014 Aug;60(2):418–27.

41. Sousa LC, Castro CF, António CC, Sousa F, Santos R, Castro P, et al. Computational simulation of carotid stenosis and flow dynamics based on patient ultrasound data - A new tool for risk assessment and surgical planning. Adv Med Sci. 2016 Mar;61(1):32–9.

42. Al-Shali KZ, House AA, Hanley AJG, Khan HMR, Harris SB, Zinman B, et al. Genetic variation in PPARG encoding peroxisome proliferator-activated receptor gamma associated with carotid atherosclerosis. Stroke J Cereb Circ. 2004 Sep;35(9):2036–40.

43. Hegele RA, Al-Shali KZ, House AA, Hanley AJG, Harris SB, Mamakeesick M, et al. Disparate associations of a functional promoter polymorphism in PCK1 with carotid wall ultrasound traits. Stroke J Cereb Circ. 2005 Dec;36(12):2566–70.

44. Delcker A, Diener HC, Wilhelm H. Influence of vascular risk factors for atherosclerotic carotid artery plaque progression. Stroke J Cereb Circ. 1995 Nov;26(11):2016–22.

45. Al-Shali K, House AA, Hanley AJG, Khan HMR, Harris SB, Mamakeesick M, et al. Differences between carotid wall morphological phenotypes measured by ultrasound in one, two and three dimensions. Atherosclerosis. 2005 Feb;178(2):319–25.

46. Pollex RL, Spence JD, House AA, Fenster A, Hanley AJG, Zinman B, et al. A comparison of ultrasound measurements to assess carotid atherosclerosis development in subjects with and without type 2 diabetes. Cardiovasc Ultrasound. 2005;3:15.

47. Riccio SA, House AA, Spence JD, Fenster A, Parraga G. Carotid ultrasound phenotypes in vulnerable populations. Cardiovasc Ultrasound. 2006;4:44.

48. Buchanan DN, Lindenmaier T, McKay S, Bureau Y, Hackam DG, Fenster A, et al. The relationship of carotid three-dimensional ultrasound vessel wall volume with age and sex: comparison to carotid intima-media thickness. Ultrasound Med Biol. 2012 Jul;38(7):1145–53.

49. Griewing B, Römer T, Spitzer C, Lüdemann J, Günther A, Kessler C. Hormone replacement therapy in postmenopausal women: carotid intima-media thickness and 3-D volumetric plaque quantification. Maturitas. 1999 May 31;32(1):33–40.

50. Johri AM, Chitty DW, Matangi M, Malik P, Mousavi P, Day A, et al. Can carotid bulb plaque assessment rule out significant coronary artery disease? A comparison of plaque quantification by two- and three-dimensional ultrasound. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2013 Jan;26(1):86–95.

51. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. JACC Cardiovasc Imaging. 2012 Jul;5(7):681–9.

52. Kim HS, Cho KI. Association of carotid artery parameters of atherosclerosis in coronary artery disease. J Cardiovasc Ultrasound. 2013 Jun;21(2):72–80.

53. Wannarong T, Parraga G, Buchanan D, Fenster A, House AA, Hackam DG, et al. Progression of carotid plaque volume predicts cardiovascular events. Stroke J Cereb Circ. 2013 Jul;44(7):1859–65.

54. van Engelen A, Wannarong T, Parraga G, Niessen WJ, Fenster A, Spence JD, et al. Three-dimensional carotid ultrasound plaque texture predicts vascular events. Stroke J Cereb Circ. 2014 Sep;45(9):2695–701.

55. 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 Mar 24;65(11):1065–74.

56. Pike D, Kirby M, Lindenmaier TJ, Sheikh K, Neron CE, Hackam DG, et al. Pulmonary abnormalities and carotid atherosclerosis in ex-smokers without airflow limitation. COPD. 2015 Feb;12(1):62–70.

57. Cheng J, Pike D, Chow TWS, Kirby M, Parraga G, Chiu B. Three-dimensional ultrasound measurements of carotid vessel wall and plaque thickness and their relationship with pulmonary abnormalities in ex-smokers without airflow limitation. Int J Cardiovasc Imaging. 2016 Jun 24;

58. Schminke U, Hilker L, Motsch L, Griewing B, Kessler C. Volumetric assessment of plaque progression with 3-dimensional ultrasonography under statin therapy. J Neuroimaging Off J Am Soc Neuroimaging. 2002 Jul;12(3):245–51.

59. 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 J Cereb Circ. 2005 Sep;36(9):1904–9.

60. Egger M, Chiu B, Spence JD, Fenster A, Parraga G. Mapping spatial and temporal changes in carotid atherosclerosis from three-dimensional ultrasound images. Ultrasound Med Biol. 2008 Jan;34(1):64–72.

61. Krasinski A, Chiu B, Spence JD, Fenster A, Parraga G. Three-dimensional ultrasound quantification of intensive statin treatment of carotid atherosclerosis. Ultrasound Med Biol. 2009 Nov;35(11):1763–72.

62. Awad J, Krasinski A, Parraga G, Fenster A. Texture analysis of carotid artery atherosclerosis from three-dimensional ultrasound images. Med Phys. 2010 Apr;37(4):1382–91.

63. Shai I, Spence JD, Schwarzfuchs D, Henkin Y, Parraga G, Rudich A, et al. Dietary intervention to reverse carotid atherosclerosis. Circulation. 2010 Mar 16;121(10):1200–8.

64. Stumpe KO, Agabiti-Rosei E, Zielinski T, Schremmer D, Scholze J, Laeis P, et al. Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study. Ther Adv Cardiovasc Dis. 2007 Dec;1(2):97–106.

65. Yamaguchi M, Sasaki M, Ohba H, Mori K, Narumi S, Katsura N, et al. Quantitative assessment of changes in carotid plaques during cilostazol administration using three-dimensional ultrasonography and non-gated magnetic resonance plaque imaging. Neuroradiology. 2012 Sep;54(9):939–45.

66. Mallett C, House AA, Spence JD, Fenster A, Parraga G. Longitudinal ultrasound evaluation of carotid atherosclerosis in one, two and three dimensions. Ultrasound Med Biol. 2009 Mar;35(3):367–75.

67. Bucek RA, Reiter M, Dirisamer A, Haumer M, Fritz A, Minar E, et al. Three-dimensional color Doppler sonography in carotid artery stenosis. AJNR Am J Neuroradiol. 2003 Aug;24(7):1294–9.

68. Kozàkovà M, Morizzo C, Andreucetti F, Palchetti P, Parenti G, Palombo C. Quantification of extracranial carotid artery stenosis by ultrafast three-dimensional ultrasound. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2001 Dec;14(12):1203–11.

69. Forsberg F, Stein AD, Merton DA, Lipcan KJ, Herzog D, Parker L, et al. Carotid stenosis assessed with a 4-dimensional semiautomated Doppler system. J Ultrasound Med Off J Am Inst Ultrasound Med. 2008 Sep;27(9):1337–44.

70. Keberle M, Jenett M, Beissert M, Jahns R, Haerten R, Hahn D. Three-dimensional power Doppler sonography in screening for carotid artery disease. J Clin Ultrasound JCU. 2000 Dec;28(9):441–51.

71. Pelz JO, Weinreich A, Fritzsch D, Saur D. Quantification of Internal Carotid Artery Stenosis with 3D Ultrasound Angiography. Ultraschall Med Stuttg Ger 1980. 2015 Oct;36(5):487–93.

72. Pfister K, Rennert J, Greiner B, Jung W, Stehr A, Gössmann H, et al. Pre-surgical evaluation of ICA-stenosis using 3D power Doppler, 3D color coded Doppler sonography, 3D B-flow and contrast enhanced B-flow in correlation to CTA/MRA: first clinical results. Clin Hemorheol Microcirc. 2009;41(2):103–16.

73. Schminke U, Motsch L, Hilker L, Kessler C. Three-dimensional ultrasound observation of carotid artery plaque ulceration. Stroke J Cereb Circ. 2000 Jul;31(7):1651–5.

74. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. Neurology. 2011 Aug 23;77(8):744–50.

75. Heliopoulos J, Vadikolias K, Piperidou C, Mitsias P. Detection of carotid artery plaque ulceration using 3-dimensional ultrasound. J Neuroimaging Off J Am Soc Neuroimaging. 2011 Apr;21(2):126–31.

76. Igase K, Kumon Y, Matsubara I, Arai M, Goishi J, Watanabe H, et al. Utility of 3-dimensional ultrasound imaging to evaluate carotid artery stenosis: comparison with magnetic resonance angiography. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2015 Jan;24(1):148–53.

77. Kuk M, Wannarong T, Beletsky V, Parraga G, Fenster A, Spence JD. Volume of carotid artery ulceration as a predictor of cardiovascular events. Stroke J Cereb Circ. 2014 May;45(5):1437–41.

78. Heliopoulos I, Papazoglou D, Piperidou H, Vadikolias K, Maltezos E, Artemis N. Carotid plaque echomorphology and serum vascular endothelial growth factor levels. Eur Neurol. 2004;51(2):104–8.

79. Heliopoulos J, Vadikolias K, Mitsias P, Artemis D, Tripsianis G, Piperidou C, et al. A three-dimensional ultrasonographic quantitative analysis of non-ulcerated carotid plaque morphology in symptomatic and asymptomatic carotid stenosis. Atherosclerosis. 2008 May;198(1):129–35.

80. Koyama S, Hashimoto T, Umahara T, Akai T, Watanabe D, Akimoto J, et al. Preoperative prediction of macrophage infiltration by 3-D tomographic ultrasound in endoarterectomized carotid plaques in elderly patients. Geriatr Gerontol Int. 2013 Oct;13(4):834–41.

81. Yamada K, Kawasaki M, Yoshimura S, Enomoto Y, Asano T, Minatoguchi S, et al. Evaluation of symptomatic carotid plaques by tissue characterization using integrated backscatter ultrasound and magnetic resonance imaging. Cerebrovasc Dis Basel Switz. 2011;31(3):305–12.

82. Egger M, Krasinski A, Rutt BK, Fenster A, Parraga G. Comparison of B-mode ultrasound, 3-dimensional ultrasound, and magnetic resonance imaging measurements of carotid atherosclerosis. J Ultrasound Med Off J Am Inst Ultrasound Med. 2008 Sep;27(9):1321–34.

83. Egger M, Spence JD, Fenster A, Parraga G. Validation of 3D ultrasound vessel wall volume: an imaging phenotype of carotid atherosclerosis. Ultrasound Med Biol. 2007 Jun;33(6):905–14.

84. Ludwig M, Zielinski T, Schremmer D, Stumpe KO. Reproducibility of 3-dimensional ultrasound readings of volume of carotid atherosclerotic plaque. Cardiovasc Ultrasound. 2008;6:42.

85. Palombo C, Kozakova M, Morizzo C, Andreuccetti F, Tondini A, Palchetti P, et al. Ultrafast three-dimensional ultrasound: application to carotid artery imaging. Stroke J Cereb Circ. 1998 Aug;29(8):1631–7.

86. Græbe M, Entrekin R, Collet-Billon A, Harrison G, Sillesen H. Reproducibility of two 3-D ultrasound carotid plaque quantification methods. Ultrasound Med Biol. 2014 Jul;40(7):1641–9.

87. Yamaguchi Oura M, Sasaki M, Ohba H, Narumi S, Oura K, Uwano I, et al. Carotid plaque characteristics on magnetic resonance plaque imaging following long-term cilostazol therapy. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2014 Oct;23(9):2425–30.

88. Ukwatta E, Awad J, Ward AD, Buchanan D, Samarabandu J, Parraga G, et al. Three-dimensional ultrasound of carotid atherosclerosis: semiautomated segmentation using a level set-based method. Med Phys. 2011 May;38(5):2479–93.

89. Landry A, Ainsworth C, Blake C, Spence JD, Fenster A. Manual planimetric measurement of carotid plaque volume using three-dimensional ultrasound imaging. Med Phys. 2007 Apr;34(4):1496–505.

90. Landry A, Spence JD, Fenster A. Measurement of carotid plaque volume by 3-dimensional ultrasound. Stroke J Cereb Circ. 2004 Apr;35(4):864–9.

91. Landry A, Spence JD, Fenster A. Quantification of carotid plaque volume measurements using 3D ultrasound imaging. Ultrasound Med Biol. 2005 Jun;31(6):751–62.

92. Zhang PF, Su HJ, Yao GH, Wu W, Zhang M, Liu CX, et al. Plaque volume compression ratio, a novel biomechanical index, is independently associated with ischemic cerebrovascular events. J Hypertens. 2009 Feb;27(2):348–56.

93. Yamada K, Yoshimura S, Kawasaki M, Enomoto Y, Asano T, Minatoguchi S, et al. Effects of atorvastatin on carotid atherosclerotic plaques: a randomized trial for quantitative tissue characterization of carotid atherosclerotic plaques with integrated backscatter ultrasound. Cerebrovasc Dis Basel Switz. 2009;28(4):417–24.

94. Lindenmaier TJ, Buchanan DN, Pike D, Hartley T, Reid RD, Spence JD, et al. One, two and three-dimensional ultrasound measurements of carotid atherosclerosis before and after cardiac rehabilitation: preliminary results of a randomized controlled trial. Cardiovasc Ultrasound. 2013;11:39.

95. Bendick PJ, Brown OW, Hernandez D, Glover JL, Bove PG. Three-dimensional vascular imaging using Doppler ultrasound. Am J Surg. 1998 Aug;176(2):183–7.

96. Wessels T, Harrer JU, Stetter S, Mull M, Klötzsch C. Three-dimensional assessment of extracranial Doppler sonography in carotid artery stenosis compared with digital subtraction angiography. Stroke J Cereb Circ. 2004 Aug;35(8):1847–51.

97. Faggioli GL, Ferri M, Serra C, Biagini E, Manzoli L, Lodi R, et al. The residual risk of cerebral embolism after carotid stenting: the complex interplay between stent coverage and aortic arch atherosclerosis. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2009 May;37(5):519–24.

98. Griewing B, Schminke U, Morgenstern C, Walker ML, Kessler C. Three-dimensional ultrasound angiography (power mode) for the quantification of carotid artery atherosclerosis. J Neuroimaging Off J Am Soc Neuroimaging. 1997 Jan;7(1):40–5.

99. Delcker A, Tegeler C. Influence of ECG-triggered data acquisition on reliability for carotid plaque volume measurements with a magnetic sensor three-dimensional ultrasound system. Ultrasound Med Biol. 1998 May;24(4):601–5.

100. Cheng J, Li H, Xiao F, Fenster A, Zhang X, He X, et al. Fully automatic plaque segmentation in 3-D carotid ultrasound images. Ultrasound Med Biol. 2013 Dec;39(12):2431–46.

101. Bar M, Roubec M, Farana R, Ličev L, Tomášková H, Školoudík D. Inter-rater reliability of carotid atherosclerotic plaque quantification by 3-dimensional sonography. J Ultrasound Med Off J Am Inst Ultrasound Med. 2014 Jul;33(7):1273–8.

102. Kalashyan H, Shuaib A, Gibson PH, Romanchuk H, Saqqur M, Khan K, et al. Single sweep three-dimensional carotid ultrasound: reproducibility in plaque and artery volume measurements. Atherosclerosis. 2014 Feb;232(2):397–402.

103. AlMuhanna K, Hossain MM, Zhao L, Fischell J, Kowalewski G, Dux M, et al. Carotid plaque morphometric assessment with three-dimensional ultrasound imaging. J Vasc Surg. 2015 Mar;61(3):690–7.