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Μεταπτυχιακή Διπλωματική Εργασία

" Carotid plaque vulnerability diagnosis by US versus CTA "

υπό

ΑΘΑΝΑΣΙΟΥ Γ. ΧΑΪΔΟΥΛΗ

Ειδικευόμενου Αγγειοχειρουργικής

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»

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Acknowledgments

The present study was conducted to fulfil part of the requirements for the acquisition of the MSc «Advanced Ultrasonic Functional Imaging and Research for Prevention and Diagnosis of Vascular Diseases» of the University of Thessaly. The study was carried out under the supervision of Assistant Professor George Kouvelos whom I sincerely thank for his guidance and help throughout the completion of this study. I would also like to emphasize the mentoring and support of Prof. Athanasios Giannoukas. Finally, I would like to thank Anna Maria Zerva for her valuable assistance during the whole period of this course.

Abstract

Aim: The carotid artery stenosis degree was the sole risk factor for potential cerebral ischemic events for many years. In recent years new data showed that the morphology of the plaque and specific characteristics are related to higher possibility of ischemic events. Ultrasound and Computed tomography angiography are two imaging techniques that are widely used nowadays. The purpose of this systematic review is to assess comparative studies including these techniques on the same groups of patients and examine the effectiveness of each technique in the detection of characteristics that the vulnerable plaque has.

Methods: A systematic review of the medical literature was conducted, utilizing PubMed, SCOPUS, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines. The results were initially filtered automatically and then manually for duplicates. After that a manual selection of studies that included both imaging techniques in the same group of people was performed. Four comparative studies than included 981 patients remained and were analyzed.

Results: The first study by Saba et. al. revealed that CTA detected 31 ulcerations with 93.75% sensitivity and 98.59% specificity compared to surgical findings, while US showed 37.5% sensitivity and 91.5% specificity.

The second study by Saba et.al. indicated a 77.2% agreement and a kappa value of 0.657 for plaque type definition, with a weighted kappa of 0.644. However, there was only an 88.4% observed agreement and a kappa value of 0.325 for plaque ulceration detection, suggesting poor agreement. Plaque morphology evaluation showed a 78.3% agreement with a kappa value of 0.513.

The third study by Anzidei et. al. revealed a significant difference between CTA and CDUS in detecting plaque morphology ($p=0.038$) and plaque ulceration ($p=0.019$).

In the fourth study by Ajduk et. al. the analysis of the ROC curve revealed MDCT's sensitivity 100% and specificity 70.4% in identifying haemorrhage within atherosclerotic plaques, while DUS exhibited a sensitivity of 100% and specificity of 48.1%.

Conclusion: There was an agreement between the two examinations in assessing plaque type, but CTA was deemed the most accurate technique for evaluating carotid artery stenosis, plaque morphology, and plaque ulceration detection. CTA also showed a notably high sensitivity and a moderate level of specificity in detecting haemorrhage within atherosclerotic carotid plaques.

Key words: CTA, US, vulnerable carotid plaque, systematic review

Περίληψη

Στόχος: Ο βαθμός στένωσης της καρωτίδας ήταν για πολλά χρόνια ο μοναδικός παράγοντας κινδύνου για εγκεφαλικά ισχαιμικά συμβάντα. Τα τελευταία χρόνια, νέα δεδομένα έδειξαν ότι συγκεκριμένα μορφολογικά χαρακτηριστικά της πλάκας σχετίζονται με υψηλότερη πιθανότητα εγκεφαλικών ισχαιμικών επεισοδίων. Ο υπερήχος και η αξονική αγγειογραφία είναι δύο τεχνικές απεικόνισης που χρησιμοποιούνται ευρέως σήμερα. Ο σκοπός αυτής της συστηματικής ανασκόπησης είναι να αξιολογήσει συγκριτικές μελέτες που περιλαμβάνουν αυτές τις απεικονιστικές τεχνικές στις ίδιες ομάδες ασθενών και να εξετάσει τη δυνατότητα κάθε τεχνικής στην ανίχνευση των χαρακτηριστικών που έχει η ευάλωτη πλάκα.

Μέθοδοι: Πραγματοποιήθηκε μια συστηματική ανασκόπηση της ιατρικής βιβλιογραφίας στις επιστημονικές βάσεις δεδομένων PubMed, SCOPUS και Central ακολουθώντας τις κατευθυντήριες οδηγίες PRISMA του 2020. Τα αποτελέσματα υπεβλήθησαν σε φιλτράρισμα αρχικά αυτόματο και στη συνέχεια από το συγγραφέα για διπλοεγγραφές. Μετά από αυτό, πραγματοποιήθηκε μια επιλογή μελετών που περιλάμβαναν και τις δύο τεχνικές απεικόνισης στην ίδια ομάδα ατόμων. Τέσσερις μελέτες που περιελάμβαναν συνολικά 981 ασθενείς ήταν αυτές που πληρούσαν τις προδιαγραφές και συνεπώς αναλύθηκαν.

Αποτελέσματα: Στην πρώτη μελέτη από τον Saba et. al. η αξονική αγγειογραφία ανίχνευσε 31 ελκωτικές βλάβες κάτι που παραπέμπει σε 93.75% ευαισθησία και 98.59% ειδικότητα σε σύγκριση με τα διεγχειρητικά ευρήματα, ενώ ο υπέρηχος έδειξε 37.5% ευαισθησία και 91.5% ειδικότητα.

Η δεύτερη μελέτη από τον Saba et. al. έδειξε 77.2% συμφωνία και συντελεστή kappa 0.657 στον ορισμό του τύπου της πλάκας, με σταθμισμένο kappa 0.644. Παρολαυτά υπήρξε μόνο 88.4% συμφωνία και συντελεστής kappa 0.325 στην ανίχνευση ελκών της πλάκας, κάτι που αναδεικνύει όχι τόσο καλή συμφωνία. Η αξιολόγηση της μορφολογίας της πλάκας έδειξε συμφωνία 78.3% με συντελεστή kappa 0.513.

Η τρίτη μελέτη από τον Anzidei et. al. ανέδειξε μια σημαντική διαφορά μεταξύ της αξονικής αγγειογραφίας και του υπερήχου στην ανίχνευση της μορφολογίας της πλάκας (p=0.038) και ελκωτικών βλαβών της πλάκας (p=0.019)

Στην τέταρτη μελέτη από τον Ajduk et. al. η ανάλυση της καμπύλης ROC ανέδειξε ευαισθησία της αξονικής αγγειογραφίας 100% και ειδικότητα 70.4% στην ανίχνευση αιμορραγίας στις αθηροσκληρωτικές πλάκες ενώ ο υπέρηχος παρουσίασε ευαισθησία 100% και ειδικότητα 48.1%.

Συμπέρασμα: Υπήρξε συμφωνία μεταξύ των δύο απεικονιστικών εξετάσεων στην αξιολόγηση του τύπου της πλάκας, αλλά η αξονική τομογραφία χαρακτηρίστηκε ως η πιο ακριβής τεχνική για την αξιολόγηση της στένωσης της καρωτίδας, τη μορφολογία της πλάκας και την ανίχνευση ελκών. Επίσης, η αξονική αγγειογραφία παρουσίασε ιδιαίτερα υψηλή ευαισθησία και μέτριο επίπεδο ειδικότητας στην ανίχνευση αιμορραγικών βλαβών εντός της καρωτιδικής αθηρωματικής πλάκας.
Λέξεις-κλειδιά: Αξονική αγγειογραφία, υπέρηχος, καρωτιδική ευάλωτη πλάκα, συστηματική ανασκόπηση

Carotid artery disease

Carotid artery disease pertains to the constriction or obstruction of the carotid arteries, significant blood vessels located bilaterally in the neck. These arteries, comprising the left and right common carotid arteries, originate from the aortic arch and the brachiocephalic artery, respectively. Each common carotid artery divides into two main branches: the internal carotid artery, responsible for supplying blood to the brain and eyes, and the external carotid artery, which provides blood to the neck, face and external parts of the head. The internal carotid arteries play a crucial role in delivering oxygen-rich blood to the brain, and when they become narrowed due to atherosclerotic plaque buildup, it can lead to strokes (1). This condition accounts for 10-15% of ischemic stroke and transient ischemic attack (TIA) cases (2). Atherosclerotic plaque formation is the primary cause of this narrowing (3).

The term atherosclerosis originates from the Greek language, indicating the thickening of the inner layer of arterial walls and the build-up of fat. Within the plaque, fatty material forms a central core, which is covered by a fibrous cap.

Atherosclerosis commences with endothelial damage in the arteries, potentially triggered by factors such as high lipid levels, smoking, high blood pressure, diabetes, genetic factors, elevated homocysteine levels, infectious agents, or combinations thereof.

This condition entails the formation of atheromatous plaques, which are fatty build-ups within the inner linings of arteries. These plaques begin with the accumulation of tiny cholesterol crystals in the intima layer and underlying smooth muscle. Over time, they expand as fibrous tissue and surrounding smooth muscle proliferate, protruding into the arteries and hindering blood circulation. The involvement of fibroblasts in generating connective tissue and calcium deposition within the lesion contributes to arterial sclerosis or hardening. Eventually, the artery's ability to compensate by widening diminishes, causing the lesion to encroach upon the artery's interior and disrupt blood flow (4).

Risk Factors

1) **Smoking**: Cigarette smoking represents one of the most intricate and least comprehended risk factors for cardiovascular diseases (CVDs). This complexity arises from the multitude of chemicals present in cigarette smoke, which undergo further alterations within the human body's detoxification systems (5,6). Additionally, individual smoking habits, intensity, and the brand of cigarettes smoked further influence the quantity, diversity, and nature of smoke chemicals individuals are exposed to. Quitting smoking holds promise for early benefits, including the reversal of platelet activation, coronary artery spasm, and ventricular arrhythmias, and remains the most clinically effective and cost-effective strategy for preventing atherosclerotic disease (7).

2) **Age:** Ageing significantly increases the risk of atherosclerotic cardiovascular disease by impacting all metabolic processes and exerting a substantial influence on atherosclerosis. While there is not a singular dominant pathophysiological mechanism that can fully explain this phenomenon, it involves multiple intricate pathways (8).

3) **Sex:** Atherosclerosis occurring outside the brain's circulation is more common in men compared to premenopausal women, primarily because men lack the protective effects of oestrogen or may experience increased exposure to vascular risk factors (9). In males, atherosclerotic plaques tend to develop earlier, exhibit greater inflammation, and are more unstable. While the overall area affected by plaque is larger in males, females may experience greater stenosis (10).

4) **Hyperlipidemia:** Lipids play a pivotal role in the development of atherosclerosis, which is regarded as a chronic condition linked to lipids and inflammation. The process is initiated and advanced by lipid peroxidation and the oxidation of LDL (low-density lipoprotein) (11).

5) **Hypertension:** Hypertension stands as one of the most widespread and potent factors contributing to cardiovascular diseases, elevating the risk of all major outcomes related to atherosclerotic cardiovascular diseases by an average of 2 to 3 times (12).

6) **Diabetes Mellitus:** In diabetes mellitus, there is a defect in insulin secretion, resulting in persistent hyperglycaemia. Insulin plays a crucial role as an anabolic hormone, and its insufficiency leads to various metabolic abnormalities affecting lipids, proteins, and carbohydrates. The hyperglycaemia, dyslipidaemia, and other metabolic changes associated with the progression of the disease significantly contribute to the development of atherosclerosis, influencing nearly every stage of the atherogenic process (13).

Other factors that are related to the ones above are genetics / family history, obesity, physical inactivity, diet, inflammation, and stress. It is important these risk factors are known to the public so that individuals can take steps to manage and control them to prevent major health issues. Lifestyle changes, regular check-ups and medical interventions when needed are the options for avoiding major events due to atherosclerosis (4).

Carotid Artery Stenosis

Clinical presentation

Asymptomatic:

Asymptomatic carotid artery stenosis refers to the narrowing of the proximal internal carotid artery by 50% or more due to atherosclerosis at the bifurcation level in individuals who have not experienced recent (within the last six months) ischemic stroke or transient ischemic attack (TIA) affecting the same side of the carotid area. Stenosis is classified as 50%-69% narrowing, while severe stenosis is defined as 70% or more (sometimes 60%) narrowing. The management of asymptomatic carotid stenosis remains uncertain but poses significant health risks for affected individuals. Only a portion of patients with stenosis will eventually experience a stroke and considering that modern medical therapy can reduce the stroke risk, deciding whether to pursue surgical management is challenging for physicians (14, 15).

Symptomatic:

Individuals diagnosed with symptomatic narrowing of the carotid artery are those who have encountered either an ischemic stroke or a transient ischemic attack (TIA) linked to the same side of the carotid artery within the previous six months. Stroke stands as the second most common cause of death worldwide, resulting in approximately 5.5 million deaths annually. Aside from its considerable mortality rate, stroke also inflicts substantial morbidity, with as many as 50% of survivors facing long-term disabilities. Consequently, stroke presents a significant public health challenge with profound economic and social impacts (16). Additionally, there is a six-month timeframe following symptomatic carotid stenosis, as arbitrarily chosen in most trials, after which the condition is categorized as asymptomatic. This is because the risk of recurrent ischemic events decreases to a similar rate observed in asymptomatic carotid stenosis after a few weeks (17).

The Vulnerable Plaque

For an extended period, the severity of narrowing in the vessel's lumen was the main factor determining whether medical or surgical intervention was necessary to address such conditions (18-20). However, recent years have seen doubt emerge regarding the exclusive reliance on luminal stenosis alone as a prognostic indicator for ischemic events in patients with mild to moderate carotid artery narrowing (21-22). Presently, attention has shifted towards examining the morphological attributes of plaques, with the belief that identifiable vulnerable characteristics could provide crucial insights into plaque stability and, consequently, the risk of stroke (23-24). Histopathological investigations of symptomatic plaques have revealed a high concentration of inflammatory cells alongside localized areas of fibrous cap loss (25). Symptomatic carotid plaques have also demonstrated elevated levels of intraplaque haemorrhage (IPH) and an increased presence of lipid-rich necrotic cores (LRNCs), neovascularization, thin fibrous caps, and plaque thrombus upon histological examination. (26,27,28)

- Carotid Intraplaque Hemorrhage

Numerous studies have revealed that patients with carotid intraplaque haemorrhage (IPH) and varying degrees of stenosis, from mild to severe, face an elevated risk of cardioembolic events (29-31). IPH is correlated independently with the extent of arterial stenosis and the occurrence of ipsilateral symptoms, even in cases of minimal arterial narrowing (32). Additionally, symptomatic carotid arteries with minimal stenosis exhibit a higher prevalence of IPH compared to asymptomatic arteries. Furthermore, the presence of IPH can expedite the progression of atherosclerotic plaque and heighten the risk of plaque rupture (33).

- Lipid Rich Necrotic Core

A sizable lipid-rich necrotic core and localized inflammation, particularly in the shoulder areas of the plaque, are regarded as indicators of plaque vulnerability (34, 35).

- Thin Fibrous Cap

Continual thinning of the fibrous cap of a carotid plaque can result in fissures and ulcerations within the plaque. This can lead to acute thrombosis, potentially obstructing the arterial lumen

due to the release of thrombogenic substances from the plaque (36). Thicker fibrous caps are better equipped to withstand pulsatile mechanical forces (37,38).

- Plaque echolucency

Detecting echolucency in carotid plaques via ultrasound serves as a predictive indicator for the risk of stroke ipsilaterally in patients with varying degrees of carotid stenosis severity (figure 1) (39).

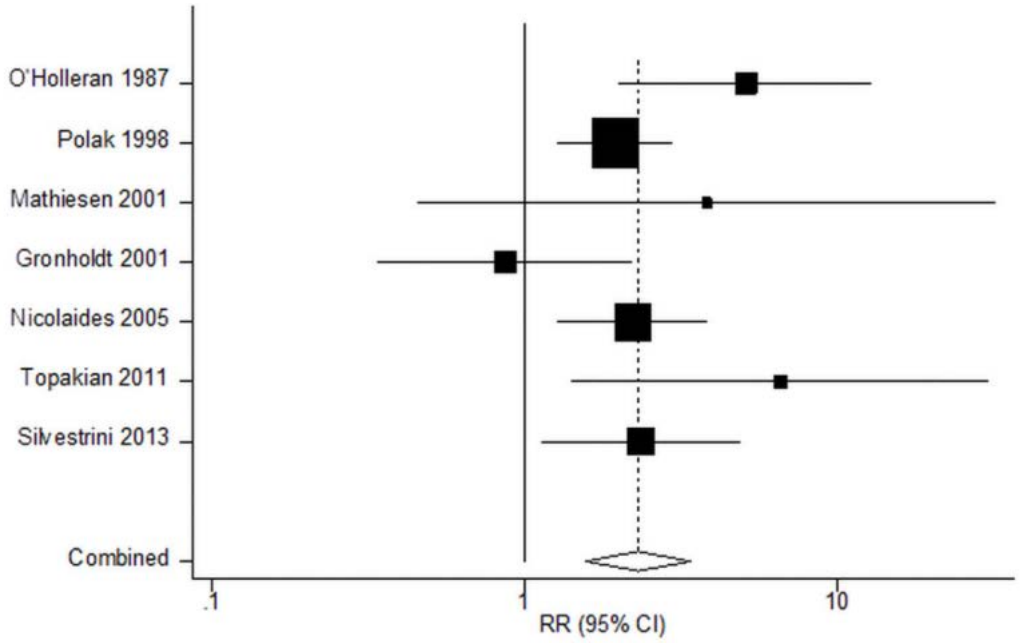

Figure 1. Forest plot illustrating the correlation between plaque echolucency determined by ultrasound and the likelihood of experiencing a stroke on the same side in the future. Figure taken from Gupta et.al (39).

Methods of measuring carotid artery stenosis by US

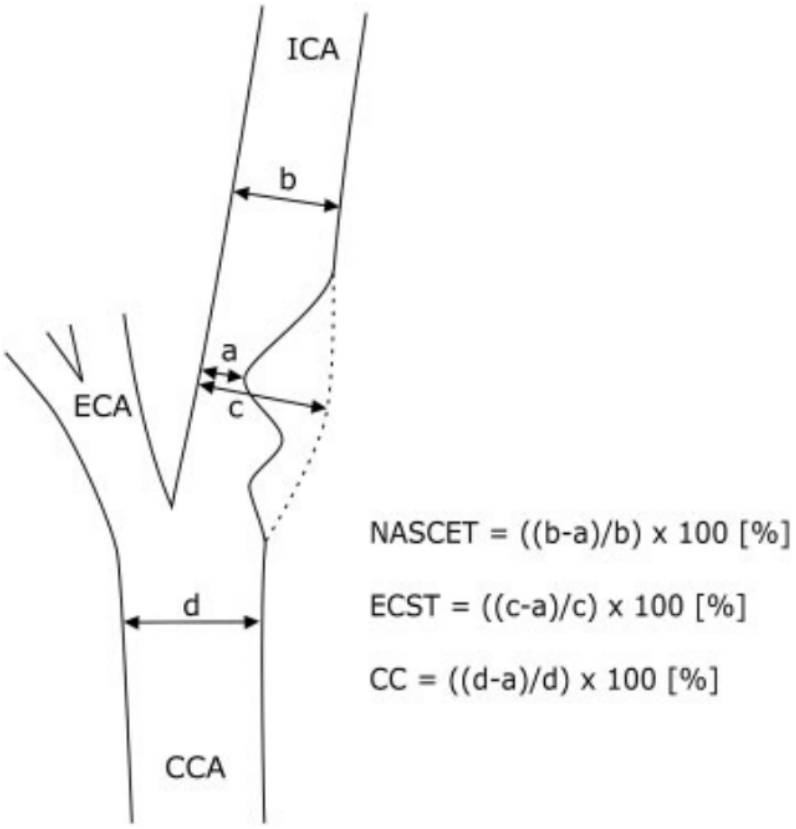

Figure 2. The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ESCT), common carotid (CC) method. CCA: common carotid artery, ECA: external carotid artery, ICA: internal carotid artery. Figure taken from Adla et al (40).

In the NASCET approach to assessing carotid artery stenosis, the degree of narrowing is determined by the ratio of the luminal diameter at the narrowest part of the diseased segment of the artery to the diameter of the artery beyond any dilation occurring after the stenosis.

In the ESCT method for measuring carotid artery stenosis, the degree of narrowing is ascertained by measuring the diameter of the narrowest segment of the artery and comparing it to the diameter of a proximal or distal segment where the artery appears normal, expressed as a percentage of narrowing.

In the CC method for evaluating carotid artery stenosis, the degree of narrowing is determined by measuring the diameter of the common carotid artery at a point unaffected by plaque build-up or kinking. Subsequently, the diameter of the narrowest point of the internal carotid artery is measured. The extent of stenosis is then expressed as a percentage by comparing the diameter of the narrowest segment to that of the normal segment.

Ultrasonography plaque classification

Geroulakos et al. (41) categorized carotid plaques based on ultrasound observations into five groups:

1. Plaques that are uniformly echolucent, with or without a visible echogenic cap at the plaque's margin.
2. Plaques predominantly echolucent, with less than 50% of the area showing echogenicity.
3. Plaques predominantly echogenic, with less than 50% of the area being echolucent.
4. Plaques that are uniformly echogenic.
5. Plaques that could not be classified due to heavy calcification and the presence of acoustic shadows.

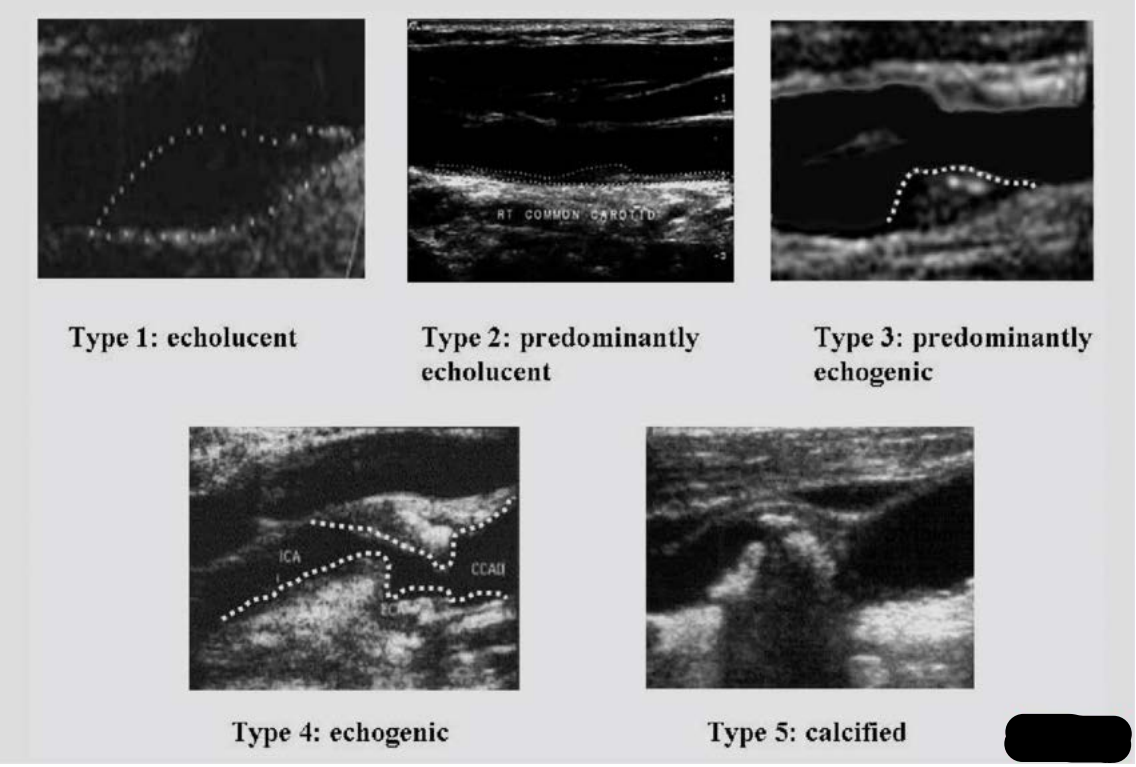

Figure 3. Plaque classification by ultrasound. Figure taken from Sirico et al (42).

Vulnerable plaque imaging characteristics

Plaque Characteristic	MDCTA	B-Mode US	CEUS
IPH	Mean ~100 HU	Echolucent	Echolucent
LRNC	Mean ~30 HU	Echolucent	Echolucent
Neovascularity	PE	ND	PE
Inflammation	PE	ND	PE
Ulceration	SI of plaque on multiplanar imaging	SI	SI
Calcification	Mean ~250 HU	Hyperechoic; posterior acoustic shadowing	Hyperechoic; posterior acoustic shadowing

Table 1. Vulnerable Plaque characteristics and imaging findings in each examination. Table from Brinjikji et al (43).

ND = not detectable, PE = plaque enhancement, SI = surface irregularity, US = ultrasonography, MDCT = multidetector-row CT, CEUS = contrast-enhanced ultrasonography, HU = Hounsfield units, IPH = intraplaque hemorrhage, LRNC = lipid-rich necrotic core

Recent Guidelines

Latest ESVS guidelines for carotid artery disease refer to a healthy way of living, control of the risk factors and medical treatment. They also refer to medication peri-operative and in case of best medical treatment approach.

Recommendation 8 — Changed

For patients with asymptomatic and symptomatic carotid disease, behavioural counselling to promote healthy diet, smoking cessation and physical activity is recommended.

Class	Level	References	ToE
I	B	O'Connor *et al.* (2020)[85], Herder *et al.* (2012)[207], Shinton *et al.* (1989)[208], Lee *et al.* (2003)[209], Strazzullo *et al.* (2010)[210]	

Recommendation 15 — Unchanged

For patients with asymptomatic or symptomatic carotid stenoses and hypertension, antihypertensive treatment is recommended.

Class	Level	References	ToE
I	A	Williams *et al.* (2018)[236]	

Recommendation 23 — New

For symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting following a transient ischaemic attack or minor ischaemic stroke, short term aspirin plus clopidogrel for 21 days followed by clopidogrel monotherapy, or long term aspirin plus modified release dipyridamole is recommended*.

Class	Level	References	ToE
I	A	Hao *et al.* (2018)[59], Diener *et al.* (1985)[301], ESPRIT Study Group *et al.* (2006)[302], Sacco *et al.* (2008)[304], King and Markus (2009)[305], King *et al.* (2011)[307]	

Recommendation 40 — Unchanged

For patients reporting carotid territory symptoms within the preceding six months and who have a 70–99% carotid stenosis, carotid endarterectomy is recommended provided the 30 day risk of death/stroke rate is <6%.

Class	Level	References	ToE
I	A	Rothwell *et al.* (2003)[357], Rothwell *et al.* (2004)[358], Rothwell *et al.* (2004)[359]	

Recommendation 12 — Unchanged

For patients with asymptomatic carotid stenosis undergoing carotid stenting, combination antiplatelet therapy with aspirin (75–325 mg daily) and clopidogrel (75 mg daily) is recommended. Clopidogrel (75 mg daily) should be started at least three days before stenting or as a single 300 mg loading dose given in urgent cases. Aspirin and clopidogrel should be continued for at least four weeks after stenting and then antiplatelet monotherapy should be continued indefinitely.

Class	Level	References	ToE
I	B	Murphy *et al.* (2019)[81], McKevitt *et al.* (2005)[221], Mannheim *et al.* (2017)[222], Gurm *et al.* (2008)[223], Rosenfield *et al.* (2016)[224], Eckstein *et al.* (2016)[225], Quinn *et al.* (1999)[226]	

Recommendation 9 — Changed

For patients with >50% asymptomatic carotid stenosis, lower dose aspirin (75–325 mg daily) should be considered, mainly for the prevention of late myocardial infarction and other cardiovascular events.

Class	Level	References	ToE
IIa	C	King *et al.* (2013)[213], Antithrombotic Trialists Collaboration *et al.* (2009)[216]	

Recommendation 13	Changed		
For patients with asymptomatic carotid stenosis, lipid lowering therapy with statins (with or without ezetimibe) is recommended for the long-term prevention of stroke, myocardial infarction, and other cardiovascular events.			
Class	Level	References	ToE
I	B	Zhan *et al.* (2018)[111], Halliday *et al.* (2010)[228], Cholesterol Treatment Trialists Collaboration (2012)[229]	

Recommendation 8	Changed		
For patients with asymptomatic and symptomatic carotid disease, behavioural counselling to promote healthy diet, smoking cessation and physical activity is recommended.			
Class	Level	References	ToE
I	B	O'Connor *et al.* (2020)[85], Herder *et al.* (2012)[207], Shinton *et al.* (1989)[208], Lee *et al.* (2003)[209], Strazzullo *et al.* (2010)[210]	

Recommendation 16	Unchanged		
For diabetic patients with asymptomatic carotid stenoses, optimal glycaemic control is recommended.			
Class	Level	References	ToE
I	B	NICE[243], NICE[244], ABCD[245], American Diabetes Association[246]	

The ESVS has also an algorithm for the management of symptomatic and asymptomatic carotid stenosis with best medical treatment (BMT), carotid endarterectomy (CEA) and/or carotid artery stenting (CAS).

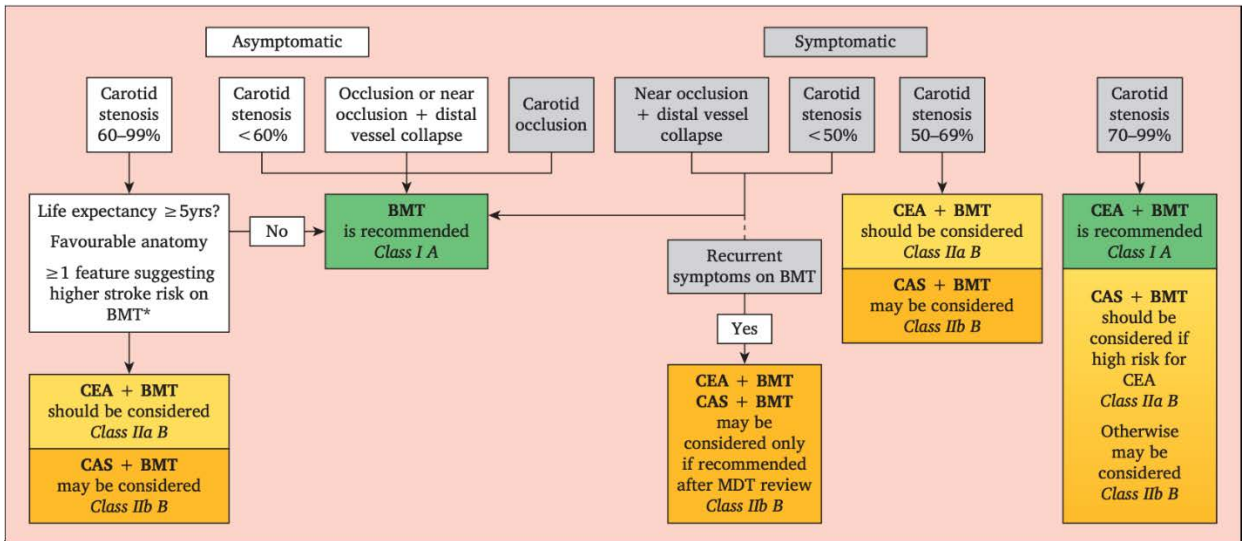

Figure 2. Management of "average risk" patients with asymptomatic and symptomatic carotid stenoses with best medical therapy (BMT), carotid endarterectomy (CEA), and/or carotid artery stenting (CAS). *See Table 8 for imaging/clinical criteria that confer an increased risk of stroke on BMT.

Methods

- Protocol Review

A systematic review of the medical literature was conducted, utilizing PubMed, SCOPUS, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The analysis included comparative studies reporting on both ultrasound (US) and computed tomography angiography (CTA) of the carotid artery. Eligible studies were observational and comparative, published up to January 2023, and focused on assessing the vulnerability characteristics of symptomatic and/or asymptomatic carotid plaques using both US and CTA imaging. Studies exclusively reporting on one imaging modality were excluded from the analysis. Additionally, case reports, case series, and studies involving experimental diagnostic models or not involving human subjects were deemed ineligible. Language was not a criterion for exclusion, provided that an English version of the article was available. Eligible studies underwent a full-text review, adhering to the predefined inclusion and exclusion criteria.

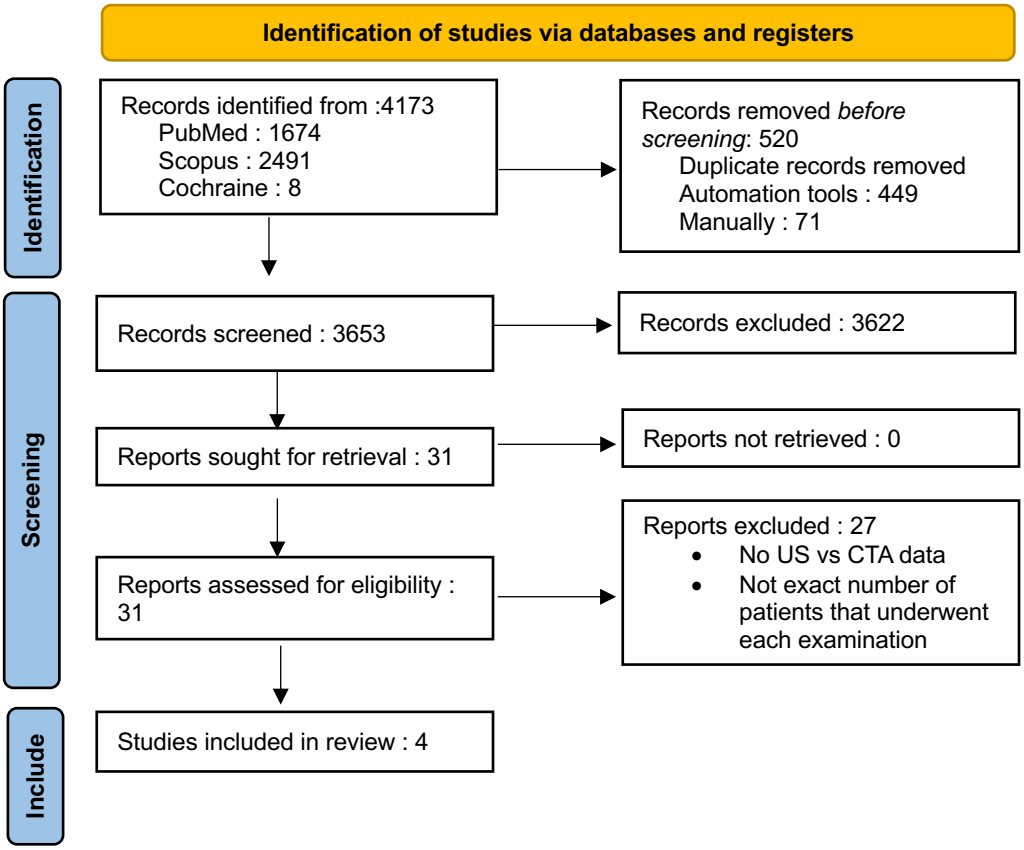

Figure 4. PRISMA 2020 flowchart. Screening process based on the PRISMA 2020 Guidelines for systematic reviews and meta-analyses.

- Search strategy

The databases PubMed, SCOPUS, and CENTRAL were systematically searched based on predefined clinically relevant questions established prior to commencing the review, following the P.I.C.O. (patient; intervention; comparison; outcome) model (refer to Supplementary Table S1). A range of terms including "stroke," "transient ischemic attack," "TIA," "amaurosis fugax," "computed tomography angiography," "CTA," "triplex ultrasound," "TUS," "duplex ultrasound," "DUS," "colour flow ultrasound," "color flow ultrasound," "carotid artery disease," "intraplaque hemorrhage," "IPH," "lipid-rich necrotic core," "LRNC," "inflammation," "plaque ulcer," "plaque thrombus," "carotid plaque vulnerability," "thin-fibrous cap," "TFC," and "carotid plaque vulnerability" were employed either individually or in combination under the Expanded Medical Subject Headings (MeSH) filter (see Supplementary Table S2). Duplicate entries were identified and removed using automation tools (EndNote 20.6). Initial screening was based on titles and abstracts, with further evaluation conducted through a full-text review for secondary selection.

P	Patient, population or problem	Patients with extracranial carotid artery plaque (symptomatic (TIA, amaurosis fugax, stroke) or asymptomatic)
I	Intervention, prognostic factor or exposure	Duplex, Ultrasound, Triplex, Color-Flow Ultrasound (DUS, US, TUS)
C	Comparison of intervention	Computer Tomography Angiography (CTA)
O	Outcome you would like to measure or achieve	Association of vulnerable carotid plaque characteristics (e.g., intraplaque hemorrhage (IPH), thin-fibrous cap (TFC), lipid-rich necrotic core (LRNC), plaque ulceration, plaque thrombus, plaque neovascularization)
	What type of question are you asking?	Does US present similar accuracy with CTA in detecting vulnerable carotid plaque characteristics? Is there any association between vulnerable carotid plaque characteristics detected in US versus CTA?
	Type of study you want to find	Randomized, non-randomized

Table 2. P.I.C.O. model

Footnote: P.I.C.O. (patient; intervention; comparison; outcome) model was used to define the clinical questions and clinically relevant evidence in the literature, TIA; Transient Ischemic Attack, DUS; Duplex ultrasound, TUS; Triplex ultrasound, CTA; Computed tomography angiography, IPH; Intra-plaque hemorrhage, LRNC; Lipid-rich necrotic core, TFC; Thin fibrous cap

- Data extraction

A Microsoft Excel spreadsheet extraction tool was created for data extraction purposes. This involved gathering general details such as author, title, publication year, and journal. Furthermore, clinical data was compiled, encompassing patient demographics such as the number of patients, their age, male-to-female ratio, and symptomatic versus asymptomatic status. Additionally, details regarding the number of evaluated plaques were recorded. Carotid plaque vulnerability characteristics, including plaque ulceration, irregular plaque surface, and plaque type, were also documented.

Author	**Year**	**Journal**	**Type of Study**	**Study Period**	**Number of Patients**	**Age (Years) Median // Range**	**Males**	**Females**
Saba et. al	2007	American Journal of Neuroradiology	Comparative study	01/2004 - 10/2005	237	64 // Range 34-87	163	74
Saba et. al	2011	European Journal of Radiology	Comparative study	01/2004 - 07/2007	658	65.3 // Range 27-88	453	205
Anzidei et. al.	2012	La Radiologia Medica	Comparative study	05/2006 - 05/2010	416	54±21.3 //Range 49-90	304	112
Ajduk et. al.	2013	Collegium Antropologium	Comparative study	NA	50	69 // Range 48-87	36	14
Total.					1361	63.8 AVG	956	405

Table 3. Main characteristics of each study

Author	**Number of Patients**	**Number of Plaques**	**Vulnerable Plaque Characteristic**	**Number of Vulnerable Plaque Characteristic (US)**	**Number of Vulnerable Plaque Characteristic (CTA)**	**Number of Vulnerable Plaque Characteristics Control Exam**	**Age (Years) Median // Range**	**Males**	**Females**	**S**	**AS**
Saba et. al.	103	NA	Ulceration	12	31	32 (Surgical speciment)	67 // Range 49-85	68	35	67	36
Saba et. al.	658	872	irregular plaque surface//Ulceration/type of plaque (Fatty, Mixed, Calcified)	289//72//(294,281,297)	294//93//(296,247,329)	NA	NA	453	205	NA	NA
Anzidei et. al.	170	336	Irregular plaque surface / Ulceration	178 / 86	168 / 64	168 / 64 (DSA)	69±6,5 // 62-90	108	62	140	0
Ajduk et. al.	50	50	Stenosis / AHA plaque type	NA	NA	NA	69 // Range 48-87	36	14	20	30

Table 4. Vulnerable plaque characteristics, symptomatic status and control examination (when existed)

Results

Following the filtering process, four eligible studies were identified.

The first study by Saba et al. (44) occurred from January 2004 to October 2005, involving 237 patients with a total of 474 carotid arteries initially studied with US and subsequently analysed with CTA. Among them, 103 patients underwent carotid endarterectomy. The analysis included assessing stenosis degree, plaque composition, and the presence of ulcerations. The results revealed that CTA detected 31 ulcerations with 93.75% sensitivity and 98.59% specificity compared to surgical findings, while US showed 37.5% sensitivity and 91.5% specificity.

The second study conducted by Saba et al. (45) spanned from January 2004 to January 2007, involving the retrospective evaluation of 658 patients who underwent both multi-detector row CT angiography (CTA) and Ultrasound echo colour Doppler (US) for carotid artery assessment. The study analysed parameters such as plaque morphology, plaque type, and the presence of ulcerations. The results indicated a 77.2% agreement and a kappa value of 0.657 for plaque type definition, with a weighted kappa of 0.644. However, there was only an 88.4% observed agreement and a kappa value of 0.325 for plaque ulceration detection, suggesting poor agreement. Plaque morphology evaluation showed a 78.3% agreement with a kappa value of 0.513.

The third study by Anzidei et al. (46) involved 170 patients with previous cerebrovascular events and suspected carotid artery stenosis, undergoing Carotid Doppler ultrasound (CDUS), CTA, and digital subtraction angiography (DSA) as a control examination. A total of 336 carotid bifurcations were studied. The analysis revealed a significant difference between CTA and CDUS in detecting plaque morphology (p=0.038) and plaque ulceration (p=0.019).

	ACCURACY		SENSITIVITY		SPECIFICITY		PPV		NPV	
	DUS	CTA	DUS	CTA	DUS	CTA	DUS	CTA	DUS	CTA
STENOSIS	76	97	67	95	87	99,8	80	97	80	97
MOPRPHOLOGY	83,9	100	86,9	100	80,9	100	82	100	82	100
ULCERS	88,7	100	87,5	100	88,9	100	65	100	65	100

Table 5. Accuracy, sensitivity, specificity, positive prognostic value and negative prognostic value characteristics of CTA and US accordingly in Anzidei et.al study.

The fourth study, conducted by Ajduk et al. (47), involved the examination of 50 carotid artery plaques extracted post-carotid endarterectomy, comprising 36 from male patients and 14 from female patients. Among these patients, 20 (40%) had symptomatic plaques, while 30 (60%) were asymptomatic. All individuals underwent both Doppler ultrasonography (DUS) and multidetector row computed tomography angiography (MDCTA). The average degree of carotid artery stenosis measured by MDCT was 82.6%, whereas by DUS, it was 80.4%. Analysis of the ROC curve revealed MDCT's sensitivity as 100% and specificity as 70.4% in identifying haemorrhage within atherosclerotic plaques, while DUS exhibited a sensitivity of 100% and specificity of 48.1%. Further scrutiny indicated a sensitivity of 21.7% and specificity of 89.8% for plaques categorized as duplex type 1, and a sensitivity of 78.2% and specificity of 59.2% for type 2 plaques. Only when hypoechogenic and mixed hypo-hyperechogenic plaques were amalgamated did duplex Doppler achieve a sensitivity comparable to MDCT, albeit at the expense of specificity (48.1%).

Conclusion

Across the four studies there was good agreement between the two examinations in assessing plaque type but poor agreement in detecting plaque ulceration. CTA was deemed the most accurate technique for evaluating carotid artery stenosis, plaque morphology, and plaque ulceration detection. CTA also showed a notably high sensitivity and a moderate level of specificity in detecting haemorrhage within atherosclerotic carotid plaques, while duplex Doppler exhibited lower sensitivity but a moderate-to-high level of specificity, particularly for plaques classified as duplex type 1, which are deemed more vulnerable.

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Appendix

Supplementary Table II. Search Strategy

Comparative studies on humans, English Studies, RCT and Observational studies Subject Area: Medicine

Time Period: 2003-2023 (last 20 years)

Exclusion criteria: 1. Case reports 2. Case Series 3. Studies reporting solely on one or the other method of imaging 4. Non-comparable studies 5. Reviews

PUBMED (HITS: 1674)	**Search:** ((((((((((((((((((((intraplaque hemorrhage) OR (IPH)) OR (lipid-rich necrotic core)) OR (lipid rich necrotic core)) OR (LRNC))) OR (thin-fibrous cap)) OR (thin fibrous cap)) OR (TFC)) OR (plaque ulcer)) OR (plaque thrombus)) OR (carotid plaque vulnerability)) OR (intraplaque hemorrhage[MeSH Terms])) OR (IPH[MeSH Terms])) OR (lipid rich necrotic core[MeSH Terms])) OR (LRNC[MeSH Terms])) OR (fibrous cap[MeSH Terms])) OR (thin fibrous cap[MeSH Terms])) OR (TFC[MeSH Terms])) OR (plaque thrombus[MeSH Terms])) OR (carotid plaque vulnerability[MeSH Terms])) AND ((((((((((((((((((computed tomography angiography) OR (ultrasound)) OR (DUS)) OR (TUS)) OR (duplex ultrasound)) OR (triplex ultrasound)) OR (color flow ultrasound)) OR (colour flow ultrasound)) OR (CTA)) OR (computer tomography angiography[MeSH Terms])) OR (ultrasound[MeSH Terms])) OR (DUS[MeSH Terms])) OR (TUS[MeSH Terms])) OR (triplex ultrasound[MeSH Terms])) OR (duplex ultrasound[MeSH Terms])) OR (ultrasound[MeSH Terms])) OR (colour flow ultrasound[MeSH Terms])) OR (color flow ultrasound[MeSH Terms])) OR (CTA[MeSH Terms]))) AND ((((((((((stroke) OR (TIA)) OR

	(transient ischemic attack)) OR (amaurosis fugax)) OR (carotid artery disease)) OR (TIA[MeSH Terms])) OR (stroke[MeSH Terms])) OR (transient ischemic attack[MeSH Terms])) OR (amaurosis fugax[MeSH Terms])) OR (carotid artery disease[MeSH Terms])) **Filters:** from 2003 - 2023
SCOPUS (HITS: 2491)	ALL (("stroke" OR "TIA" OR "transient ischemic attack" OR "amaurosis fugax" OR "carotid artery disease") AND ("computed tomography angiography" OR "duplex ultrasound" OR "triplex ultrasound" OR "color-flow ultrasound" OR "ultrasound" OR "US" OR "CT A") AND ("intraplaque hemorrhage" OR "IPH" OR "lipid-rich necrotic core" OR "LRNC" OR "thin-fibrous cap" OR "thin fibrous cap" OR "TFC" OR "plaque ulcer" OR "plaque thrombus" OR "carotid plaque vulnerability")) AND (LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-

	TO (PUBYEAR , 2010) OR LIMIT- TO (PUBYEAR , 2009) OR LIMIT- TO (PUBYEAR , 2008) OR LIMIT- TO (PUBYEAR , 2007) OR LIMIT- TO (PUBYEAR , 2006) OR LIMIT- TO (PUBYEAR , 2005) OR LIMIT- TO (PUBYEAR , 2004) OR LIMIT- TO (PUBYEAR , 2003) OR LIMIT- TO (PUBYEAR , 2002) OR LIMIT- TO (PUBYEAR , 2001) OR LIMIT- TO (PUBYEAR , 2000)) AND (LIMIT- TO (SUBJAREA , "MEDI")) AND (LIMIT- TO (PUBSTAGE , "final")) AND (LIMIT- TO (LANGUAGE , "English")) AND EXCLUD E (PUBYEAR , 2002) OR EXCLUDE (PUBYE AR , 2001) OR EXCLUDE (PUBYEAR , 2000))

CENTRAL (HITS: 8)	#1 stroke with Cochrane Library publication date Between Jan 2003 and Jan 2023 #2 [mh "stroke"] with Cochrane Library publication date Between Jan 2003 and Jan 2023 #3 TIA with Cochrane Library publication date Between Jan 2003 and Jan 2023 #4 [mh "TIA"] #5 transient ischemic attack with Cochrane Library publication date Between Jan 2003 and Jan 2023 #6 [mh "transient ischemic attack"] with Cochrane Library publication date Between Jan 2003 and Jan 2023 #7 amaurosis fugax with Cochrane Library publication date Between Jan 2003 and Jan 2023 #8 [mh "amaurosis fugax"] with Cochrane Library publication date Between Jan 2003 and Jan 2023 #9 carotid artery disease with Cochrane Library publication date Between Jan 2003 and Jan 2023 #10 [mh "carotid artery disease"] with Cochrane Library publication date Between Jan 2003 and Jan 2023 #11 computed tomography angiography with Cochrane Library publication date Between Jan 2003 and Jan 2023 #12 [mh "computed tomography angiography"] with Cochrane Library publication date Between Jan 2003 and Jan 2023 #13 duplex ultrasound with Cochrane Library publication date Between Jan 2003 and Jan 2023 #14 triplex ultrasound with Cochrane Library publication date Between Jan 2003 and Jan 2023

	#15 [mh "color flow ultrasound"] 0 #16 color flow ultrasound with Cochrane Library publication date Between Jan 2003 and Jan 2023 #17 CTA with Cochrane Library publication date Between Jan 2003 and Jan 2023 #18 [mh "duplex ultrasound"] 0 #19 [mh "triplex ultrasound"] 0 #20 intraplaque hemorrhage with Cochrane Library publication date Between Jan 2003 and Jan 2023 #21 [mh "intraplaque hemorrhage"] #22 IPH with Cochrane Library publication date Between Jan 2003 and Jan 2023 #23 [mh "IPH"] #24 lipid-rich necrotic core with Cochrane Library publication date Between Jan 2003 and Jan 2023 #25 [mh "lipid-rich necrotic core"] #26 LRNC with Cochrane Library publication date Between Jan 2003 and Jan 2023 #27 thin-fibrous cap with Cochrane Library publication date Between Jan 2003 and Jan 2023 #28 [mh "thin-fibrous cap"] #29 TFC with Cochrane Library publication date Between Jan 2003 and Jan 2023 #30 [mh "TFC"] #31 plaque ulcer with Cochrane Library publication date Between Jan 2003 and Jan 2023 #32 plaque thrombus with Cochrane Library publication date Between Jan 2003 and Jan 2023 #33 [mh "plaque thrombus"]

	#34 carotid plaque vulnerability with Cochrane Library publication date Between Jan 2003 and Jan 2023 #35 [mh "carotid plaque vulnerability"] #36 {OR #1-#10} #37 {OR #11-#19} #38 {OR #20-#35} #39 {AND #36-#38}