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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

"RISK STRATIFICATION FOR STROKE AND MYOCARDIAL INFARCTION IN PATIENTS WITH ASYMPTOMATIC CAROTID ARTERY STENOSIS"

υπό

ΣΤΥΛΙΑΝΟΥ-ΧΡΥΣΟΒΑΛΑΝΤΗ ΔΑΙΟΥ
ΕΙΔΙΚΕΥΟΜΕΝΟΥ ΚΑΡΔΙΟΛΟΓΙΑΣ

Υπεβλήθη για την εκπλήρωση μέρους των απαιτήσεων για την απόκτηση του Μεταπτυχιακού Διπλώματος Ειδίκευσης "Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων"

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Αναπληρωματικό Μέλος:

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Τίτλος Εργασίας στα Ελληνικά:

“Διαστρωμάτωση κινδύνου αγγειακού εγκεφαλικού επεισοδίου και εμφράγματος του μυοκαρδίου σε ασθενείς με ασυμπτωματική καρωτιδική νόσο”

ΕΥΧΑΡΙΣΤΙΕΣ

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ABSTRACT

Background: Atherosclerotic cardiovascular disease includes cerebrovascular disease, mainly ischemic stroke, and ischemic heart disease, the world's primary causes of death globally. Carotid artery disease is associated with increased risk of cardiovascular and cerebrovascular events, mainly myocardial infarction (MI) and stroke. Several clinical and imaging features play a significant role in stratifying the patients with high risk of MI and stroke to provide the best possible medical treatment or intervention such as carotid endarterectomy or stenting.

Objective: To summarize and stratify the risk of stroke and MI in patients with asymptomatic carotid artery stenosis (ACAST).

Methods: We performed a structured search of the PubMed database for peer-reviewed research of the literature between 1981 and 2020 regarding the ACAST and the risk of stroke and MI.

Results: We analyzed data regarding ACAST patients' identification with a high risk of stroke and MI. The available studies used different methods to evaluate these outcomes, and the results of different studies are rather conflicting as a result of different study designs, combinations methods tested, small study samples, and patient population heterogeneity.

Conclusion: To sum up, recognizing the patients with ACAST at a high risk of stroke and MI remains a major clinical challenge. Several clinical, anatomical, and imaging parameters were associated in this setting. Large cohort studies are needed to elucidate further the high-risk features associated with a higher risk of stroke and MI in patients with ACAST.

Keywords: Carotid artery disease, Asymptomatic carotid artery stenosis, stroke myocardial infarction, risk stratification,

ΠΕΡΙΛΗΨΗ (ΣΤΑ ΕΛΛΗΝΙΚΑ)

Εισαγωγή: Η αθηρωματική καρδιακή νόσος περιλαμβάνει την αγγειακή εγκεφαλική νόσο, κυρίως το ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο, και την ισχαιμική καρδιακή νόσο που αποτελούν τις κυρίαρχες αιτίες θανάτου παγκοσμίως. Η στένωση καρωτίδων σχετίζεται με αυξημένο κίνδυνο εμφράγματος του μυοκαρδίου και αγγειακού εγκεφαλικού επεισοδίου. Πληθώρα κλινικών και απεικονιστικών χαρακτηριστικών διαδραματίζουν σημαντικό ρόλο στη διαστρωμάτωση κινδύνου των ασθενών με ασυμπτωματική καρωτιδική νόσο, έχοντας ως στόχο την καλύτερη δυνατή θεραπεία ή παρέμβαση όπως η καρωτιδική ενδαρτηρεκτομή ή η τοποθέτηση stent.
Αντικείμενο: Η σύνοψη και διαστρωμάτωση του κινδύνου αγγειακού εγκεφαλικού επεισοδίου και εμφράγματος του μυοκαρδίου σε ασθενείς με ασυμπτωματική καρωτιδική νόσο.
Μέθοδοι: Πραγματοποιήθηκε δομημένη αναζήτηση της βάσης δεδομένων PubMed για αναζήτηση βιβλιογραφίας από το 1981 έως το 2020 σχετικά με την ασυμπτωματική καρωτιδική νόσο και τον κίνδυνο αγγειακού εγκεφαλικού επεισοδίου και εμφράγματος του μυοκαρδίου.
Αποτελέσματα: Αναλύθηκαν τα δεδομένα που συλλέχθηκαν. Οι διαθέσιμες μελέτες χρησιμοποίησαν διαφορετικές μεθόδους και τα αποτελέσματα αυτών είναι αντικρουόμενα λόγω του διαφορετικού σχεδιασμού της κάθε μελέτης, του μικρού αριθμού και της ετερογένειας του πληθυσμού.
Συμπέρασμα: Συνοψίζοντας, η αναγνώριση των ασθενών με ασυμπτωματική καρωτιδική νόσο ως υψηλού κινδύνου αποτελεί μείζονα κλινική πρόκληση. Περαιτέρω μελέτες απαιτούνται για την εξακρίβωση των κλινικών στοιχείων που σχετίζουν τον υψηλό κίνδυνο εμφράγματος και εγκεφαλικού επεισοδίου σε ασθενείς με ασυμπτωματική καρωτιδική νόσο.

Λέξεις – Κλειδιά: Νόσος των καρωτίδων, Ασυμπτωματική καρωτιδική νόσος, αγγειακό εγκεφαλικό επεισόδιο, έμφραγμα του μυοκαρδίου, διαστρωμάτωση κινδύνου

Table of Contents

Introduction

GLOBAL BURDEN OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Atherosclerosis constitutes an inflammatory arterial disease that includes metabolic and lipid alterations and belongs to cardiovascular disease's major causes (CVD). Atherosclerotic cardiovascular disease (ACD) involves two significant pathologic entities, the cerebrovascular disease (mainly ischemic stroke), and the ischemic heart disease (IHD). They represent the world's third and first causes of death, respectively, with a vast number of deaths each year [1]. Atherosclerotic aortic disease and peripheral vascular disease belong to the other less prevailing complications of atherosclerosis. Although the mortality rate due to ACD was increased significantly since 1990, the cardiovascular mortality rates/100.000 individuals adjusted for age decreased from 1990 to 2010 globally. In the aforementioned period, the mortality rates seem to differ by GDP. As far as ischemic stroke is concerned, a reduction was reported in 2010 for countries with higher-income and minor differences in lower-income countries with higher mortality rates. Concerning IHD, higher-income countries demonstrated higher rates than lower-income ones, while in 2010, a reduction in mortality rates in countries with high-income ($p=0.02$) was observed [2]. Although the ACD mortality rate is decreasing globally, the absolute number is increasing.

The pathologic course that leads to atherosclerosis is quite complicated. It is characterized by increased levels of low-density lipoprotein cholesterol that modify the permeability and progressively affect the arterial walls [3]. That may induce an inflammatory response, where circulating monocytes adhere to endothelial cells, which in turn express adhesion molecules and selectin, thus promoting the monocytes' migration to the subendothelial space (Figure 2). Subsequently, monocytes are transformed into foamy macrophages that are rich in free fatty acids, esters, and cholesterols, penetrate the arterial walls and lead to a pathological intimal thickening lesion converting the lipid pool to a necrotic core. Besides, the atherosclerotic plaque containing foamy macrophages is vulnerable to plaque rupture or fissure leading to fatal thrombotic events [4]. This review will:

1) Briefly summarize the global, national burden and epidemiology of cardiovascular diseases
2) Analyze briefly the definition and etiology of myocardial infarction (MI) and stroke

3) Summarize the way of carotid artery stenosis measurement and the evidence and recommendations for carotid intervention in asymptomatic patients
4) Stratify the risk of MI and stroke based on the critical appraisal of the high-risk features in asymptomatic patients

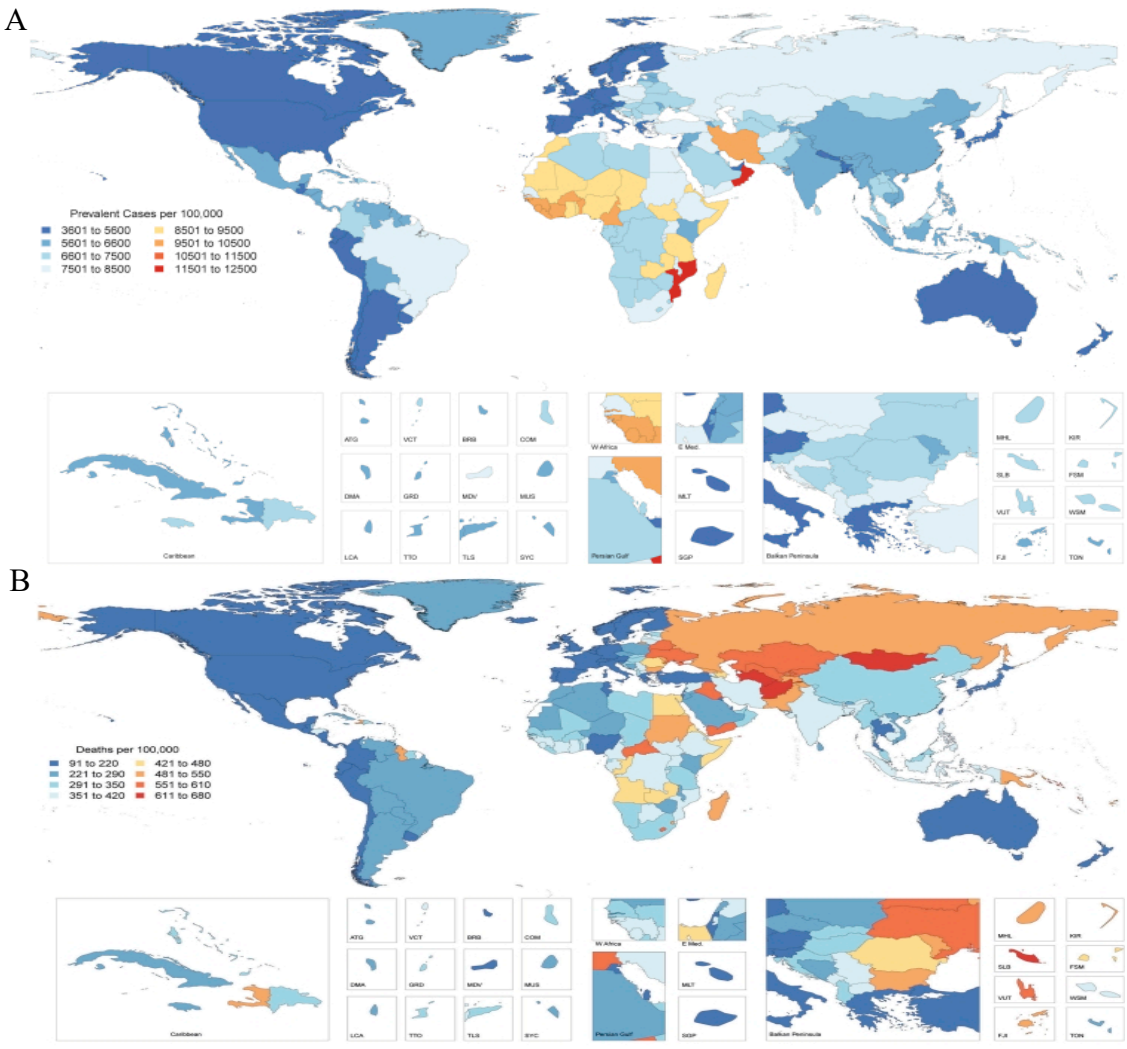


Figure.1. Cartogram A shows Age-standardized prevalence for cardiovascular disease and cartogram B shows age-standardized death rate for cardiovascular disease

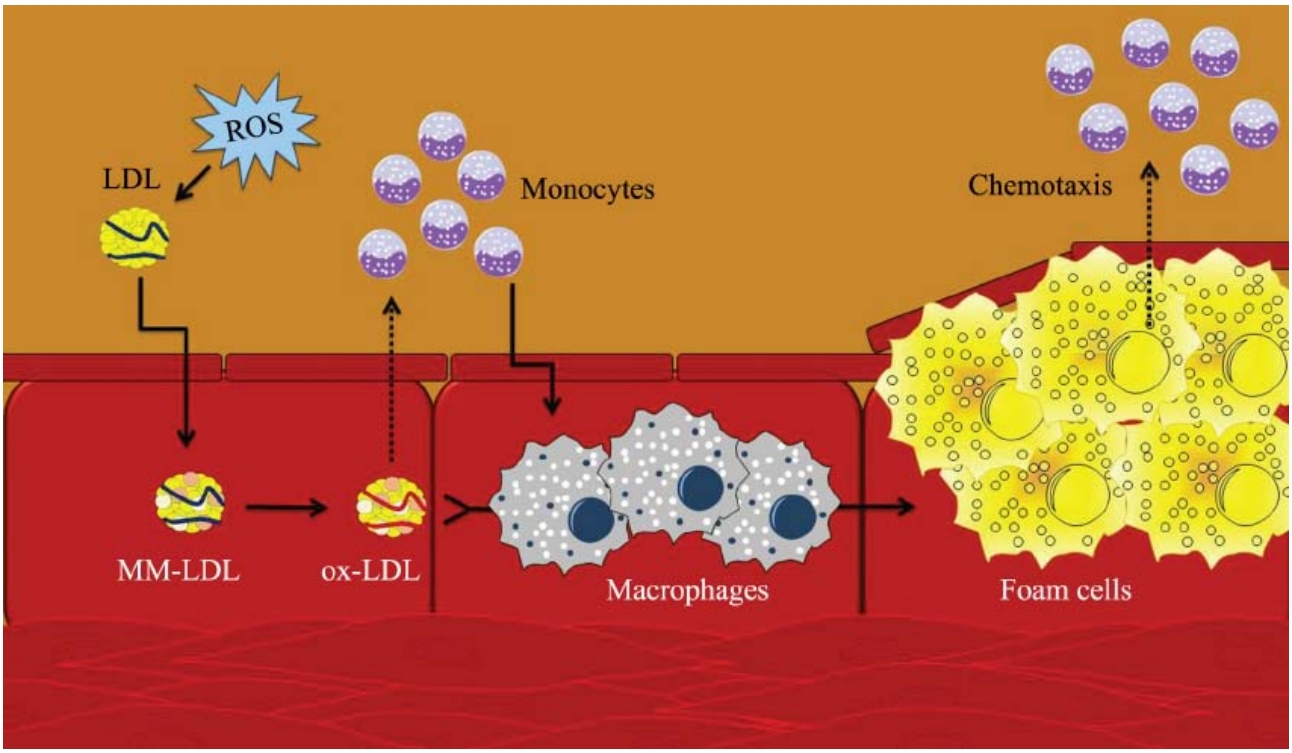


Figure 2. Process of atherosclerotic plaque formation

GLOBAL AND NATIONAL EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE AND MYOCARDIAL INFARCTION

CVD is the leading cause of morbidity and mortality worldwide, recording approximately 3.9 million deaths/year (45% of the total deaths), while research focuses on prevention as it is more beneficial than the treatment of its complications. Also, an essential public health issue remains the identification of asymptomatic CVD in the subclinical phase with a significant economic impact [1]. It is responsible for approximately 3.9 million deaths/year (45% of the total deaths) with more than 85 million people with CVD in Europe in 2015 and nearly 11 million new cases each year [5]. IHD is the first cause of death globally and separately, with MI, the most acute presentation, being the number one cause of death worldwide. 7.29 million MIs and 110.55 million cases of IHD were reported in 2015. The prevailing cases of IHD were recorded after 40 years, and the prevalence of the disease increased in the older age groups. Approximately 10.88 million cases of IHD were reported, with the higher number of cases in the age category between 75 to 79 years with 11,203 cases/100.000 (95% Uncertainty Interval [UI]: 9610 to 13178 cases per 100.000) compared to 40 to 44 with 290 cases/100.000 (95% UI: 255 to 328 cases per 100.000). As far as regions are concerned, Eastern Europe demonstrated the highest IHD prevalence adjusted for age in 2015 with 4.140 cases/100.000 (95% UI: 3811-4499 cases/100.000) with Central Asia and Central Europe following. In 2015, 8.92 million deaths due to IHD were recorded (95% UI: 8.75-9.12 million

deaths), making IHD the primary cause of death globally [6]. MI seems to remain a significant cause of mortality in women, even though the IHD develops 7-10 years later on average in women compared to men. Interestingly, acute coronary syndrome seems to occur more frequently (3 to 4 times) in men than in women younger than 60 years of age, but older than 75, women represent a significant part of the patients [7]. Also, women present more frequently with atypical symptoms and later than in men [8,9]. Thus, it is crucial to maintain alertness for MI in women with the potential symptoms of ischemia.

CVD is also responsible for 23 percent of the total disability-adjusted life years (DALYs) lost in Europe and estimated to cost the European Union approximately 210 billion per year [10]. Greece, as a European Union member, had one of the lower CVD risk rates globally, due to the healthy Mediterranean diet and increased physical activity [11]. Recently, studies reported an increase in CVD incidence in the last decades that is mainly associated with changes in modifiable risk factors responsible for the majority of the CVD events during the last years [12-16]. As far as MI risk factors are concerned, the INTERHEART study assessed the prevalence of nine potentially modifiable risk factors. They reported that they were strongly related to acute MI in 52 countries such as smoking, psychosocial stressors, dyslipidemia, DM, hypertension, obesity, a diet low in fruits and vegetables, alcohol consumption, and physical inactivity.

According to the ATTICA study in Greece, during a follow-up of 10 years of 3,042 individuals, 5.7% of men and 2.0% of women died with an overall 10-year all-cause mortality rate of 3.8%. CVD was accounted as the leading cause of death with a 51.1%. Interestingly 42.4 patients died from IHD, and 4.4% died from stroke. The main CVD risk factors that were highlighted were smoking, physical inactivity, obesity, hypertension, hypercholesterolemia, and DM (Figure 3) [17].

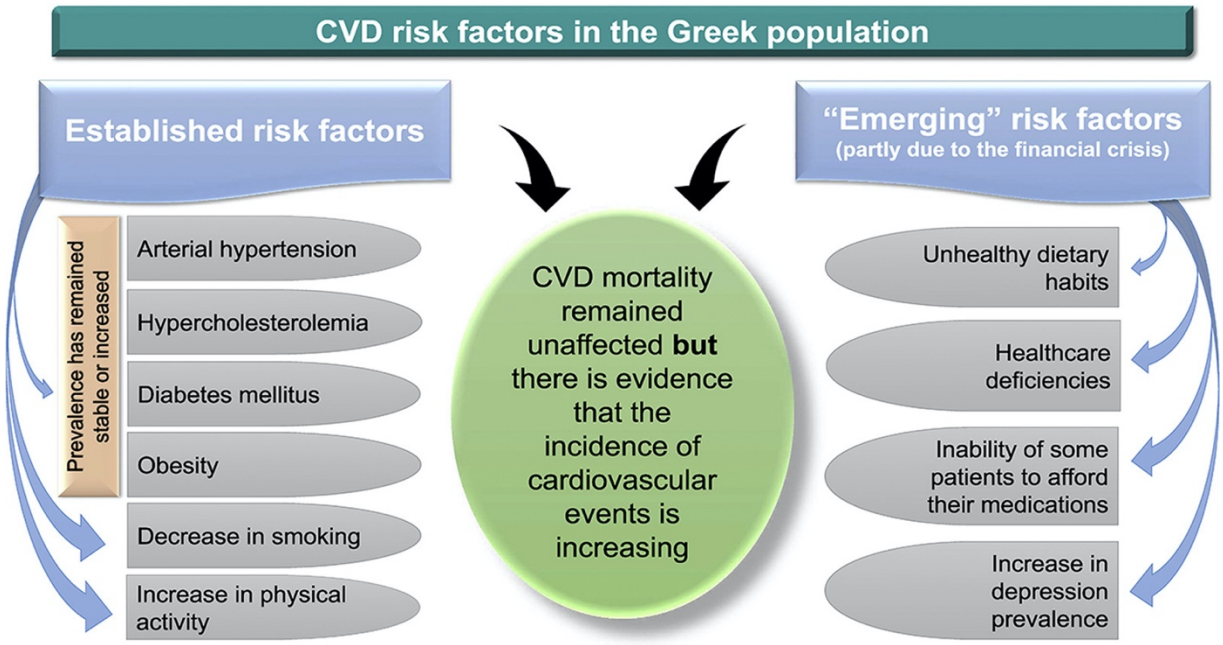


Figure 3. Cardiovascular Disease risk factors in Greek population

After establishing more sensitive cardiac biomarkers, the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) joined forces to define MI based on a clinical and biochemical perspective. They reported that myocardial injury identified with abnormal biomarkers during acute myocardial ischemia should be designated as MI [18]. Furthermore, the development of more sensitive biomarkers of myocardial injury further revised the definition itself, especially in patients who underwent cardiac surgery or coronary procedures. The third universal definition of MI was introduced in 2012 by ACC/ESC/AHA/WHF Taskforce [19]. Studies also demonstrated that myocardial injury defined as elevated cardiac troponin value is frequently confronted clinically with an unfavorable prognosis [20,21]. Even though myocardial injury is a prerequisite for MI, it is a pathologic entity itself. Mainly, to diagnose MI, more criteria in addition to biomarkers are required, as myocardial injury of non-ischemic etiology may arise due to cardiac and non-cardiac conditions (myocarditis, renal failure) [22]. Thus, the clinicians must discriminate if the patients suffered from a myocardial injury of non-ischemic etiology or one of the MI subtypes. If there is no evidence of myocardial ischemia, the diagnosis of myocardial injury is made. Currently, the fourth universal definition of MI is adhered by the clinicians (Table 1).

Myocardial Infarction Type	Characteristics
Type 1	Myocardial infarction due to either rupture of a plaque, ulceration, fissuring or erosion with a resultant obstruction of myocardial blood flow and acute myocyte necrosis. The majority of the patients with ST-segment elevation MI (STEMI) and many with non-ST-segment elevation of MI (NSTEMI) belong to this category
Type 2	Ischemic myocardial necrosis due to a marked increase in myocardial oxygen demand or a marked decrease in myocardial blood flow. That most commonly occurs without a thrombosis of the coronary arteries or a plaque rupture
Type 3	Sudden cardiac death related to coronary arterial thrombosis
Type 4	Myocardial Infarction associated with PCI: 4a) Myocardial Infarction associated with PCI 4b) Stent thrombosis associated with PCI 4c) Restenosis associated with PCI
Type 5	Myocardial Infarction associated with CABG

Table 1. Definition of MI according to the fourth universal definition

GLOBAL EPIDEMIOLOGY OF STROKE

Globally, ischemic, hemorrhagic, and other strokes belong to the third and second causes of CVD DALYs and the 13th and 4th largest in general. The DALY of ischemic stroke comes first, followed by hemorrhagic and other strokes in North America with high income and Central, Eastern Europe (Figure 5, Figure 6). In 2015, there were recorded 5.39 million acute first-time ischemic strokes (95% uncertainty interval: 5.02-5.73 million), approximately 3.58 million acute first-time hemorrhagic and other types of strokes (95% uncertainty interval: 3.34-3.82 million), and overall 42.43 million of CVD cases (95% UI: 42.07 to 42.77). The region with the highest stroke prevalence was Oceania, followed by Eastern Europe, Central and Southeast Asia. In contrast, the lowest prevalence of stroke was reported in Central Latin America. The prevalence of ischemic stroke adjusted for age was highest than hemorrhagic stroke in most regions. Stroke is the second commonest cause of death in Europe, causing 1.1 million deaths annually [1]. About 1.4 million

strokes occur each year, in a population of 715 million European inhabitants. It is considered a significant financial burden of death on the healthcare system with enormous financial costs exceeding 38 billion euros [6].

According to the World Health Organisation (WHO), stroke is a focal, frequently global deprivation of neurological function with a duration of more than 24 hours or leading to death, with a vascular etiology. Transient ischemic attack (TIA) is defined similarly, lasting less than 24 hours [23]. Several imaging examinations, specifically magnetic resonance imaging (MRI), have shown that many individuals suffering from TIA have acute infarction evidence and proposed a revision of the worldwide known definition.

At first, the American Heart Association (AHA) defined TIA as a short event of neurological disturbance resulting from focal temporary cerebral ischemia, which is not related to acute cerebral infarction. Furthermore, ischemic stroke is characterized as neurologic impairment triggered by focal cerebral or retinal infarction. Infarction definition describes a retinal or brain cell death, due to ischemia, based on neuroimaging, neuropathological and clinical evidence of permanent injury. Silent infarction is characterized as neuropathological or imaging evidence of retinal/cerebral infarction without acute neurological dysfunction [24]. It can be categorized as hemorrhagic, ischemic, or subarachnoid. According to Acute Stroke Treatment (TOAST) classification (Figure 4), ischemic stroke can be subdivided further into small-vessel occlusion, large-artery atherosclerosis, cardioembolism, a stroke of undetermined etiology, and stoke of other undetermined etiology [25].

The primary cause of ischemic strokes is mainly due to an embolic or a thrombotic episode that decreases the brain’s blood flow. In a thrombotic event, the brain’s blood flow is obstructed due to dysfunction intravascularly, usually after an arterial dissection, atherosclerotic disease, inflammatory condition, or fibromuscular dysplasia. Contrarily, in an embolic event, debris from elsewhere in the body blocks blood flow through the affected vessel.

Ischemic stroke has an heterogeneous pathogenesis. Cerebral infarction can be categorized into large vessel atherothrombotic, cardioembolic, and lacunar. Although several other standard criteria exist, a gold standard does not exist for rendering any of these diagnoses. At first, atrial fibrillation belongs to the most common cause of cardiac thrombus that can cause embolism to the brain is atrial fibrillation. Large and medium-sized arteries will have evidence of atherosclerosis, most commonly in older patients. However, an infarct is rarely due to extensive vessel atherosclerosis unless it is possible to cause a 50 percent reduction in the lumen of the artery that supplies the zone where the infarct is located. Lacunar stroke that is mainly attributed to

lipohyalinosis, is a small infarct distributed along the penetrating vessel. Perhaps 1/3 of the patients suffer from a stroke of undetermined etiology due to a lack of evidence for any cause or several potential causes [26]. The leading causes of carotid territory and ischemic stroke are thromboembolism from the small vessel intracranial disease (25 percent), middle cerebral artery or internal carotid artery (25 %), cardiac embolism (20 percent), other specified rarer causes (5%), and various unknown causes despite of investigation (25 percent) [27]. The 10-15 percent of all strokes follow thromboembolism from a previous ACAST greater than 50% [28].

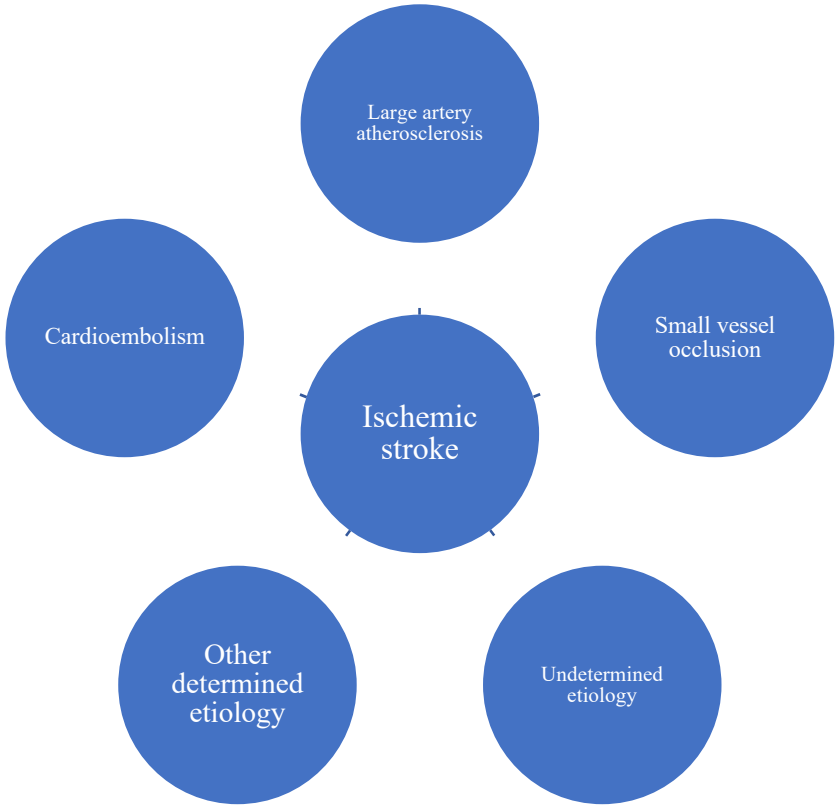


Figure 4. TOAST classification of ischemic stroke subtypes

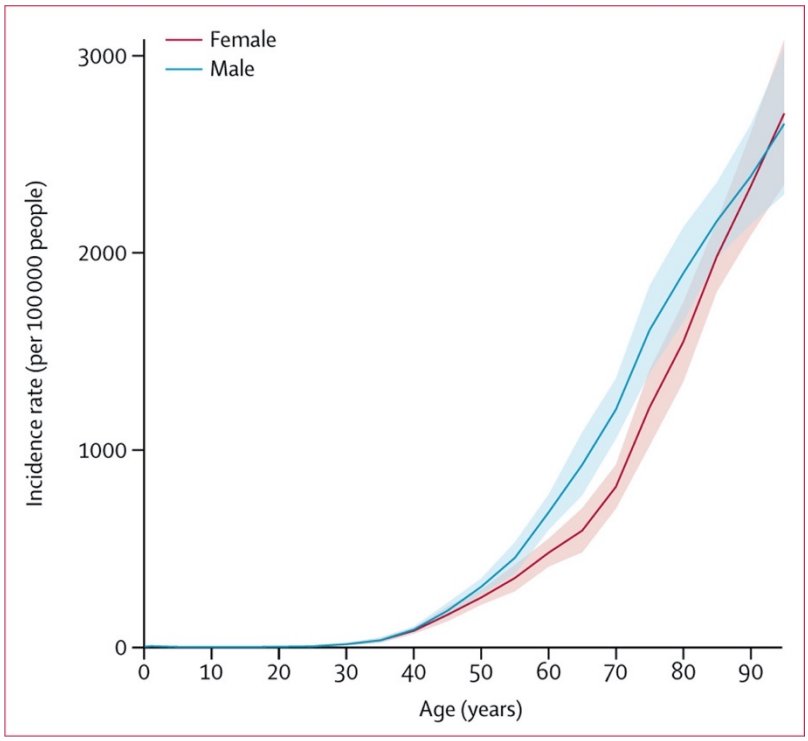


Figure 5. Global Incidence of stroke by age and sex, 2016

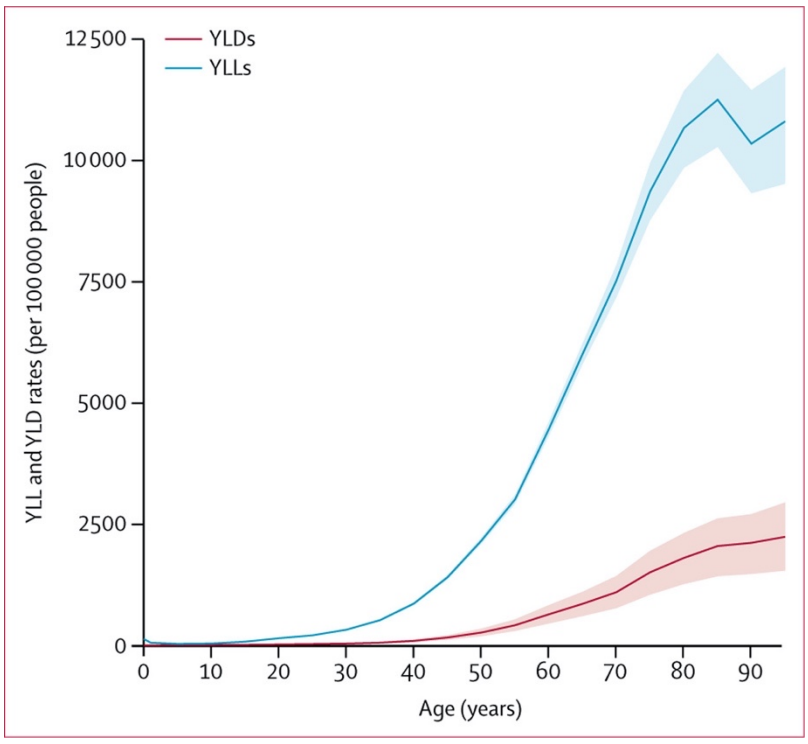


Figure 6. Age-standardised rates of years of life lost (YLLs) and years lived with disability (YLDs) due to stroke for both sexes, by age, 2016

Asymptomatic Carotid Artery Stenosis and Screening

ACAST is confirmed by the luminal carotid artery narrowing in the absence of focal neurological deficit or previous stroke in the last 6 months [29]. The prevalence of ACAST in 23,706 individuals with an average age of 61 years reported in four population-based cohort studies (Malmö Diet and Cancer Study, Tromsø study, Cardiovascular Health Study, and the Carotid Atherosclerosis Progression Study) was 2% for the moderate stenosis >50% and 0.5% for the severe stenosis >70% (Figure 7) [30]. Thus, the prevalence of ACAST seems to increase with age and appears to be higher in men than women (Figure 8). Furthermore, the disease's prevalence is increased in individuals with several other forms of ACD, such as abdominal aortic aneurysm and peripheral artery disease. ACAST is associated with lower-limb peripheral artery disease, 20-43% of patients with a stenosis of >50% and 12-13.7% with a stenosis of >70% [31,32]. Almost 10% of the patients had bilateral disease, while 5% had a bilateral carotid stenosis >70%. A meta-analysis by Ahmet et al. confirmed further these results, reporting a prevalence of 25-28% for stenosis >50% and 14% for >70% [33]. Similarly, patients with abdominal aortic aneurysm had a significantly high prevalence of carotid stenosis [34].

Medical treatment advancement competes with any potential benefit in surgical and radiological interventions in individuals with ACAST [35]. Marquardt et al. found that the stroke annual rate was 0.34% in 1153 individuals with ACAST with greater than 50% stenosis without a comparison to surgical intervention [36]. Another systematic review in 2009 showed the effects of best medical therapy (BMT) for ACAST by highlighting the falling rates of stroke and the cost-effectiveness of medical intervention [37]. The North American preventative task force announced recommendations about carotid artery screening [38]. The low prevalence and the risks of screening, such as identifying false-positives and risk of strokes associated with angiography, seem to outweigh the potential benefits in the small number of identified patients with carotid artery stenosis. That was also demonstrated by a study that hypothetically estimated that screening of 4348 individuals would prevent a negligible number of strokes after 5 years [39].

However, in patients with higher risk of carotid stenosis, such as those suffering from several risk factors of atherosclerosis or with the presence of carotid bruits, guidelines exist that support screening [40]. A more significant benefit of screening would come if it were performed in a group with an increased prevalence of carotid artery stenosis and a greater risk of stroke. Notably, the BMT seems to be 8 times more cost-effective than surgical intervention in ACAST [41]. Still, there are no risk stratification tools to identify patients with a higher risk of carotid artery stenosis. Also, there are no randomized control trials (RCT) that compare screening to no screening and CVD outcomes and stroke outcomes.

Presently, risk stratification models for CVD use both risk factors that are modifiable and non-modifiable. The most widely used risk score, the Framingham risk score, uses systolic blood pressure, gender-specific variables of age, hypertension treatment, cholesterol, smoking, and diabetes mellitus (DM) status to stratify the risk of CVD mainly in primary care [42]. An alternative risk score, QRISK that also uses a family history of CVD, history, and BMI, is used in the UK [43]. Despite these tools, low- and intermediate-risk groups are characterized by most cardiovascular (CVS) events [44]. The possibility of atherosclerosis is not excluded since there is a lack of common risk factors. Despite the lack of a stratification tool, carotid intima-media thickness (cIMT) can function as a surrogate marker for identifying intermediate-risk individuals who could benefit from BMT regarding preventing CVS events. Multiple studies report that elevated cIMT thickness is associated with early atherosclerosis and atherosclerosis elsewhere in the body [45,46]. Individuals with cIMT higher than 75% compared to average or more significant than 1mm have a considerable risk of CVD, while those with cIMT lower than 50% have a standard wall thickness [47].

Furthermore, a 0.1mm increase in carotid wall thickness is correlated with a 1.15 increase in the relative risk of CVS event [48]. Therefore, cIMT can be used as an additional tool for stratifying patients at risk [49,50]. The executive task force for screening for heart attack prevention and education (SHAPE) recommendation is screening individuals with ACAST between the age of 45 and 75 [51]. The Society of Atherosclerosis Imaging and Prevention recommended that the most appropriate cIMT screening group is the intermediate-risk group of patients [52]. However, cIMT was not incorporated in the traditional risk scores, as the addition of cIMT to the Framingham risk score provided only a small benefit in the prediction of risk, as demonstrated by a meta-analysis by Den Rujiter et al. Although there is a significant association between cIMT and CVS events, studies that incorporated cIMT into the current risk stratification tools provided variegated findings. Further research is required on this field with adjustment for age and standardization of the study techniques to create a place for cIMT on the risk stratification tools to prevent CVS disease and stroke [49].

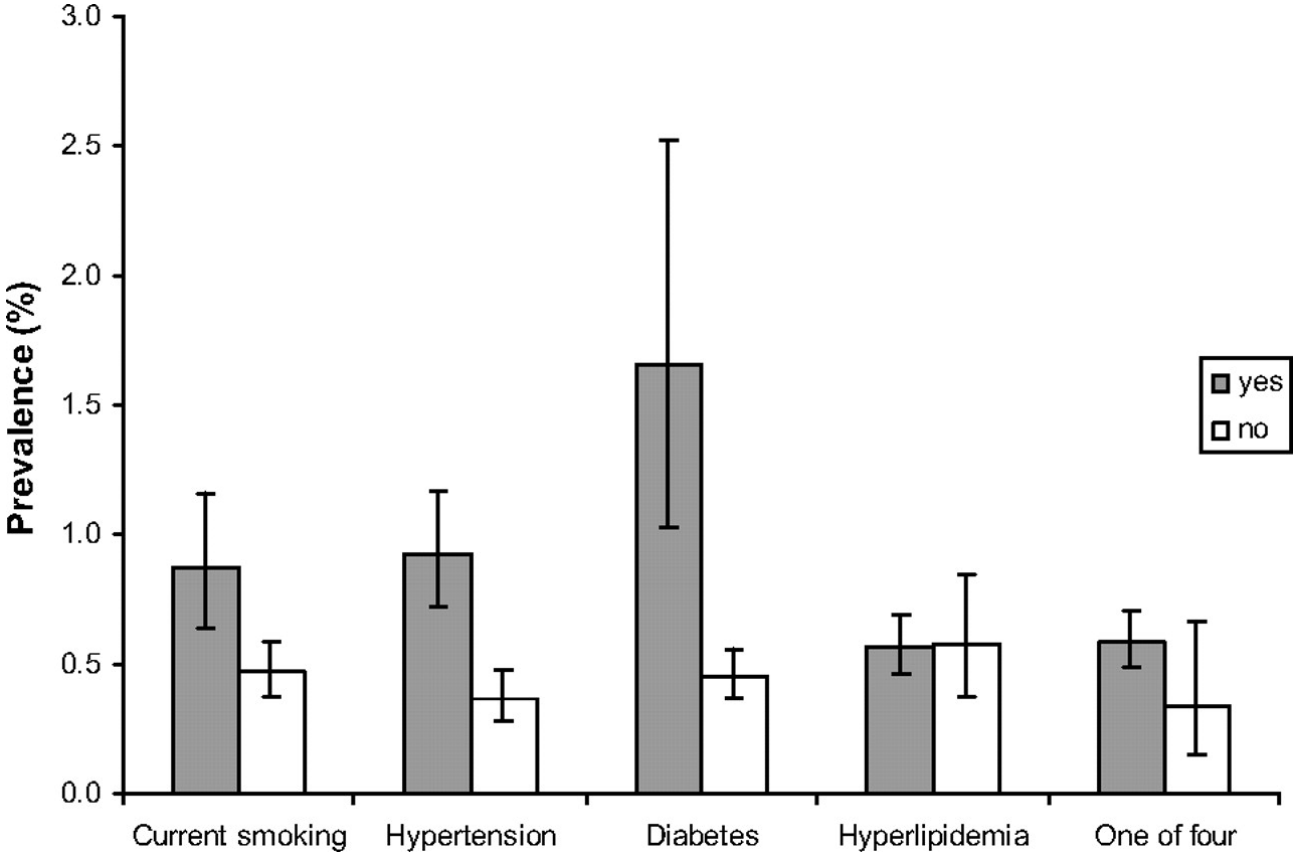


Figure 7. Prevalence of severe stenosis in subgroups

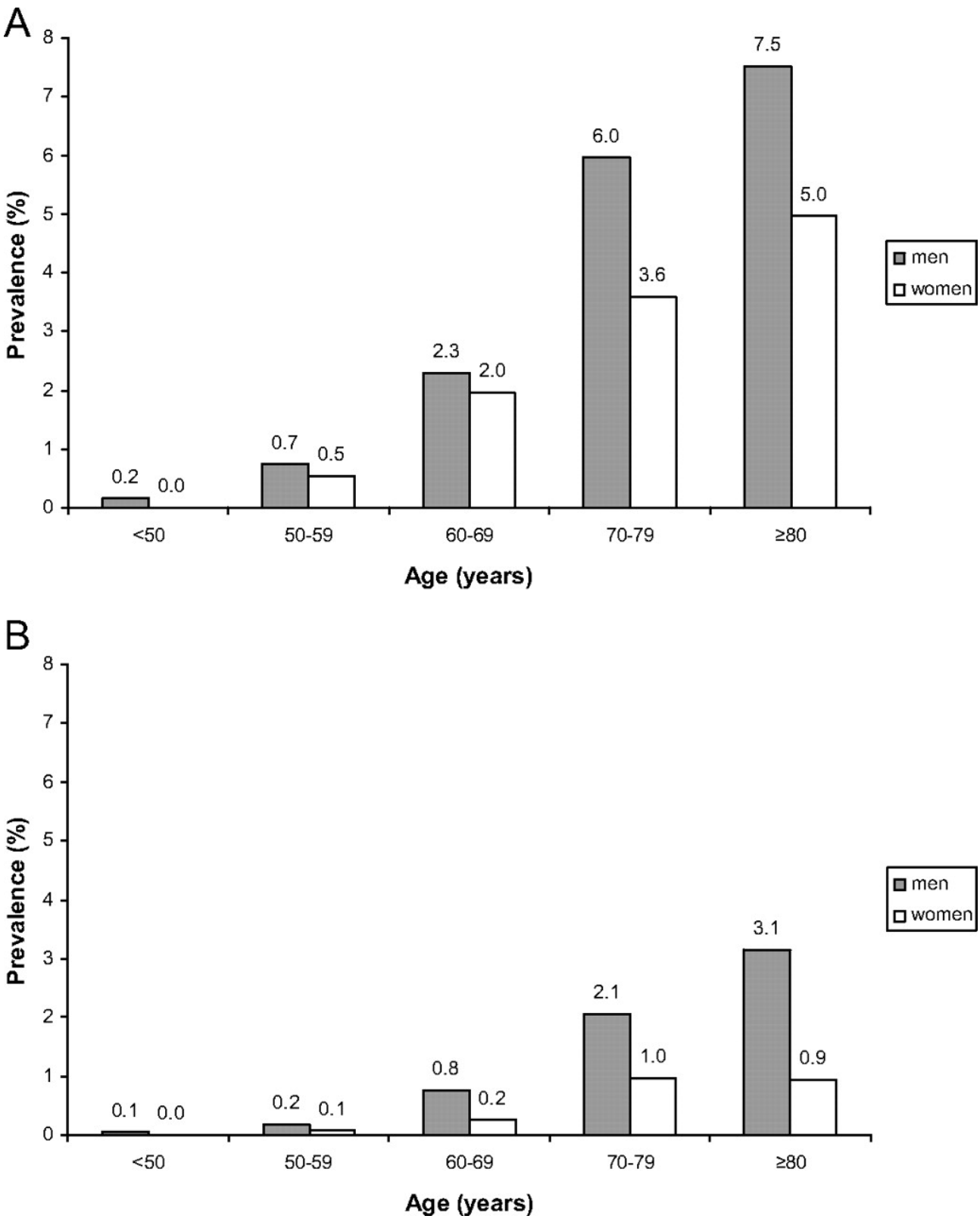


Figure 8. Age- and sex-specific prevalence estimates of moderate (A) and severe ACAST (B) in men and women

Methods of estimating Carotid Artery Stenosis Severity and Imaging Techniques

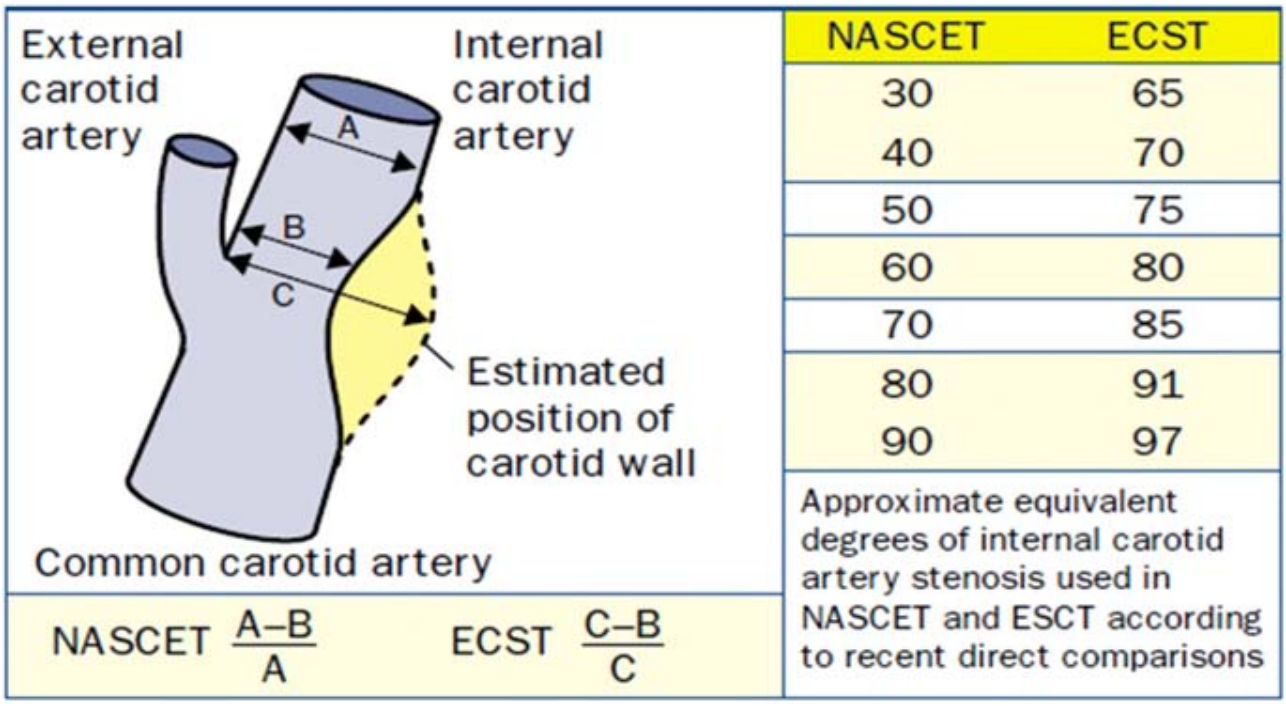
The two significant trials with regards to carotid artery stenosis severity are the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [53] and the European Carotid Surgery Trial (ECST) [54]. Although they use different methods to assess the stenosis severity, both use the same numerator, the lumen's minimum residual diameter. As far as the denominator is concerned, NASCET uses the diameter of a healthy internal carotid artery segment above the stenosis, and the ESCT uses the residual luminal diameter, most frequently, the carotid bulb. Therefore, the outcome is different in each method, promoting further confusion. Practically, a 75% ECST stenosis is equal to 50% NASCET stenosis and 85% ECST stenosis is equivalent to 70% NASCET stenosis (Figure 9) [55]. The dilemma about which measurement is preferable was solved by the ESVS guidelines that adopted NASCET as the choice method. However, in one case, the ECST method provides a significant advantage over NASCET. In individuals with significant volume plaques within the carotid artery bulbs, the NASCET method will not provide a reliable assessment of the stenosis severity. In a similar situation, the NASCET method will provide a stenosis of <50% and the ECST greater than 70%. Therefore, in this situation, individuals with large volume plaques following the ECST measurement of >70% stenosis are candidates for revascularization.

In these two major studies, patients underwent intra-arterial angiography that has now been neglected due to its complications (e.x stroke associated with angiography). In the Asymptomatic Carotid Atherosclerosis Study, half of the strokes were associated with angiography.

The first-line imaging method is most frequently the duplex ultrasound with several advantages. It is characterized by low cost and accessibility, and it uses peak systolic velocity, end-diastolic velocity, and their ratios in the common carotid artery and internal carotid artery to assess the stenosis based on the NASCET method [56]. Other imaging modalities that may be used are computed tomographic angiography and magnetic resonance angiography that can image the supra-aortic trunks, aortic arch, distal internal carotid artery, carotid bifurcation, and the intracranial circulation that is compulsory in patients for carotid artery stenting. Imaging methods requiring the administration of contrast can be used, such a contrast enhanced MRA with higher sensitivity than non-contrast techniques. However, the application of contrast is a substantial disadvantage.

After comparing Duplex ultrasound, magnetic resonance angiography, and computed tomographic angiography in a meta-analysis by Wardlaw et al., they all provided similar results in detecting a

significant internal carotid artery stenoses [57]. However, it was reminded that if duplex ultrasound is the only examination performed before CEA, another operator should perform a second.



NASCET	ECST
30	65
40	70
50	75
60	80
70	85
80	91
90	97

Approximate equivalent degrees of internal carotid artery stenosis used in NASCET and ESCT according to recent direct comparisons

Figure 9. Comparison between the two widely known methods for the estimation carotid artery stenosis. The NASCET trial and the ECST trial.

Methods

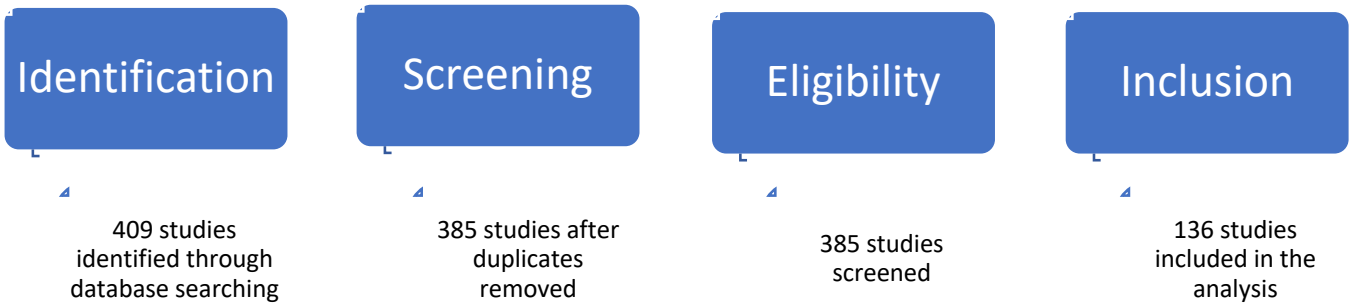
The PubMed database was extracted to identify the papers between 1984 to 2019 regarding asymptomatic carotid artery stenosis and the risk of myocardial infarction and stroke, and data extraction was performed based on updated information. The following terms were searched for the association of future stroke risk and asymptomatic carotid stenosis; “asymptomatic carotid artery stenosis,” “asymptomatic carotid disease,” “asymptomatic carotid stenosis and stroke,” “asymptomatic carotid disease and stroke,” “asymptomatic carotid artery and stroke,” “asymptomatic carotid disease and cerebrovascular accident.” We searched the following terms for the association of the risk of myocardial infarction with asymptomatic carotid stenosis: “asymptomatic carotid disease and myocardial infarction,” “asymptomatic carotid artery stenosis and myocardial ischemia,”

The reference list of the retrieved articles was also analyzed. After a careful evaluation, we selected the most essential and appropriate papers to conduct our review and used it as the central core of our research, the risk of myocardial infarction and stroke in patients with asymptomatic carotid artery stenosis. Therefore, we followed a screening of potential records, 385 articles were reviewed for eligibility, and reference lists were screened. The inclusion criteria for this review were full-length research articles published in peer-reviewed academic journals with no limits set on language, date of publication, or gender. The exclusion criteria included abstracts, conference presentations or posters, letters to the editor or book chapters, unpublished papers, or retrospective designs.

Results

After a thorough investigation of the published literature, 136 articles were selected, which focused on the risk stratification of myocardial infarction and stroke in patients with asymptomatic carotid artery stenosis (Table 1). Several parameters and groups of patients were identified according to several factors, such as clinical, imaging, and laboratory ones. A higher risk of future stroke was identified in ACAST patients with a personal history of CVD, coronary artery disease, as well as in the elderly population and in patients that underwent a coronary artery bypass grafting (CABG). Similarly, an increased risk of MI is met in a specific group of patients. Among the patients with several factors such as inflammation markers, lipid profile, DM, anti-hypertensive and antiplatelet drugs may also play a crucial role. In the following analysis, the optimal medical therapy, the intervention procedures, and the identification of patients at high risk of stroke and MI are thoroughly discussed. The detailed representation of the number of studies selected is provided

in the following graph:



DISCUSSION

Optimal Medical Therapy and Risk Factor Control

Smoking plays a crucial role in stratifying the risk in patients with ACAST. It is associated with an increase in the internal carotid artery stenosis greater than 50% with an odds ratio [OR] of 2.3 (95% confidence interval [CI]: 1.8 to 2.8) and greater than 70% with an OR of 3.0 (95% CI, 2.1 to 4.4) [57] and increase of plaque progression [58]. Furthermore, approximately 5% of male smokers aged >65 have >50% ICA stenosis [59]. Smoking seems to significantly increase the late ischemic stroke with a relative risk increase [RRI] of 1.9 (95% CI 1.7 to 2.2), as demonstrated by a meta-analysis composed of 32 studies [60]. A meta-analysis also demonstrated the benefit of moderate or high physical activity in reducing ischemic stroke by 25% via a beneficial effect in body weight, blood pressure, or other risk factors [61]. In another meta-analysis of 25 studies with 2 million people, it was demonstrated that obesity significantly increases the risk of future stroke with a RRI of 1.64 (95% CI, 1.36 to 1.99) [62].

Antiplatelet Therapy

The risk of bleeding events is the major concern of individuals with ACAST as far as the antiplatelet therapy is concerned, since an actual benefit in reducing the future stroke risk is not provided. First, the Asymptomatic Cervical Bruit study demonstrated no difference in ischemic events or mortality after randomizing patients with stenosis greater than 50% to aspirin (325mg) versus placebo during an average follow-up of 2.3 years [63]. On the contrary, the Asymptomatic Carotid Emboli Study [64] found that antiplatelet therapy was an independent predictor of lower TIA/ ipsilateral stroke rates and any stroke/CVS death in ACAST patients with 70-99% stenosis [65]. Coronary artery disease is present in up to 2/3 of individuals with ACAST [66]. A study of 11,391 patients with ACAST >50% reported a 5-year all-cause mortality of about 63% late cardiac deaths, an average mortality related to cardiac events of about 2.9% each year [67]. Furthermore, Park et al. demonstrated that patients receiving aspirin before the stroke onset did not have a reduced severity of stroke at presentation and improved functional outcomes at the exit from the hospital. That was mostly found in patients with large artery atherosclerotic strokes [68]. CHARISMA study with 7% of ACAST patients with 50-99% stenosis also reported no benefit from dual antiplatelet therapy compared to a single one [69]. In addition, a meta-analysis highlighted the aspirin benefit on serious vascular event with a 12% relative risk reduction, mainly due to a reduction in non-fatal MI (0.18% vs. 0.23%, $p< 0.0001$), without a significant net effect on stroke (0.20% vs. 0.21%, $p= 0.4$) [70]. To sum up, the primary agent used in patients with ACAST is aspirin, followed by clopidogrel in those who are intolerant to aspirin.

Hypertension

Hypertension is associated with an increased risk of carotid artery disease [71]. The therapeutic management of hypertension in individuals with carotid artery stenosis promotes the disease's regression and reduces its progression [72]. The ELSA study that compared lacidipine with atenolol reported a benefit of lacidipine in reducing cIMT progression and atherosclerotic plaque quantity despite a minor effect in blood pressure [73]. Although angiotensin-converting enzyme inhibitors provide a similar effect, calcium-channel blockers decrease cIMT progression more than angiotensin-converting enzyme inhibitors, diuretics or beta-blockers [74]. No RCT investigated the outcomes of antihypertensive treatment on the prevention of stroke in individuals with ACAST. However, a Chinese RCT conducted in patients with hypertension and without a history of MI or stroke demonstrated a reduction in the first stroke event with the combination of enalapril and folic acid compared to enalapril alone. Interestingly, a meta-analysis of 25 RCTs involving hypertensive individuals without a history of vascular disease reported a decrease in late stroke with a reduction of stroke proportional to the reduction of systolic BP [75]. Clinically, blood pressure in patients with ACAST should be kept lower than <140/90 mmHg.

Diabetes Mellitus

DM is also related to a higher risk of ACAST, dyslipidemia, and hypertension [30]. However, studies demonstrating the increase of plaque burden or plaque instability in patients with DM do not exist [76]. Banerjee et al. showed that DM duration is independently associated with the stroke risk when adjusting for risk factors, as it increases 3% per year and triples in diabetes greater than 10 years [77]. Zhang et al. highlighted that there is no effect of tight glycemic control in reducing stroke risk; however, it reduces various complications related to DM [78]. Interestingly, a 60% decrease in CVS events (95% CI, 0.25 to 0.69, $p<0.001$) and CVS deaths (95% CI, 0.19-0.94, $p=0.04$) were shown in patients with type 2 DM that received anti-platelet, statin and antihypertensive treatment [79]. The UKPDS reported 44% relative risk reduction in stroke (95% CI, 11-65, $p= 0.013$) in patients with tight BP control in compared to patients with less controlled BP [80].

Lipid-lowering therapy

An analysis of patients randomized in ACST-1 who were receiving statins found that the 10-year stroke risk/death was 7.6% in individuals following CEA vs.13.4% in BMT. In those who were not receiving statins, the 10-year risk of stroke was 17.9% post CEA vs. 24.1% compared to BMT, highlighting a beneficial effect of statins regarding stroke risk in patients with ACAST [81]. Although there are insufficient data regarding the intensity and the dosage of statin therapy in individuals with ACAST compared to symptomatic ones, research in both categories recommend high-intensity statin treatment with a reduction by 50% of low-density lipoprotein with either rosuvastatin 20-40mg or atorvastatin 40-80mg or with a low-density lipoprotein level of <1.8 mmol/L (70mg/dl) [82-84]. Furthermore, a Cochrane review of 18 RCTs, including 56,934 patients evaluating statins' contribution in CVD, reported reductions in stroke events, revascularization procedures, and all-cause mortality in individuals randomized to statins [85]. Therefore, statins are hugely advocated for the long-term prevention of MI, stroke, and other CVS events in individuals with ACAST.

Carotid Endarterectomy and Carotid Artery Stenting

Although Carotid endarterectomy (CEA) and carotid artery stenting (CAS) constitute an effective abiding prevention approach for stroke in individuals with symptomatic carotid stenosis, it remains

uncertain which is the most appropriate intervention for the long-term prevention of CVS episodes in individuals with ACAST, and if they are more effective than BMT.

CEA can be conducted under local or general anesthesia with or without a shunt use (Figure 10). The stroke and mortality rate did not show a difference between these two patterns in patients following a CEA procedure, as reported by the General Anaesthesia versus Local Anaesthesia for carotid surgery (GALA) trial [86]. However, performing CEA includes risks such as perioperative MI and post-operative hematoma [87]. Individuals with concurrent coronary artery disease and contralateral carotid artery occlusion have an increased risk for CEA [88,89]. Three large RCTs that compare CEA and BMT in ACAST patients include Veterans Affairs (VA) Cooperative Study between 1983-1987, the Asymptomatic Carotid Atherosclerosis Trial (ACAS), and the Asymptomatic Carotid Surgery Trial-1 (ACST-1) [90-92]. An absolute risk reduction in neurological episodes of 12.6% was reported in VA Cooperative study in 444 individuals following CEA compared to BMT with a median follow-up of 4 years ($p<0.01$) without a significant difference in the combined endpoint of stroke and death [90]. ACAS in 1987-1993 that recruited 1,662 patients reported a reduction of 5-year risk of the combined endpoint of ipsilateral stroke and perioperative stroke or death by 53% in patients with CEA compared to BMT (5.1% vs. 11.0%; $p=0.004$) [91]. ACST-1 that included 3,120 patients demonstrated a reduction in relative stroke risk of 4.1% at 5 years ($p=0.0001$) and 4.6% at 10 years (CEA 13.4%, BMT 17.9%; $p=0.009$) [92,93]. However, these studies randomized patients between the 1980s and 2000s when effective BMT was not available.

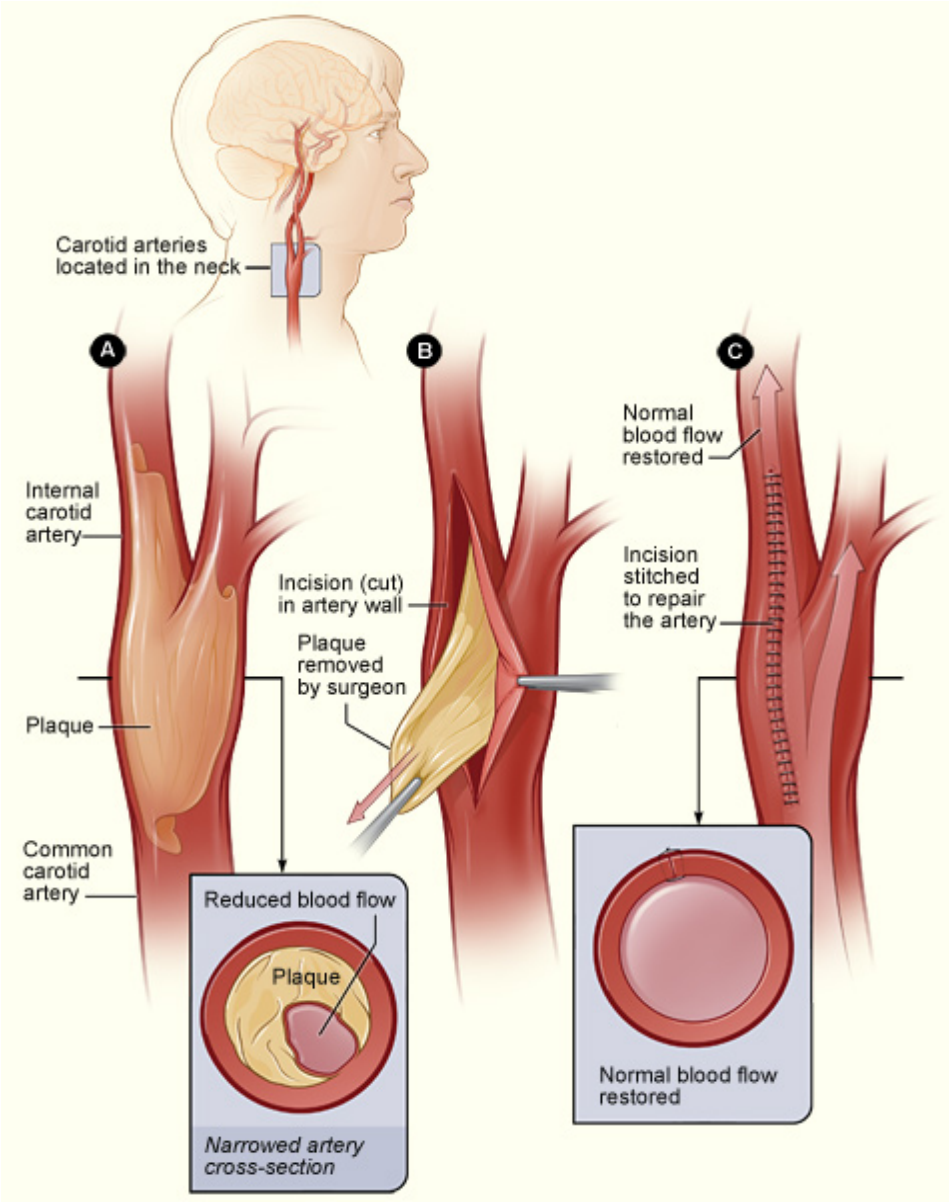


Figure 10. The CEA process. The “A” figure shows plaque buildup within carotid artery. Figure B shows the incision in the carotid artery and the following plaque removal. Figure C shows the stitching procedure of the carotid artery and the restoration of normal blood flow and normal blood flow restored. The image included demonstrates an artery cross-section with plaque removed and blood flow restored.

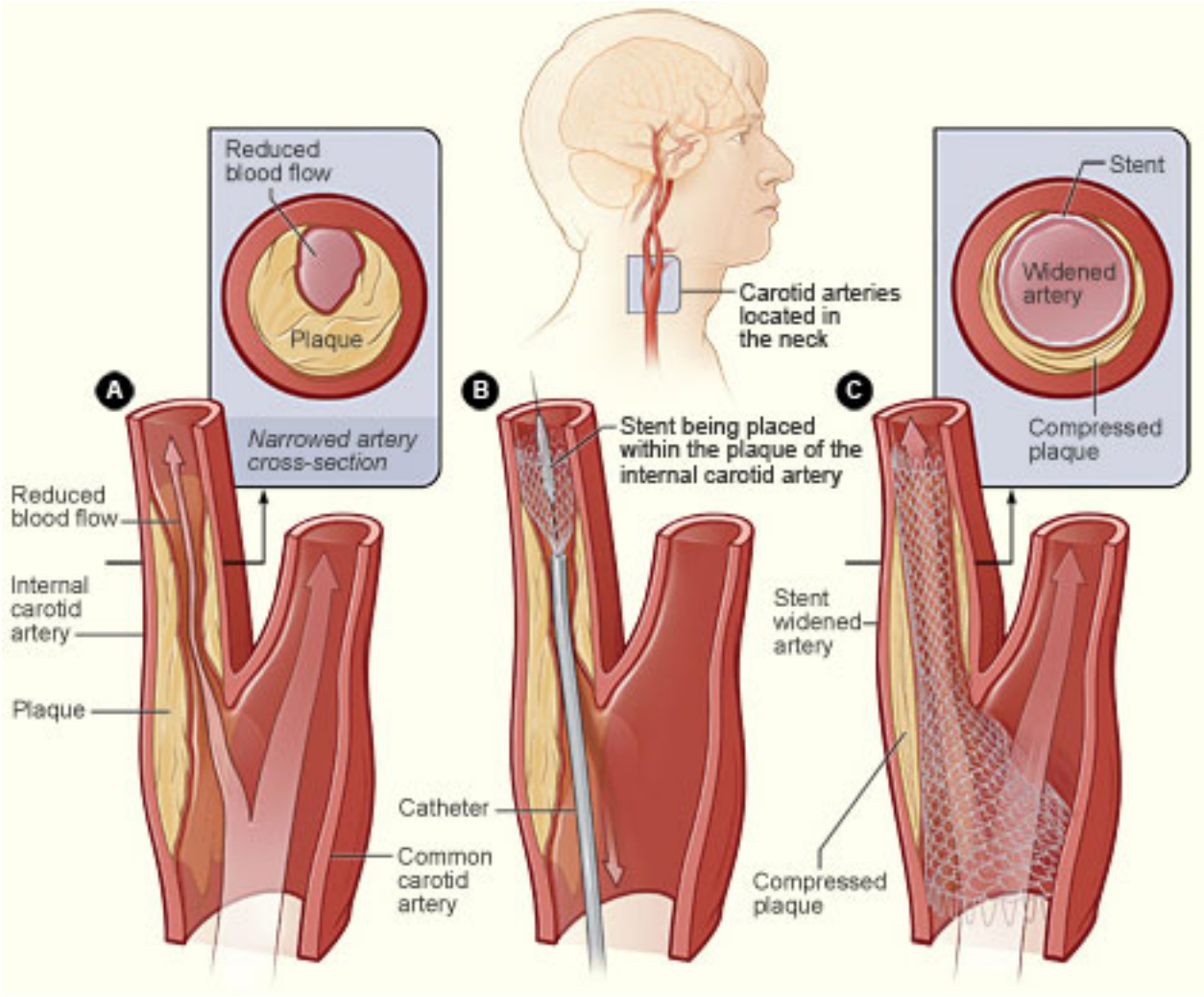


Figure 11. The CAS process. Figure “A” demonstrates the plaque buildup in internal carotid artery and the obstructed blood flow. Figure “B” shows the stent placement in the carotid artery to maintain the artery. Figure “C” demonstrates blood flow restoration in the stented artery.

CAS is usually performed with local anesthesia. A catheter is placed into the common femoral artery through the brachial or carotid artery and is promoted until it reaches the common carotid artery (Figure 11) [94]. It is less invasive than CEA, and it can be conducted in individuals with various comorbidities with an increased risk for CEA. CAS carries out a higher stroke risk in symptomatic compared to asymptomatic patients [95,96]. Higher age accounts as an independent prognostic factor of inadequate outcome after CAS, probably due to more advanced atherosclerotic disease in the old age [96,97]. That may include more tortuous carotid vessels and commoner plaques in the aortic arch. CEA and CAS comparison in several RCTs did not report definitive results due to the diversity of the sample tested, the variety of endovascular devices, different endpoints, varied endovascular experience of interventionalists, and different embolic use

protection devices. The Carotid Revascularisation Endarterectomy versus Stenting Trial-1 (CREST-1) was a multi-center RCT that included 1181 asymptomatic patients and used embolic protection devices 96.1% of the patients [98]. CAS reported a greater peri-procedural mortality risk and stroke risk than CAS in symptomatic individuals and insignificant in patients with ACAST (p=0.02 and p=0.15, respectively). The peri-procedural occurrence of stroke or death was higher in CAS than CEA in symptomatic individuals (p=0.02), and insignificant in them with ACAST (p=0.15). Symptomatic patients after CEA procedure presented with more MIs than ACAST patients [98]. In ACAST individuals, only the 4-year rate of stroke or death was significant, 4.5% after CAS and 2,7% following CEA (p=0.07) [98]. Furthermore, the composite endpoint of stroke, MI, or death presented no difference between CEA and CAS groups in symptomatic and ACAST patients after an average follow-up of 10 years. Because CREST-1 included in the beginning only symptomatic patients and the asymptomatic ones were added later, the effectiveness of CAS versus CEA in patients with ACAST is not reliable.

SAPPHIRE trial compared CAS with CEA in 334 patients (97 symptomatic patients, 237 asymptomatic patients) with increased operative risk (approximately 75.5% of patients undergoing CEA had coronary artery disease) [99]. Overall, fewer individuals that underwent CAS received re-intervention than those with CEA without a difference in the composite endpoint of stroke, death, or MI at 30 days [99]. However, the equivalent outcome at 1 year in patients with CAS was 9.9% compared to 21.5% in the CEA group (p=0.02). That can be explained due to more comorbidities leading to an increased incidence of procedural MI in the CEA group compared to CAS (p=0.03). At 3 years, stroke and the composite endpoint of death, stroke, or MI was similar in patients with ACAST following CEA and CAS [100]. SAPPHIRE outcomes should be taken into account with caution due to CEA patients' high-risk, leading to an increased rate of procedural events.

The Asymptomatic Carotid Trial-1 (ACT-1) demonstrated CAS non-inferiority to CEA within 30 days of the procedure regarding the composite endpoint of stroke, death, or MI during the first 30 days the procedure in patients with ACAST [101]. In 5 years, the ipsilateral stroke rate was 2.7% after CEA compared to 2.2% following CAS (p=0.51), confirming the equality between CAS and CEA in the long-term prevention of stroke.

Identification of Asymptomatic Patients at High Risk of Stroke

Plaque echolucency and juxtaluminal hypoechoic areas

In the last years, the plaque structure and constitution have been researched extensively to identify and stratify stroke risk. Plaque echolucency, one of the essential plaque characteristics and juxtaluminal black plaque, can be quickly evaluated via ultrasound. Several ultrasonographic features of the carotid plaques are related to an elevated long-term stroke risk in patients with ACAST. Essentially, the ACSRS group demonstrated a reduction in ischaemic event-free survival in plaques with more than 1 discrete white area ($p<0.0001$), size greater or equal to 80mm ($p<0.0001$), or a gray-scale median less than 15 ($p<0.0001$) in 1,121 patients [102]. That came in accordance with several other studies [103,104] and confirmed previous outcomes that showed that the history of contralateral stroke or TIA ($p<0.0001$ and $p=0.002$) and increased severity of the stenosis (measured by ECST method) were both related to a reduction of retinal or cerebral ischemic event-free survival [102].

Several studies also reported that plaque echolucency was associated with intraplaque hemorrhage or necrotic core lipid-rich, mostly found in symptomatic patients than ACAST [105,106]. The greater stroke risk in individuals with ACAST was investigated in association with plaque echolucency, and the majority of them independently demonstrated a strong relation between the two entities [107-109, 110-112]. A post-hoc analysis, including 814 patients in the medical arm of the ACST-1 also highlighted that plaque echolucency was related to increased risk of future stroke in asymptomatic patients [113]. Patients with echolucent plaques (n=403) had an increased risk of ipsilateral stroke in comparison to those without (n=411) at 5 years (8.0% vs 3.1% respectively; $p=0.009$) [113]. After adjusting other risk factors, plaque echolucency was significantly related to increased risk of ipsilateral stroke with a hazard ratio [HR] of 2.5 (1.2-5.3, $p=0.014$). However, in 10 years, the overall stroke was similar independently of the plaque echolucency [113]. Although the study should be repeated in a larger sample of patients, the increased use of statins in ACST-1 may also explain why the association was not reproduced at 10 years due to a possible carotid plaque stabilization.

A study from Grønholdt et al. found that plaque echolucency was related to stroke risk, only in symptomatic individuals with stenosis of the carotid artery and not in those with ACAST [114]. Recently, a meta-analysis by Gupta et al. with 7557 patients and an average follow-up for 37.2 months, reported a beneficial relation between the echolucency of the plaque and the risk of future ipsilateral stroke in carotid artery stenosis severities from 0%-99% with a RR of 2.31 (95% CI,

1.58-3.39, p <0.001) and in individuals with stenosis of ≥ 50% with a RR of 2.61 (95% CI, 1.47-4.63, p=0.001) [115]. 1741 patients were diagnosed as echolucent-positive, and the remaining 5816 as echolucent-negative. In total, 141 ipsilateral strokes occurred in patients that were diagnosed negative for echolucency. Also, patients with ≥ 50% of carotid stenosis had a greater stroke risk with a RR of 2.61 (95% CI, 1.47-4.63, p=0.001) [115]. The relation between the increased risk of ipsilateral stroke and plaque echolucency was also confirmed in another meta-analysis by Jashari et al. The predictive value of the plaque echolucency can be increased further, combined with microemboli detected with TCD. Asymptomatic carotid emboli study demonstrated that the carotid plaque echolucency was related with an increased ipsilateral risk of stroke greater than 600% with an HR of 6.43 (95% CI 1.36-30.44, p=0.019), while the combination of emboli detected with TCD and plaque echolucency was related to an increased ipsilateral stroke risk >1000% with an of HR 10.61 (95% CI, 2.98-37.82, p= 0.0003) [111].

A high-risk factor is the juxtaluminal black plaque, which are hypoechoic areas without a visible fibrous cap. Multiple cross-sectional studies associated these areas with the presence of neurological symptoms [116-118]. Notably, Griffin et al. showed that echolucency assessed by the combination of juxtaluminal hypoechoic area and gray-scale median density was related to symptomatic plaques (OR: 6.7, 95% CI, 4.08 to 10.91) [117]. Kakkos et al. also tested the hypothesis that juxtaluminal black areas can predict future ipsilateral strokes in patients with ACAST [119]. They found that juxtaluminal hypoechoic area's size was associated with the risk of stroke in individuals with ACAST, as the 5-year ipsilateral event rate was 3% in patients with a juxtaluminal hypoechoic area <4 mm^2, 21% in patients with an area of 4 to 8mm, 36% in patients with an area between 8-10mm and 43% in patients with an area greater than 10mm (median annual rates: 0.6%, 4.2%, 7.2%, 8.6% respectively). A cut off at 8mm^2 was able to identify the patients with an increased risk of fatal stroke (OR 18.7 (4.1-85.9; p<0.001) and at 8 years (HR 19.6 (4.3-89.6); p<0.001). The authors suggested that juxtaluminal black areas greater than 8mm^2 can produce a larger ulcer, inducing a more significant embolus that may lead to a massive brain infarct and a stroke with fatal consequences. However, the measurement of juxtaluminal black areas is complex, depends on inter and intra-observer variability, and error can be introduced by vessel tortuosity, position, and calcification, which may reduce the validity of the findings.

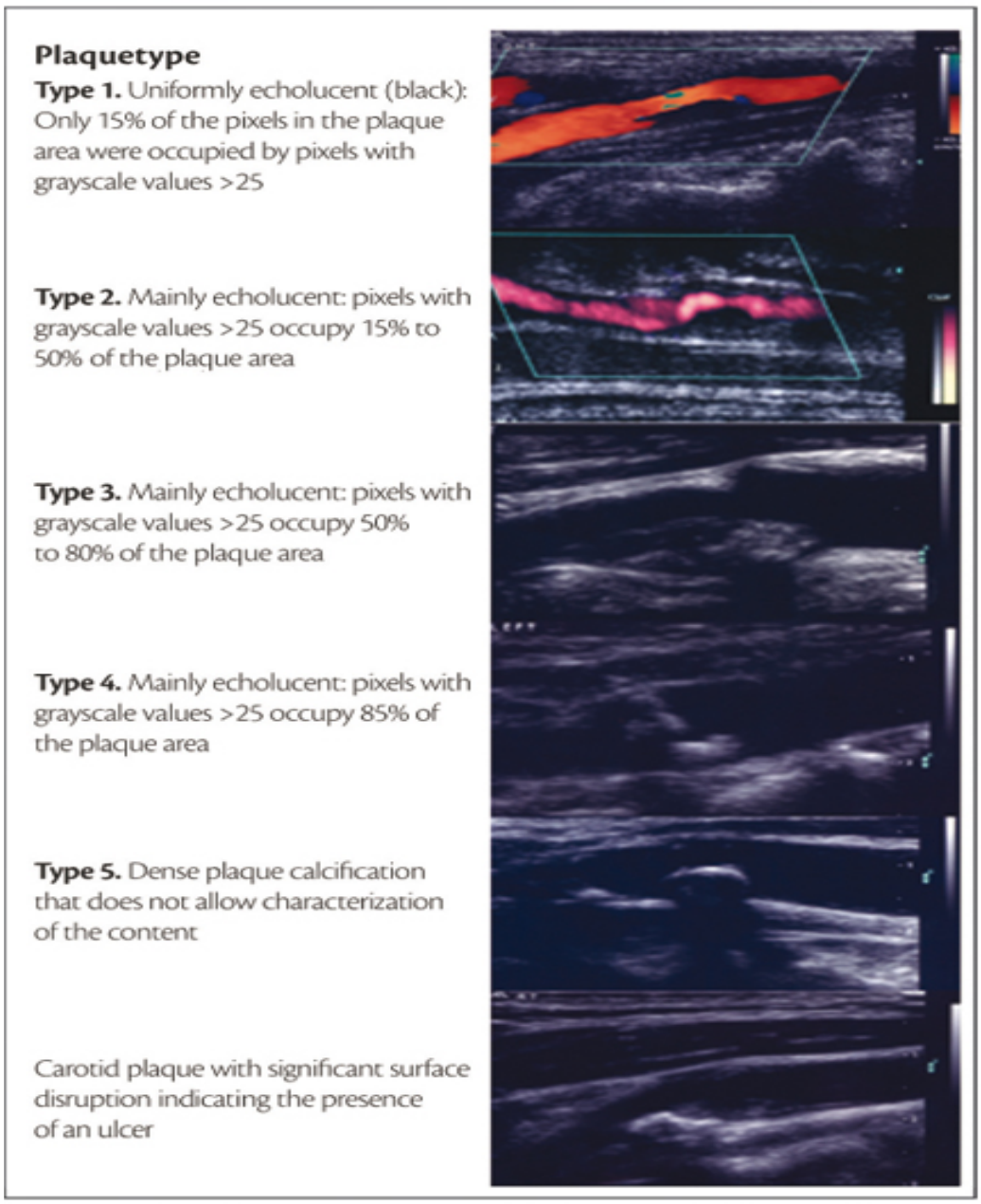


Figure 12. Gray-Weale Classification; Carotid artery plaque morphology and characteristics

The effect of carotid bruits

A large meta-analysis of twenty-eight studies, including 17,913 patients for 67,708 patients-years, investigated the relation between the presence of carotid bruit and the high risk of future stroke, TIA, or stroke death. Among the studies comparing individuals with and without bruits, the stroke ratio was 2.5 in 5 studies (95% CI, 1.8-3.5, $p< 0.0005$), 4.00 for TIA in 5 studies (95% CI, 1.8-9.0, $p<0.0005$), and 2.7 for stroke death in 3 studies (95% CI, 1.33-5.53, $p=0.002$). In a larger number of studies (n=26), stroke rates for the patients with carotid bruits were 1.6 per 100 patients-years (95% CI, 1.3-1.9, $p< 0.0005$) compared to 1.3 per 100 patient-years in 13 studies (95% CI, 0.8-1.7, $p<0.005$) in patients without bruits. TIA rates were 2.6 per 100 patient-years in 24 studies

(95% CI, 2.0-3.2, p<0.0005) for patients with carotid bruits compared to 0.9 per 100 patient-years in patients without bruits in 5 studies (95% CI, 0.2-1.6, p=0.02) and stroke mortality rates were calculated at 0.32 (95% CI, 0.20-0.44, p<0.005) for patients with bruits in 13 studies compared to 0.35 for them without in 3 studies (95% CI, 0.00-0.81, p=0.17) [120].

Microemboli detection on Transcranial Doppler

Transcranial Doppler is a non-invasive, real-time, and most inexpensive method used to image the intracranial vasculature usually conducted in three acoustic windows, transorbital, transforaminal and transtemporal. The transducer frequency is set at 2 MHz to permit the signal through the calvaria [121]. More technologically developed TCD devices have been developed, focusing on portability, convenience, and remote capability of the procedure. These devices monitor the patients with ACAST by detecting microembolic signals and periprocedural for the same purpose in patients undergoing CEA. A possible side effect is thermal injury, most frequently in higher frequencies and transorbital acoustic window.

The primary definition used for microembolic signals includes typically visible short-duration and high-intensity signals at the spectrum of the Doppler flow, which occurs randomly at the cardiac cycle. They sound like a click, whistle, or chirp, and they present an intensity increase greater than 5 dB from the background signal. However, moderate carotid artery stenosis includes multiple frequencies [122,123].

Microemboli detection is well noted during TCD examination to estimate the stroke risk in patients with ACAST (Figure 13). Spence et al. demonstrated that ACAST individuals with more than 2 microemboli per hour had a greater risk of one-year ipsilateral ischaemic stoke (1500%) in comparison to those without identified microemboli (15.6% vs. 1.0%) [124]. In 2010, Spence et al. highlighted the importance of BMT in 468 patients with ACAST. They reported a reduction in CVS events (before effective BMT, 17,6% vs. after, 5,2%) and in microemboli detected with TCD (12,6% vs 3,7%, respectively) [125]. An international study involving multiple centers on 467 patients came in accordance with those results, where patients with ≥1 microemboli had an increased risk of 1-year ipsilateral stroke in comparison to patients without microemboli with an HR of 5.57 (550% higher, 95% CI, 1.61-19.32, p=0.007) [126]. Detection of embolus with TCD validity was highlighted in another meta-analysis of five studies with 677 patients in total, where the embolic signals in TCD was a major predictor of ischaemic stroke with an OR 7.46 (95% CI 2.24 to 24.89, p=0.001) [127].

In contrast, only a small observational cohort study with 202 patients resulted in an increased stroke risk in patients with ACAST with microemboli; however, it considered underpowered. The small sample size and the methodology were the main flaws of this study [128].

They considered one microembolus positive with a test repeatability between intervals of 6 months, while research shows that >2 microembolic signals in the last hour determines the ACAST patients with increased stroke risk [129,130].

Concluding, TCD-detected microemboli emerged when the 2017 guidelines of the European Society of vascular surgery recommended intervention based on microemboli detected with TCD [131], determining the importance of this method for identifying patients both with low and high absolute stroke risk.

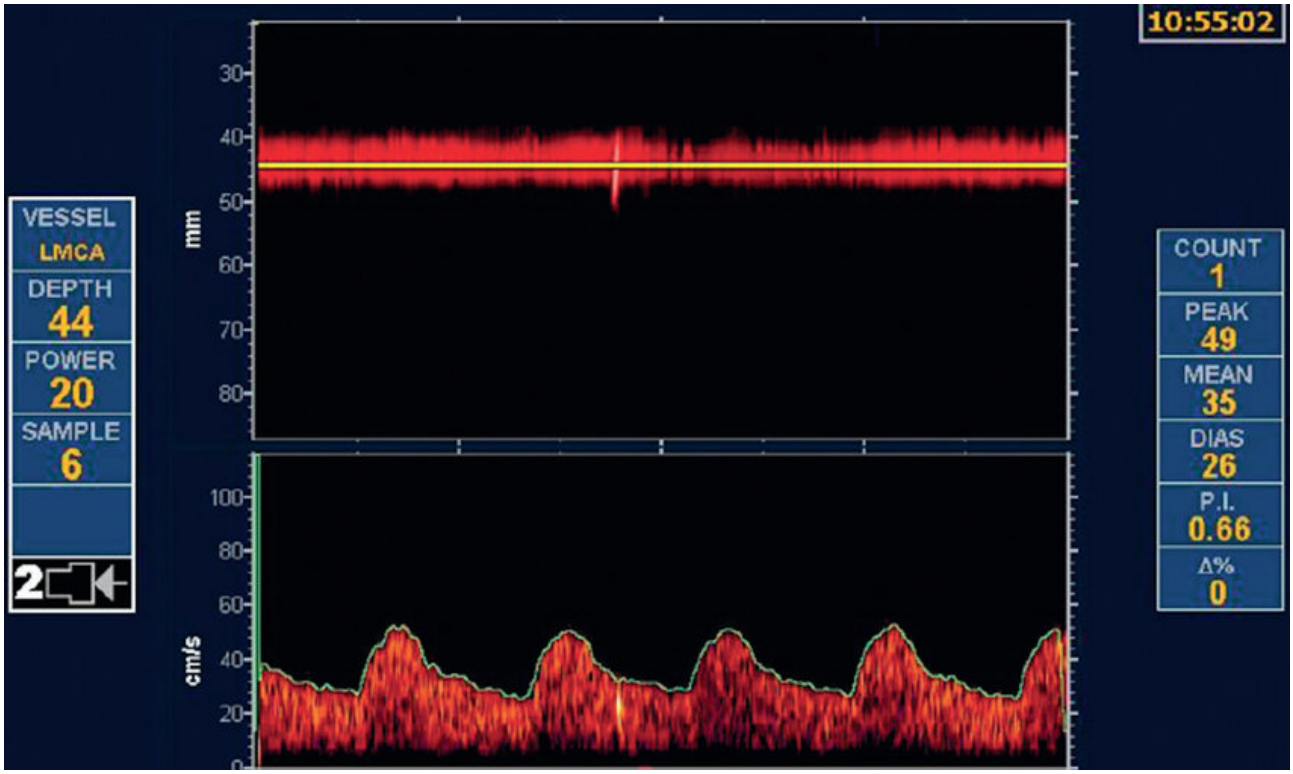


Figure 13. Embolus detection in TCD. Microembolus in a patient with asymptomatic carotid stenosis

Silent embolic infarcts on brain CT or MRI

Silent embolic infarcts (SEI), previous stroke, or TIA seems to be associated with a higher long-term stroke risk in asymptomatic patients.

First, the Cardiovascular Health Study and then the Rotterdam Scan study highlighted the correlation between SEI on MRI and CT scans and a higher risk of stroke event [132,133]. Two studies, one from Japan and ACSRS, demonstrated that SEI belongs to stroke independent predictors [134,135]. ACSRS was an international cohort study with 1,115 patients with ACAST of 50-99% measured with the ECST method for at least 5 years [136]. A substudy of ACSRS [137]

consistent with ACST-1 findings demonstrated that SEIs were associated with a higher risk of future ipsilateral stroke in asymptomatic patients. Notably, in a group of 821 individuals with stenosis of 60-99%, patients with the presence of SEI on brain CT or MRI had a higher risk of future ipsilateral stroke in comparison to those without SEI with an HR of 3.0 (95% CI 1.46-6.29; p=0.002, annual stroke rate: 3,6% vs. 1.0%) [134]. Patients with stenosis of 60-79% and the presence of SEIs had a higher cumulative stroke and TIA rate than those without SEIs (p=0.005). That demonstrates that SEI presence in patients with ACAST constitutes another essential method for assessing the ACAST patients with increased risk for a future ipsilateral ischemic stroke [138]. Despite the fact that the substudy failed to show an actual association between future risk of stroke and SEIs in patients with stenosis <60%, probably due to the small sample of patients, it is interesting how the improvement of BMT can affect this correlation in our era.

Cerebrovascular Reserve (CBR)

Cerebral perfusion pressure is reduced by increasing the degree of carotid stenosis. The mechanism of cerebral autoregulation induces the dilation of cerebral arterioles to maintain the cerebral blood flow. The stroke risk can be greater in case of a reduction in cerebral perfusion pressure, for example, during a hypotensive episode, which will also decrease the cerebral blood flow. Several studies pointed out that a reduction in CBR is correlated with an increased risk of stroke in ACAST patients [139-143]. In 106 patients with ACAST as a part of the substudy of ACES, readings with TCD of the middle cerebral artery were measured, and a meta-analysis of similar studies was done to maximize the power of these findings [143]. The meta-analysis, including 3 further studies, demonstrated that impaired CBR was associated with an increased risk of stroke or TIA (OR 4.8 (1.9-12.1); p=0.001), ipsilateral stroke (OR 6.1 (1.3-29.5); p=0.02), any stroke or TIA (OR 1.6 (1.9-10.9); p=0.0006) and any stroke (OR 4.7 (1.7-12.9); p=0.003). A secondary analysis reported that impaired CBR was related to embolic signals that may explain the strong correlation, although with the uncertainty of its clinical utility due to the limited use of TCD [143].

Interestingly enough, the original substudy of ACES did not show any difference in stroke/TIA (p=0.16) or TIA (p=0.52) in patients with/without impaired CBR, probably due to the small number of ischemic events. Normal CBR may range from 15% to 40%, and values lower than 10% suggest impaired CBR [144]. A meta-analysis of 13 studies that included 991 patients showed an almost 400% higher risk of stroke in patients with ACAST with impaired CBR (OR: 3.96; 95% CI, 2.60-6.04), with a potential limitation being that in the majority of the studies the investigators were lined to the results of CBR [144]. The authors verified that, beyond various limitations, most

studies pointed out that reduced CBR may identify ACAST patients with increased stroke risk. However, the small population of these studies questions the validity of the findings, limiting their applicability.

Intraplaque hemorrhage using MRI

Stroke risk in patients with ACAST can be assessed by the severity of the components of the carotid plaque assessed by MRI. Higher risk of ischemic events was presented in patients with specific plaque characteristics such as intraplaque hemorrhage, lipid-rich necrotic core, or with a rupture of the fibrous cap [145-147]. That was further confirmed by a meta-analysis that included 779 patients with these particular characteristics. They reported an HR of 4.59 (2.91-7.24) for intraplaque hemorrhage, 3.00 (1.51-5.95) for lipid-rich necrotic core, and 5.93 (2.65-13.20) for a thinning/rupture of the fibrous cap as predictors of future stroke and TIA. These results function as independent factors of the future stroke risk that cannot be estimated by a measurement of the lumen stenosis, and they suggest that carotid plaque MRI assesses the patients with increased risk that could benefit from revascularization [148]. However, the variability used in the MRI techniques for the imaging of the carotid plaque requires further clarification to improve the clinical applicability of the results. MRI studies that are implemented as a part of CREST-2 and ECST-2 may elucidate further the results [149-151].

Progression of the severity of stenosis

While there is no vigorous evidence regarding the carotid artery stenosis severity and the stroke risk in asymptomatic individuals, the stenosis progression can be related to increased risk of stroke in individuals with ACAST. We can suppose that the progression of the ACAST severity despite BMT's implementation is not a good prognostic factor. However, multiple reasons may induce ACAST progression despite effective BMT, such as resistant atherosclerosis [152,153]. ACSRS reported that an 8-year cumulative ischaemic stroke rate was 0% in patients with regression of stenosis, 9% in unchanged stenosis, and 16% in stenosis progression. The progression of carotid plaque doubled the rate of annual stroke and cumulative stroke rate across all stenosis degrees among 50-99% measured by the ECST method and 70-99% with the NASCET method. This may be the reason for the lower retinal or cerebral ischemic event rate survival ($p < 0.001$) and stroke-free survival ($P = 0.05$) in patients with progression of carotid stenosis versus those with regressing or stable stenosis degree. The use of statin and the effective monitoring of the carotid plaque features would improve the effectiveness of BMT and, as it would be biologically expected, would reduce further or stabilize the plaque size. However, ACSRS demonstrates that the progression in ACAST severity is a predictor of future stroke [154]. Interestingly, Conrad et al. demonstrated that

the progression of ACAST is not a good prognostic factor despite BMT that failed to prevent the development of ipsilateral neurological symptoms or the carotid disease progression [155]. However, the relation of carotid plaque progression and the future CVS events will require further evaluation in larger types of studies before these findings can be applied to everyday clinical practice.

Carotid plaque burden provides an advantage compared to carotid intima-media thickness (cIMT) in CVS outcomes prognosis. A study from Canada that compared total plaque volume, total plaque area, and progression/regression of cIMT as predictors of CVS outcomes showed that the total plaque volume measurement is preferable to total plaque area or cIMT [156]. In patients with ACAST, plaque burden predicted stroke risk and not the percentage of stenosis [157]. A study by Sillesen et al. demonstrated that plaque burden was also associated with coronary calcium compared to IMT that it was not. It also appeared to be as prognostic as coronary calcium [158].

Carotid ulceration

Carotid ulceration was first described as a risk factor for neurological symptoms when ulcerated plaque removal relieved those symptoms [159,160]. It was reported that ulceration is a risk factor for ipsilateral symptomatology based on the pathogenetic mechanism of arterio-arterial embolism of the existing thrombus [161-164]. The clinical significance of the ulceration of the carotid plaque has been pointed out in multiple studies. The North American Symptomatic Carotid Endarterectomy Trial showed that ulceration of the carotid plaque was related to a 350% increase in the relative risk of stroke [165]. Madani et al. highlighted that asymptomatic patients with more than three ulcers in both carotid arteries demonstrated a 3-year stroke risk or mortality ($p=0.03$, respectively), equivalently to microemboli ($p=0.003$) [166]. The significance of contrast-enhanced ultrasound in detecting ulcerated plaques is essential as it is better than color Doppler ultrasound and can indicate the carotid plaques associated with an increased potential of thromboembolic event [167,168]. Three-dimensional carotid ultrasound-based texture analysis can also predict future CVS events and evaluate the composition of the carotid plaque [169,170].

Identification of Asymptomatic patients at high risk of Myocardial Infarction

The carotid plaque existence constitutes an essential risk factor of CVS events in all types of symptomatic vascular disease. The Reduction of Atherothrombosis for Continued Health (REACH) registry included 45,227 individuals in total with a follow-up of 4-years, where the information on carotid atherosclerosis was evaluated in 23,364 patients. Of them, 10,725 patients had carotid atherosclerosis. The results were analyzed after the adjustment for the geographic region and the CVS risk factors, and they demonstrated an increase in the risk of coronary events by 22% in individuals with carotid atherosclerosis when compared to patients without. A relative increase was presented by 18% in individuals with several risk factors, by 46% in patients with cerebrovascular disease (95% CI, 28-65%), 37% in those with peripheral artery disease (95% CI, 17-60%), and by 25% in those with coronary artery disease (95% CI, 16-35%). Carotid atherosclerosis was related to a higher risk among patients with previous MI but without a history of stroke or between patients with previous stroke but without a history of MI.

Interestingly, in both groups, carotid atherosclerosis functioned as a predictor of coronary risk for any coronary event, independently with HRs of 1.36 in individuals suffering from an ischemic stroke and 1.32 in those with MI. The HR for major coronary endpoints was 1.54 for the first group and 1.37 for the second one [171]. Thus, carotid atherosclerosis presents a cumulative effect on the risk of coronary events.

Besides, Steinvil et al. investigated carotid atherosclerosis as a CVS event prognostic factor, even in patients without a known coronary artery disease. They included 1391 patients that underwent coronary angiography and carotid ultrasound and doppler on the same day. The average and the median follow-up were 1574 and 1702 days. Individuals with carotid atherosclerosis and carotid artery stenosis had an increased risk of composite major adverse CVS event in comparison to them without established coronary artery disease (HR=1.69 [0.95-3.01]; p=0.07 and HR=3.17 [95% CI, 1.52-6.60]; p<0.01, respectively), but not in them with known coronary artery disease. Furthermore, carotid artery stenosis was associated with higher all-cause mortality in individuals without established coronary artery disease (HR=2.93 [1.09-7.87]; p=0.03) among those with coronary artery disease [172]. Therefore, carotid artery stenosis and carotid atherosclerosis belong to the independent prognostic factors of major adverse CVS events among individuals that underwent coronary angiography.

Nadareishvili et al. included 106 individuals for 5 years to evaluate the risk of stroke and other vascular events. They found a 10- and 15-year risk of ipsilateral stroke of 5.7% and 8.7%

respectively in patients with lesser internal carotid artery stenosis (0 to 49%) and 9.3% and 16.6% in patients with higher carotid artery stenosis (50 to 99%). MI and non-stroke vascular death percent were found at 10.1% and 24.0%, respectively. Furthermore, age, DM, and internal carotid artery stenosis function as predictive factors of the increased risk of non-stroke vascular death and MI. This study highlighted the increased long-term risk of MI and non-stroke vascular death and pointed out the research focus for preventing CVS events [175].

The SMART study in 2007 that enrolled 2684 subjects with type 2 DM or arterial disease, without a history of a cerebral ischemic event assessed the degree of ACAST with duplex scanning for a median of 3.6 years. None of the individuals that underwent CAS or CEA and vascular events were recorded. Interestingly, during the follow-up, a first vascular event occurred in 9% (253) of the patients, while ACAST of greater than 50% was presented in 8% (221). The CI rate for subsequent vascular events post-5 years was 12.3% (95% CI, 10.7 to 13.9), 8.0% for MI (95% CI, 6.6 to 9.4) and 2.2% for cerebral infarction (95% CI, 1.4 to 2.8). After adjusting for gender and age, ACAST of greater than 50% was correlated to an increased risk of subsequent vascular events (HR:1.5, 95% CI, 1.1 to 2.1). Thus, ACAST in patients with arterial disease or type 2 DM seems to be an independent prognostic factor of vascular events [176].

Park et al. investigated 1390 individuals with coronary artery disease proven by coronary angiography and underwent carotid artery examination 1-day pre- or post-coronary angiogram and followed up for 54.2 ± 23.9 months. They found that the patients with carotid plaque had increased risk of acute coronary syndrome and CVS risk factors (34.2% vs. 24.6%, $p<0.001$) compared with those without. The univariate analysis found that carotid plaque was related to hard MACE (cardiac death, MI, stroke), and total MACE and cIMT was a total MACE predictor. On the multivariate analysis, carotid plaque presence was associated with hard MACE ($p=0.008$), total MACE ($p=0.004$), and cardiac death ($p<0.004$), and cIMT correlated with total MACE ($p=0.017$). Therefore, the carotid plaque presence is considered a predominant prognostic factor of MACE and cardiac death, especially in individuals with coronary artery disease. That may highlight the importance of coronary artery intervention and the role of intense medical treatment in individuals with known coronary artery disease [177].

The effect of carotid bruits on Cardiovascular events

Carotid bruits are related to a higher risk of CVS events. First, a study by Chambers et al. investigated 500 asymptomatic patients with neck bruits in a prospective clinical study and followed them for an average of 4 years (mean of 23.2 months) clinically and with ultrasonography. They demonstrated an one-year incidence of cardiac ischemic events at 7%, cerebral ischemic events at 6%, and sudden cardiac death at 4%. They also reported a 75% higher incidence of stroke

in patients with severe carotid artery stenosis compared to those without. Thus, they concluded that carotid artery disease functions as a dependent predictor for a cerebral event and an independent prognostic factor of cardiac ischemic episodes [173]. A large meta-analysis of 22 studies, including 20 prospective cohorts, corroborated with this hypothesis. It included 17,295 patients with an average number of 273 individuals (range 38-4736) followed up for four years (2-7). Individuals with carotid bruits had an MI rate of 3.69 (95% CI, 2.97 to 5.40) per 100 patient-years (n=8 studies) compared to 1.86 (0.24-3.48) per 100 patient-years in individuals without bruits (n=2 studies). Individuals with carotid bruits had an increased rate of CVS death per year (n=16 studies) than in those without bruits (n=4 studies) [2.85 (2.16-3.54) per 100 patient-years compared to 1.11 (0.45-1.76) per 100 patient-years]. Last but not least, in the four trials that patients with and without bruits were possible, the OR of CVS death was 2.27 (1.49-3.49) and for MI was 2.15 (1.67-2.78) [174].

Progression of the severity of stenosis

Recently, a large meta-analysis including 100,667 patients with an average age of 62 and a follow-up of 3.7 years was published. It demonstrated that a reduction of 10μm of cIMT progression each year resulted in a relative CVD risk of 0.91 (95% CI, 0.87-0.94), with an additional relative CVD risk of 0.92 (0.87-0.97) independently of progression of cIMT. When the reduction of cIMT was summarized, a 10,20,30,40 μm reduction each year would provide risks of 0.84, 0.76, 0.69, and 0.63 accordingly [178]. It appears that cIMT progression can be used as a delegate marker for the prediction of CVD risk.

Sabeti et al., with 1065 patients, investigated the carotid stenosis progression by Doppler velocity criteria. The incidence of MACE was investigated in patients for an average follow-up of 3.2 years. They showed a progression of the carotid stenosis in 9% of the patients evaluated by duplex ultrasonography and reported 495 major acute CVS events in 40% of them. They also demonstrated that the individuals with progressive carotid stenosis had an increased risk of CVE compared to them with non-progressive disease with a 2.01 for composite major acute CVS events (95% CI, 1.48-2.67, p<0.001), 2.38 for MI (95% CI, 1.07-5.35, p=0.044), 1.59 for coronary events (95% CI, 1.10-2.28, p=0.011), 2.00 for stroke (95% CI, 1.02-4.11, p= 0.035), 2.42 for peripheral vascular events (95% CI, 1.61-3.62, p<0.001),1.75 for CVD (95% CI, 1.03 to 2.97, p=0.039).

Thus, stenosis severity progression might play an important role in predicting MI [179]. Similarly, a study by Balestrini et al. in 523 individuals with ACAST of 50% to 69% came in accordance with these results. The patients were followed-up for 12 months and assessed during an average duration of 42 months (IQR, 38-45) after the evaluation by a second ultrasound. The progression of carotid stenosis was correlated with vascular events (HR, 21.57; 95% CI, 11.81-39.39, p < 0.001). During the follow-up, 96.7% of individuals without carotid stenosis progression

did not experience a vascular event. Among the patients with carotid stenosis progression, 53.7% of patients suffered from a vascular event and 27.1% from an ipsilateral stroke [180].

Platelets demonstrate an essential role in atherosclerosis pathogenesis and function as a surrogate marker to predict the clinical outcome and atherosclerosis progression in patients with ACAST. Mayer et al. investigated this hypothesis in 1006 individuals with ACAST that were evaluated by ultrasonography. In an average duration of 3.1 years (IQR, 2.5-3.5), 316 MACEs were recorded. Higher levels of mean platelet volume were related to a higher risk of MACES. Individuals with levels of mean platelet volume higher than the fifth quintile had a greater event rate (41.3% vs. 29.3%, $p<0.001$) with an HR for MACE of 1.65 (95% CI 1.26-2.16, $p<0.001$) in comparison to individuals with levels of mean platelet volume in the first to the fourth quintile [181].

Since atherosclerosis is a systemic inflammatory disease, high-sensitivity C-reactive protein seems to be related to carotid atherosclerosis' short-term progression. Schlager et al. investigated 1065 patients with ACAST at baseline and after 6 to 9 months. The carotid stenosis' progression was estimated in 9% of the patients after 6 to 9 months, and 381 CVS events occurred in 337 individuals (27%) after a follow-up of 3 years (IQR, 2.5 to 3.5). High-sensitivity C-reactive protein levels were higher in patients with progression of carotid artery stenosis ($p <0.001$) and correlated with the first CVS event ($p<0.001$). They demonstrated an HR of first CVS event, in accordance with hs-CRP increase of 1.41 (95% CI, 0.92 to 2.17), 1.76 (95% CI, 1.17 to 2.66), 2.22 (95% CI, 1.48 to 3.32), and 2.41 (95% CI, 1.61 to 3.60) respectively [182].

Carotid plaques

Komorovsky et al. showed that hard carotid plaques exist more commonly in individuals with complex coronary lesions than in patients with simple coronary lesions, which seems to increase with the increased coronary artery disease extent [183]. Mosleh et al. tried to evaluate the risk of predicting MI or obstructive coronary artery disease based on carotid plaque morphology assessed by CTA. They found that individuals with calcifications smaller than 3 mm and larger ones on CTA or with low-attenuation plaques showed an increased risk of MI or obstructive coronary artery disease [184]. Hamada et al. also evaluated the relation between carotid plaque composition and coronary artery disease in 97 patients who underwent CEA or CAS. They reported that 33 individuals were diagnosed with 44 episodes of coronary artery disease. Multivariate logistic analysis showed that plaque/muscle ratio (OR, 3.0; 95% CI, 1.4-10.1), contralateral carotid occlusive disease (OR, 6.5; 95% CI, 1.7-22.9) and ASO (OR, 5.7; 95% CI, 1.8-18.9), determining

that these factors and high-intensity carotid plaque on T1-weighted MRI independently predict coronary artery disease [185].

Conclusion

Carotid artery stenosis is associated with an increased risk of cerebral and cardiac events, especially stroke and MI. While various possible interventions exist, the choice between the BMT and interventional procedure (CEA/ CAS) is still a dilemma. The advancement of BMT and the possible periprocedural inherent events favors even more the BMT in several patients. Therefore, it is essential to identify the groups at high risk of stroke and MI to maximize the absolute benefits of carotid intervention. Several clinical, anatomical, and imaging features play a crucial role in that matter. Carotid plaque echolucency, composition and morphology, inflammation markers, and microembolic signals are the essential characteristics in stratifying patients' risk with carotid artery disease. Also, the stenosis progression and plaque composition and morphology are important features to predict future events. Carotid artery disease character, as in ACD, has a significant impact on cardiac events as well. More specifically, carotid plaque composition, morphology, and the progression of severity of stenosis are associated with a higher risk of MI and cardiac death. Although several features are used to risk-stratify patients with ACAST, it is unclear whether the primary prevention or the interventional procedure is the most optimal strategy. Further studies are required to maximize the potential of the current methods and markers to quickly identify the patients with ACAST at high risk to provide the most optimal therapy and avoid the devastating consequences of MI and stroke.

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