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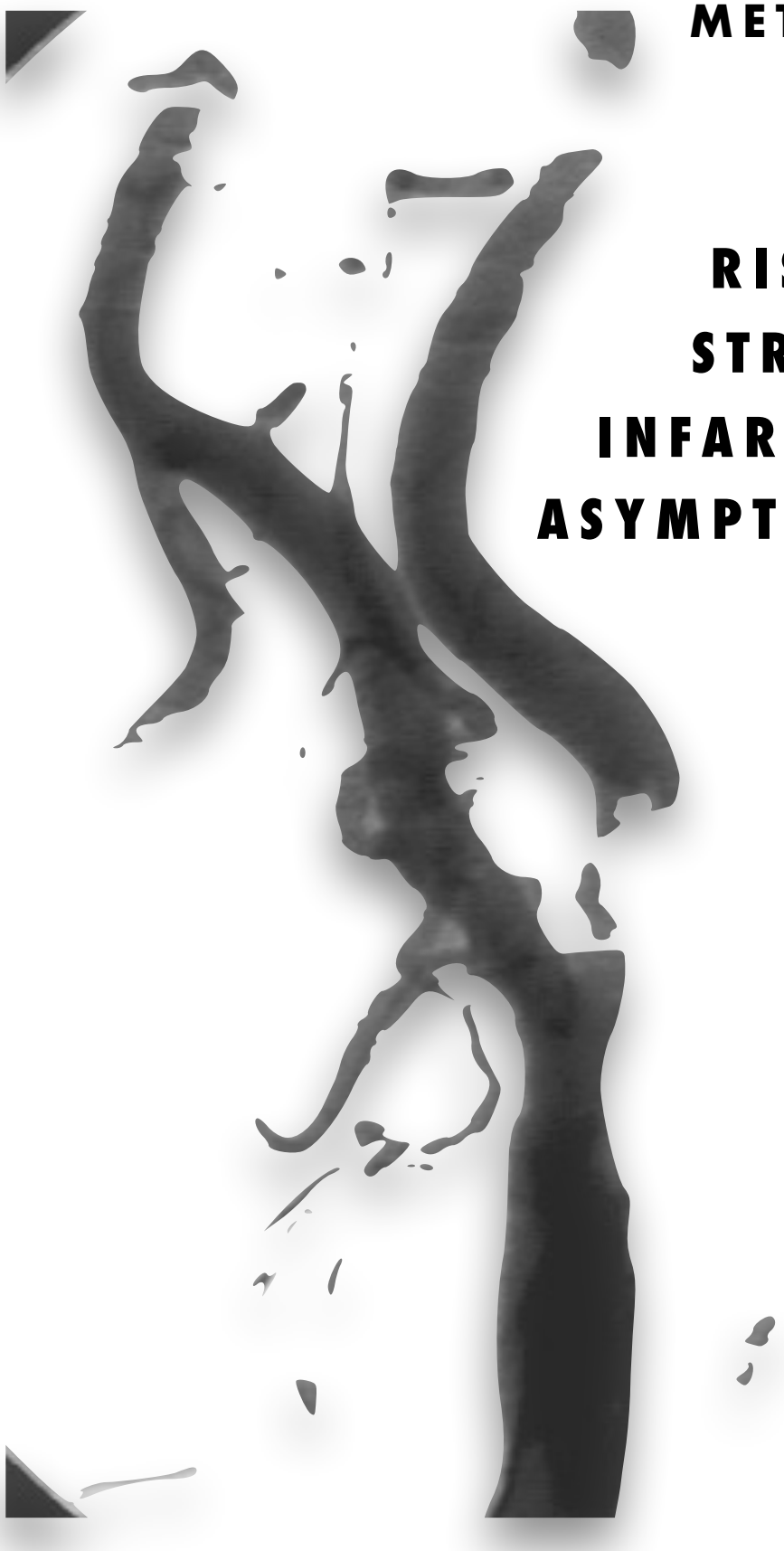

ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

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

του

ΝΙΚΑ ΔΗΜΗΤΡΙΟΥ
Επεμβατικού Καρδιολόγου

Υπεβλήθη για την εκπλήρωση μέρους των απαιτήσεων για την απόκτηση του

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Τίτλος εργασίας στα Ελληνικά:

"Βαθμονόμηση κινδύνου εκδήλωσης αγγειακού εγκεφαλικού επεισοδείου και εμφράγματος του μυοκαρδίου σε ασθενείς με ασυμπτωματική νόσο καρωτίδων"

PREFACE - THANKSGIVINGS

Cardiovascular disease is the number one killer in western societies. Atherosclerotic disease regards a sole disease, with different manifestation in almost all vascular territories. Carotid stenosis is one of the most important and easy-to-identify form of atherosclerotic disease. Either with clinical examination (audible cervical bruit) or with specific ultrasound examination, carotid stenosis of various degrees can be revealed. Years of research have concluded that the presence of atherosclerotic stenosis, even the asymptomatic one, is a sign of increased risk for future cardiac and vascular events, including the most important ones: stroke and myocardial infarction. But not all patients carry the same risk for future events. Therefore, not all patients will benefit from a possible intense medical treatment or even surgical operation to prevent upcoming myocardial infarctions or strokes. Some of those patients may possibly undergo unnecessary and potentially dangerous interventions to treat carotid stenosis, either with surgical endarterectomy or with percutaneous angioplasty and stenting. Additionally, most of those patients will require antiplatelet and hypolipidemic therapy. However, some may be at elevated risk for myocardial infarction, death and stroke, and may need potent pharmacological prevention with the intention to meet significantly lower targets as regard as the traditional risk factors modification, like blood pressure, glucose and LDL cholesterol.

This postgraduate thesis was carried out with this question in mind. Who are the patients at high risk for future cerebrovascular events, and how can they be identified? A scientific and personal clinical question, the answer of which has yet to be answered. To tackle this question a thorough review of the existing literature was performed. A large number of studies have been checked in detail in order to select the most appropriate. A lot of studies have been rejected and others have been not included due to methodological problems and studies' quality. The remaining ones have been analyzed and presented in this manuscript with deeply critical view. The scope of the present manuscript is to carefully identify clinical characteristics, anatomical features and markers which may provide significant value in categorizing patients with asymptomatic carotid stenosis in respect to future risk for cardiovascular events. This manuscript regards the product of a meticulous and detailed research of the published literature under the guidance of my friend Prof. George Ntaios. With the completion of this work, I would also to thank Prof. Athanasios Giannoukas and Prof. Miltiadis Matsagas for their teaching and guidance during this long postgraduate course. Firstly and foremost, I would like to emphasize the support and mentoring of Prof. Giannoukas, whose willing and trust onto myself to work and accomplish this task, will always be an honor and privilege. Last but not least, I feel delighted to express my deep appreciation to the rest of the scientific faculty for their valuable assistance, patience and understanding during the whole period of this teaching course.

ABSTRACT

Atherosclerotic cardiovascular disease is the leading cause of mortality worldwide. Carotid artery disease regards an important manifestation of atherosclerotic disease and is usually associated with presence of coronary artery disease. Presence of carotid disease is associated with elevated risk for both cardiac and cerebral events, predominantly stroke and myocardial infarction. However, not all patients with asymptomatic carotid disease are at the same risk for either stroke or myocardial infarction. Several different anatomical, clinical and imaging parameters have been identified to be associated with higher risk for stroke or myocardial infarction, indicating that those patients may benefit from intensive medical treatment or interventional procedures more than others with asymptomatic carotid stenosis. In the present manuscript, a thorough research of the published literature was performed, to gather all available data in an effort to understand and recognize those patients who are at higher risk for future cardiac and cerebral events. Moreover, an extensive review of the current data regarding the epidemiology, the incidence and the burden of asymptomatic carotid stenosis in both the general population and patients with coronary disease is also presented.

Key words:

Asymptomatic carotid stenosis, myocardial infarction, stroke, risk stratification

ΠΕΡΙΛΗΨΗ (ΣΤΑ ΕΛΛΗΝΙΚΑ)

Η αθηρωματική καρδιαγγειακή νόσος αποτελεί την κυριότερη αιτία θανάτου παγκοσμίως. Η στένωση των καρωτίδων αποτελεί μία από τις σημαντικότερες κλινικές εκδηλώσεις της καρδιαγγειακής νόσου, και συνήθως συνυπάρχει με την στεφανιαία νόσο. Η παρουσία καρωτιδικής νόσου συνδυάζεται με αυξημένο κίνδυνο εκδήλωσης καρδιακών και εγκεφαλικών συμβάντων, με προεξέχοντα το αγγειακό εγκεφαλικό επεισόδιο και το έμφραγμα του μυοκαρδίου. Πάρα ταύτα, οι ασθενείς με ασυμπτωματική στένωση καρωτίδων δεν έχουν όλοι τον ίδιο κίνδυνο εκδήλωσης των καρδιακών και εγκεφαλικών συμβάντων. Ένας σημαντικός αριθμός κλινικών, ανατομικών και απεικονιστικών παραμέτρων έχουν εντοπισθεί να σχετίζονται με αυξημένο κίνδυνο μελλοντικού εγκεφαλικού ή εμφράγματος του μυοκαρδίου, υποδεικνύοντας μία σημαντική κατηγορία ασθενών που πιθανόν να ωφελούνται περισσότερο από πιο εντατική φαρμακευτική αγωγή ή ακόμα και επεμβατική παρέμβαση, σε σχέση με τους υπόλοιπους ασθενείς με ασυμπτωματική καρωτιδική νόσο. Στη παρούσα εργασία, έγινε μια ενδελεχής έρευνα στη διεθνή βιβλιογραφία, προκειμένου να αναδείξουμε τους παράγοντες εκείνους που σχετίζονται με αυξημένο κίνδυνο ασθενών με ασυμπτωματική νόσο καρωτίδων, σε μία προσπάθεια να ξεχωρίσουμε τις κατηγορίες εκείνες των ασθενών που είναι σε υψηλότερο κίνδυνο εκδήλωσης αγγειακού εγκεφαλικού επεισοδίου ή εμφράγματος του μυοκαρδίου. Επιπλέον, θα παρουσιαστεί μια εκτεταμένη ανασκόπηση των δεδομένων σχετικά με την επιδημιολογία, την επίπτωση και το μέγεθος της ασυμπτωματικής καρωτιδικής νόσου, τόσο στο γενικό πληθυσμό όσο και σε ασθενείς με στεφανιαία νόσο.

Λέξεις- Κλειδιά:

Ασυμπτωματική στένωση καρωτίδων, έμφραγμα του μυοκαρδίου, κατηγοριοποίηση κινδύνου.

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INTRODUCTION

GLOBAL AND NATIONAL BURDEN OF ATHEROSCLEROTIC DISEASE

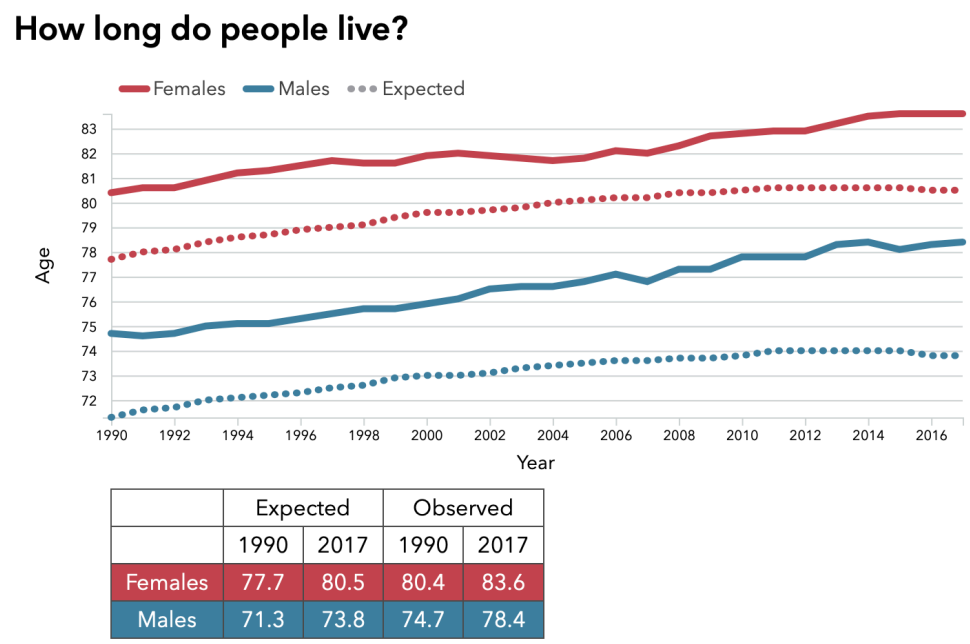
Atherosclerotic cardiovascular disease (ACD) is the leading cause of mortality worldwide. Data from the WHO Global Health Observatory indicate, that although the age-adjusted ACD mortality rates are decreasing, the absolute number of individuals dying from ACD will increase substantially due to the growth of the population and aging (1),(2). ACD included two major conditions: ischemic heart disease (IHD) and cerebrovascular disease (CVD). Both regard an important global epidemic which puts an enormous burden to the population and societies in terms of public and personal costs.

Traditional risk factors like hypertension, hyperlipidemia, diabetes and smoking continue to be the most important risk factors for ACD. Interestingly, recent data show that there is a positive relation between ACD and financial status of the society; a country's Gross Domestic Product (GDP) has shown to be correlated ACD mortality, especially cardiac mortality. Cardiovascular mortality decreased globally from 1990-2010, but with important differences according to GDP; higher income countries had higher rates, comparing to the lower income ones (3). However, as wealthier countries managed to sufficiently address the problems and incidence of traditional risk factors, the poorest ones did not. That means, as those low/middle income countries are getting wealthier and adopt the western way of living, an increasing

burden of ACD is expected, attributable mainly to increased incidence BMI and diabetes. Indeed, data from a recent comparative analysis between countries - with different GDP - showed that in all countries IHD remained the primary cause of death, but the rates of age-adjusted IHD mortality are decreasing in wealthier countries whereas in low/middle income ones remained approximately the same (4). In some of those countries, increased prevalence of hypertension and smoking were identified as the most contributors for high IHD mortality rates. It is logical that, the modern economical and political transition in those countries contributed to the IHD mortality rates.

In accordance to the western societies trends, IHD and stroke remain the leading causes of death in Greece, as well. According to the Institute of Health Metrics and Evaluation (IHME), Seattle, WA, USA, which analyses data from the Global Burden of Disease project, although the Life Expectancy increased substantially from 2007 to 2017 (from 80.5 to 83.6 years for females, and from 73.8 to 78.8 years, for males), the rates of IHD and Stroke increased by 4.3% and 1.8%, respectively, during the same period (Figure 1 & 2) (5). In the same analysis, IHD and Stroke surpassed significantly Low Back Pain and Lung Cancer, as the leading causes for disability and death combined (Figure 3).

According to the same observatory, behavior habits prevail the top leading contributors to the incidence of ACD in Greece, with smoking being the first one, even though slightly decreased by 3.6%, and dietary risks being the second.



	Expected		Observed	
	1990	2017	1990	2017
Females	77.7	80.5	80.4	83.6
Males	71.3	73.8	74.7	78.4

Figure 1. *Life expectancy in Greece during 1997-2017 period. Source: Institute of Health Metrics and Evaluation (IHME), Seattle, WA, USA*

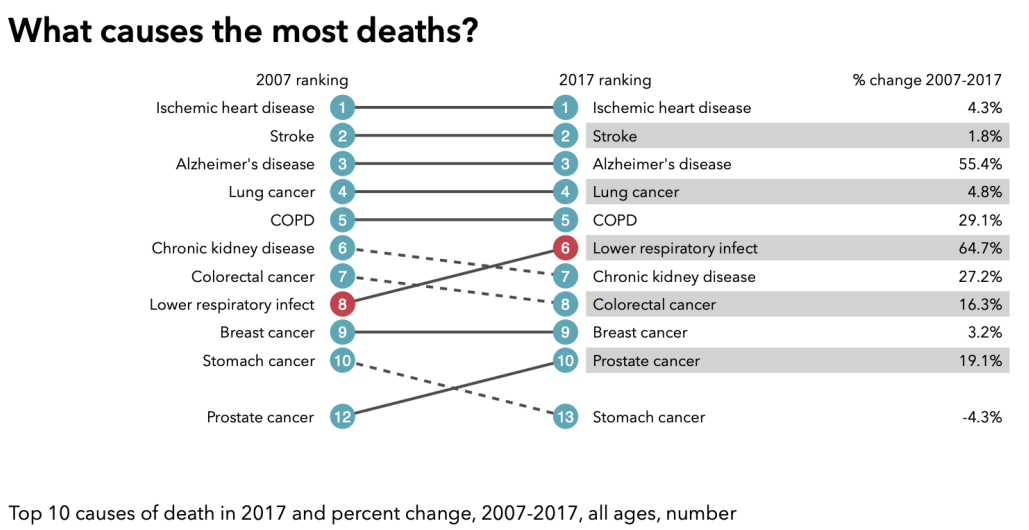


Figure 2. *Causes of death in Greece between 2007-2017. Source: Institute of Health Metrics and Evaluation (IHME), Seattle, WA, USA*

Hypertension and the rest of the traditional risk factors follow with substantial decrease in all of them, except diabetes which show significant increase by 16.8% during the last decade.

Since ACD remains the most common cause of death and one of the most important causes of morbidity, it is expected to regard one of the mostly contributors to national health expenditure, at least in Western societies. According to the Center of Disease Control and Prevention(CDC) Foundation, an independent nonprofit and sole entity created by US Congress to support the CDC, a total annual cost of $320 billions, nearly $1 billion a day, has been estimated to be spent in medical cost and lost of productivity to treat 1.5 million heart attacks and strokes each year. Additional studies have confirmed the huge economic burden need to treat and prevent ACD in modern times, both in US and in Europe (6), (7). In European Union (EU), a total cost of €210 billion per year, is spend in treatment and productivity losses(8). Around 53%

(€111 billion) is due to health care costs, 26% (€54 billion) to productivity losses and 21% (€45 billion) to the informal care of people with CVD. Early data from the THESIS study, 800 patients with IHD, peripheral artery disease (PAD) and multiple risk factors were recruited in Greece(9). According to this study, the total annual expenditures were estimated to be €7.5 billions at the National level and €6,017/patient. This cost ranged from €10,098/patient with PAD to €1,813/ patient with multiple risk factors. The annual direct health-care cost was €5,056/patient.

An average of almost equal of high expenditures have been reported in patients suffering from ischemic stroke. Early reports, show that the direct in-hospital cost for all stroke was €1,551,445 for a total of 4674 days (€331.9 per day in-hospital). The mean in-hospital cost per stroke patient was €3624.9 (+/-2695.4). If you account the same amount of money for almost 30.000 stoke cases / year in Greece, the total National cost could be as high as €108 millions / year spend only in direct hospital expenditures. The costs were estimated to be significantly higher, for every day of prolonged hospitalization and proportional to the stroke severity (10) (11).

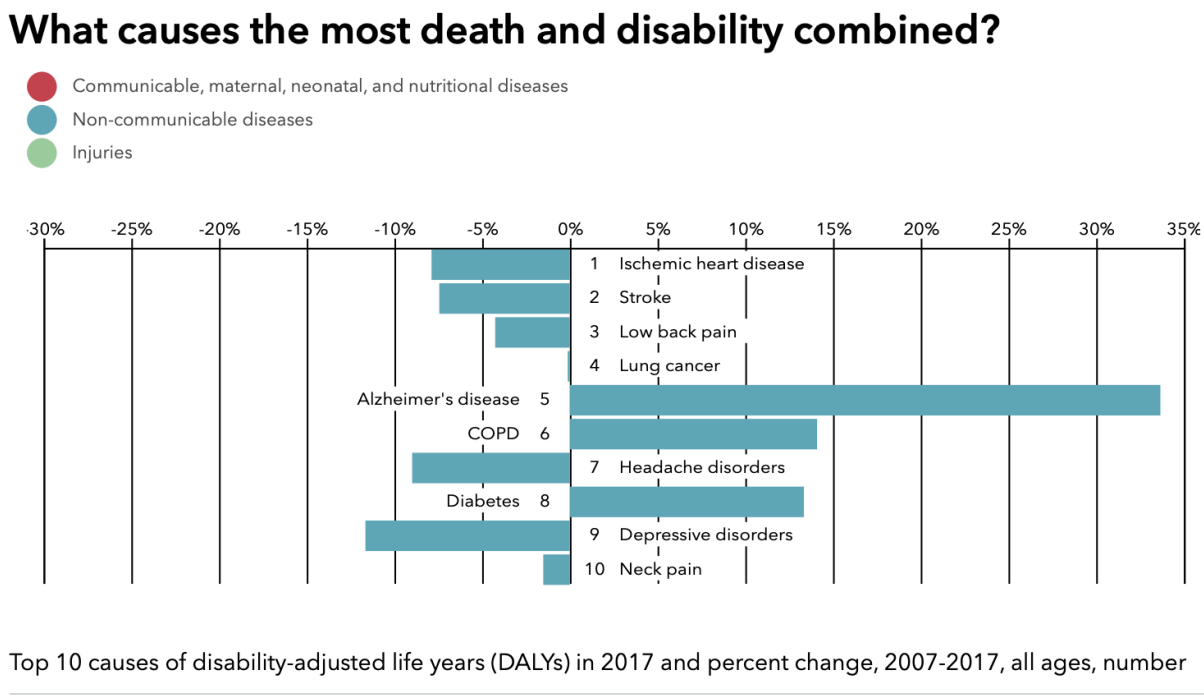


Figure 3. *Top 10 causes of disability-adjusted life years (DALYs) in 2017 and percent change, 2007-2017, all ages, number, in Greece. Source: Institute of Health Metrics and Evaluation (IHME), Seattle, WA, USA*

Taken all previous data into account, it is obvious that ACD regard an important health problem with substantial social and economic consequences, for Western populations and financially evolving societies, alike. Two of the most important manifestations of this disease are the CORONARY Artery Disease and CAROTID Artery Disease. Both diseases may run asymptomatic for several years until they first present with either myocardial infarction or stroke, respectively. Unfortunately, both presentations are associated with such a high mortality and morbidity, which makes them two of the most important acute syndromes that, in modern years, have gained first priority to be urgently treated. In all national healthcare systems advanced protocols for immediate treatment of both acute myocardial infarction and acute stroke, based on international scientific guidelines, have been established, making procedures like primary percutaneous coronary interventions (PCI), thrombolysis and acute stroke interventions (e.g. thrombectomy) the primary therapeutic management for myocardial infarction and stroke, respectively (12-15).

Apart from the emergent treatment of acute presentation of both Coronary and Carotid Artery disease, significant effort has been given in the early recognition of patients who at high risk for either myocardial infarction or stroke. There is an increasing amount of data supporting that patients suffering of coronary artery disease are having high probability of carotid artery disease and stroke and vice versa. To better understand the prevalence and the co-incidence of coronary and carotid artery disease a brief presentation of global and national epidemiology of both coronary and carotid artery disease is needed.

GLOBAL AND NATIONAL EPIDEMIOLOGY OF CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION

Coronary artery disease is the most common in Western world, disease with its acute representation, the acute myocardial infarction, to be the number one killer. Globally, there were an estimated 7.29 million cases of acute myocardial infarction, and 110.55 million prevalent cases of IHD (95% UI: 100.68 to 121.80 million cases) in 2015 (16). In recent data significant differences between different countries were noted in terms of two-year mortality (adjusted for 16 different factors), which ranged from 2.5% in Northern Europe to 7.4% in Latin America, indicating considerable room for improvement in terms of acute myocardial infarction management (17) (Figure 4).

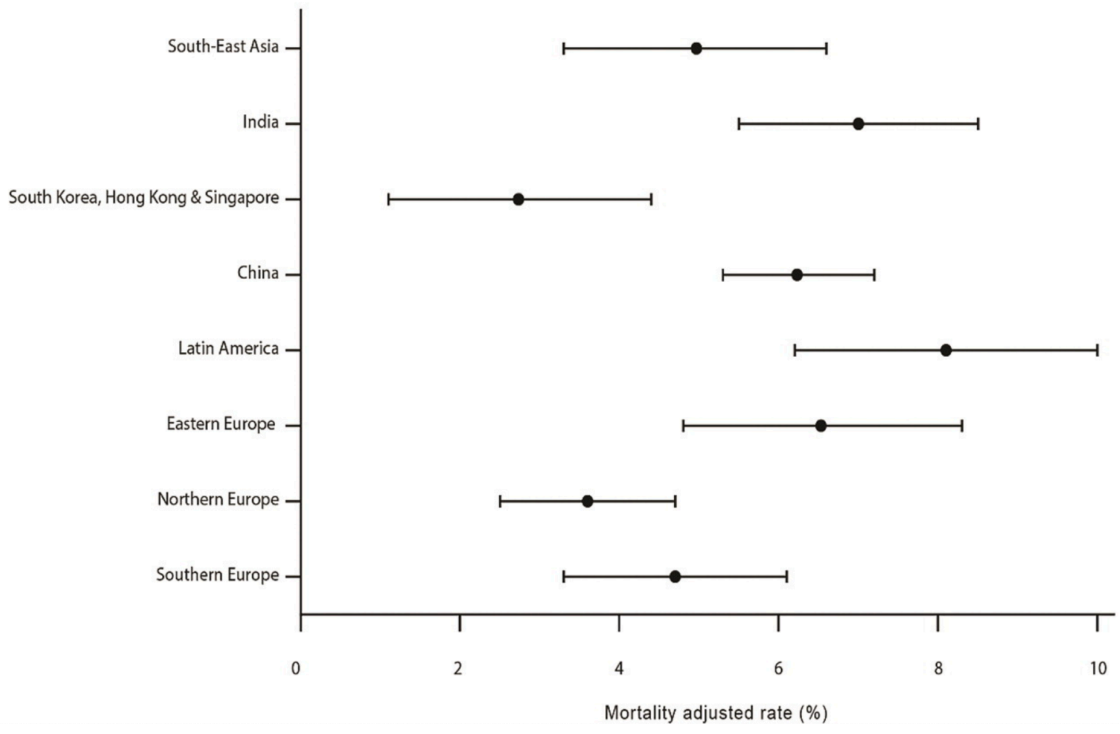


Figure 4. *Two-year mortality rate after myocardial infarction in different geographical areas, adjusted for several baseline factors. (From Ref 13).*

In US and Europe the incidence of myocardial infarction has declined significantly; in US the incidence is estimated about 1.5 million cases / year, thus about 600 cases / 100,000 of population with significant decrease in death toll, while in Europe there was in significant decline in both incidence and death rates associated with myocardial infarction(8, 16, 18). Unfortunately, prehospital rates of cardiac deaths associated with myocardial infarction remained steady the last decade (8, 18).

In Greece, according to the Stent For Life Initiative, the annual hospital admission for myocardial infarctions (ST-Segment elevation Myocardial Infarction / STEMI) was 11,731 and for those without ST-segment elevation (NSTEMI) was 9,956, accounting for almost 20,000 of new cases / year (19). Most of those events, are mainly associated with modifiable risk factors. However, due to the stable percentages of smokers the rate of STEMI infarctions remained approximately the same. According to the ATTICA study, half of individuals died from cardiovascular events; 42.2% died from ischemic heart disease while 4.4% died from a stroke(20). Intense Social-Economical crisis significantly affected incidence of myocardial infarction, at least in parts of Greece, with the oldest to have been inflicted the most(21, 22).

Recently a new definition was proposed for myocardial infarction, including several types of presentation, according to the etiology and underlined pathophysiology. Universal consensus led to the publication of the new revised criteria for five (5) types of myocardial infarction (Table 1) For the purposes of the present review, only the myocardial infarction of Type 1, 2, and 3 will be included. Even though, clear definition of the type of myocardial infarction, usually is not given, a further analysis will be done to recognize which specific type of myocardial infarction was used as outcome in the studies included in this research.

Table 1. Types of myocardial infarction according to the fourth universal definition. PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery By-Pass Grafting

	Types of Myocardial Infarction
1	Type 1: MI is due to acute coronary atherothrombotic myocardial injury with either plaque rupture or erosion and, often, associated thrombosis. Most patients with ST-segment elevation MI (STEMI) and many with non-ST-segment elevation MI (NSTEMI) fit into this category.
2	Type 2: MI includes patients with evidence of acute myocardial ischemia who do not have acute coronary atherothrombotic injury but instead have oxygen supply-demand imbalance from other reasons. This occurs most often due to the presence of coronary artery disease, which limits increases in coronary perfusion in cases of severe anemia, significant arrhythmias and other stressors
3	Type 3:MI continues the concept that there may be an occasional patient who has characteristic symptoms of myocardial ischemia but whose cTn values have not become elevated because the patient succumbs before values are measured or who is stricken by sudden death with evidence of MI by autopsy.
4	Type 4: Myocardial infarction associated with PCI
5	Type 5: Myocardial infarction associated with CABG
6	Type 6: Myocardial injury - Multifactorial etiology.

Coronary artery disease remains the most common disease in the Western societies. The most important manifestation of ischemic heart disease, the acute myocardial infarction, is the leading cause of death in modern societies. Therefore, significant and rather vigorous effort should be made to identify populations in higher risks for suffering the devastating complications of cardiovascular disease.

GLOBAL AND NATIONAL EPIDEMIOLOGY OF CAROTID ARTERY DISEASE AND STROKE

Atheromatic carotid stenosis, is regarded one of the most important causes for stoke. Almost 20% of ischemic strokes are attributed to carotid stenosis. The basic mechanism is embolism; atheromatic plaque fragments or thrombotic material caused by reduced or stagnated blood flow (in case of severe stenosis) may dislodge from the site of stenosis and embolize distally to brain circulation. Anatomically, the carotid bifurcation and especially the proximal part of the internal

carotid artery (ICA), implicating or not the external carotid artery (ECA), is the most prominent site where severe atheromatic stenosis may occur. However, specific differences in anatomical pattern of the stenosis, especially as regard as the implication of very proximal or more distal part of ICA, has been found between males and females; in males ICA stenosis appear more distally compared to females. Particular hemodynamic forces lead to accumulation of cholesterol rich plaques at the site of bifurcation and create atheromatic stenosis of variant degrees. Therefore, notable effort has been put in identifying patients with asymptomatic carotid disease, and more importantly those who at high risk for stroke.

In general population, prevalence of asymptomatic carotid disease is varying between studies. A recent meta-analysis which included data from four (4) major epidemiological studies contacted in Germany and the Nordic countries, report prevalence of moderate asymptomatic carotid stenosis between 0.3-5.7% and severe between 0.0-1.7%, in general population (23). As expected, prevalence is increasing with age and it is higher in men compared to women. (Figure 5).

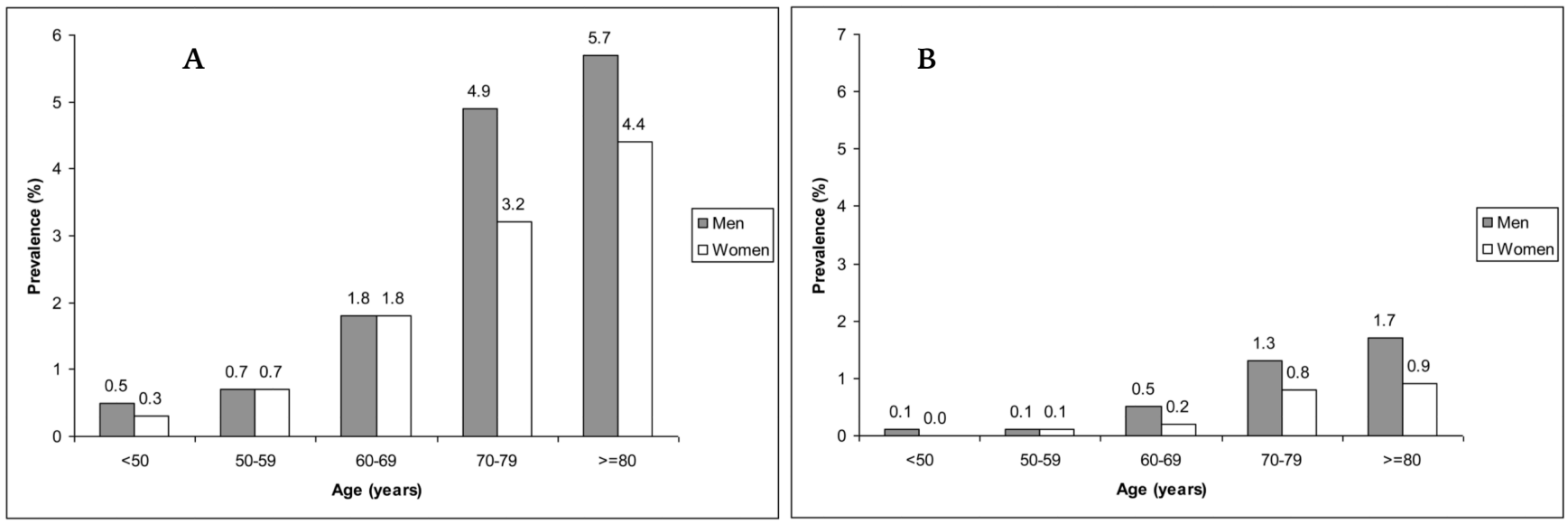


Figure 5. *Prevalence of asymptomatic carotid disease in General population, adjusted for several risk factors (smoking, hypertension, diabetes and hyperlipidemia).* ***A,*** *stenosis >50%,* ***B,*** *stenosis >70%. (adopted from Ref. 23).*

As expected, asymptomatic carotid disease is more prevalent in patients suffering from other forms of ACD, like peripheral artery disease (PAD) or abdominal aortic aneurysm (AAA). Early epidemiological studies confirm high prevalence of asymptomatic carotid disease in patients with lower-limb PAD (20.0 - 43% for carotid stenosis >50% and 12.0 - 13.7% for stenosis >70%)(24, 25). Ten percent (10.0%) of those patients had bilateral disease, whereas a smaller portion of them (5.0%) had bilateral severe carotid stenosis >70%. A more recent met-analysis confirmed high rates of prevalence (25-28% and 14% for ICA stenosis >50% and >70%, respectively)(26). The same holds true for patient with AAA, where a significantly higher prevalence of ICA stenosis was found (53.0%)(27). Importantly, more than a third of them (38.0%) had significant stenosis as this was estimated with duplex ultrasound criteria (peak systolic flow velocity(PSFV) ≥125 and <230 cm/s). Obviously, it seems that carotid disease is an inherited disease in high number of patients suffering from other forms of ACD, and therefore additional exams may be required to recognize those patients with significant carotid stenosis, in order to reduce, if possible, the risk for a future stroke.

Stroke still remains the leading cause of morbidity and disability worldwide. In United States, an estimated 7.0 million individuals aged >20 years are self-reporting having a stroke. Overall stroke prevalence has been calculated at

2.5%, with a declined trend among individuals aged > 65 years, while remained the same in younger ages (28). Figures in Europe share the same data. According the Rotterdam Study, the prevalence of self reported stroke was ranging from 2.5%

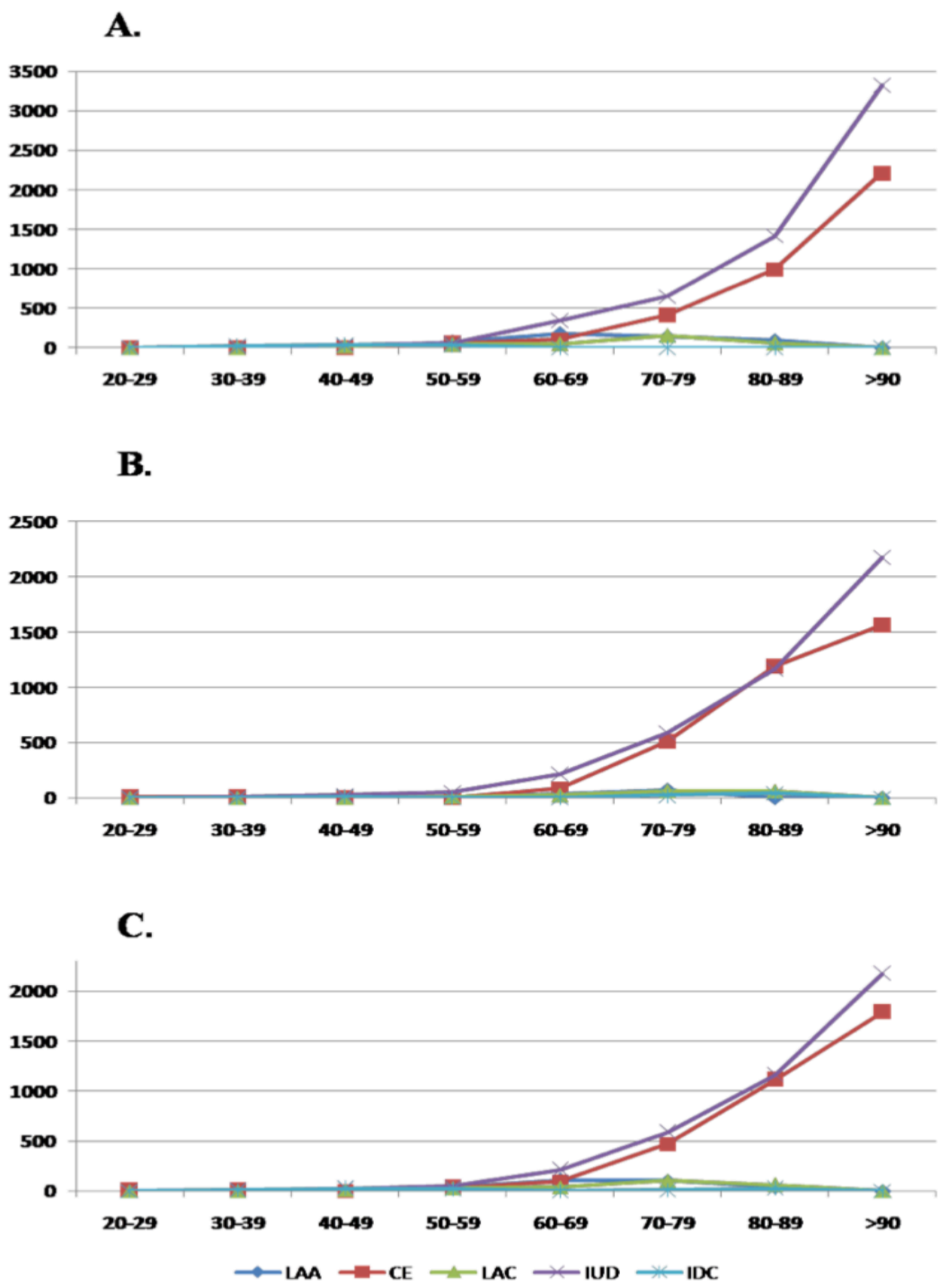


Figure 6. *Incidence rates per 100,000/person-years according to ischemic stroke subtype.* ***A.*** *Male,* ***B.*** *Female,* ***C.*** *Overall, LAA: large artery atherosclerosis, CE: cardioembolism, LAC: Lacunar infarction, IUD: unidentified, IDD: infarct of other determined cause. (From Ref . 32).*

in middle aged men to 11.6% in octogenarians, while in women it was ranging from 1.6% to 10.5% for the same age groups (29). Recently updated data from the same study, report significant reduction in stroke prevalence in men, but not in women (30). In both case though, due to increased aging population, the prevalence of stroke survivors, is projected to increase, especially among the elderly female patients. Given the high social and financial impact of stroke's disability, this could pose a significant problem that all modern societies have to deal with effectively.

Data regarding epidemiological distribution of stroke in Greece are limited. Initial data from specific closed areas in Greece demonstrate rather high incidence of stroke events. In the landmark study by Vemmos et al, conducted in Arcadia

prefecture, in South-East of Greece, between 1993 and 1995, the incidence rate of first - ever stroke, for subjects aged 45-84 years was 319.4 cases/100,000 persons. Of them 81% and 85% were ischemic type of strokes for men and women, respectively(31). The one-month mortality rate was 26.6% (95% CI, 22.9% - 30.2%), with no differences between males and females. Case-fatality increased with age and was higher for intracerebral hemorrhage than for cerebral infarction. Tsivgoulis et al. showed that in 24-month period (2010-2012) the incidence of first-ever stroke events - of whatever reason (hemorrhagic and ischemic ones) - in Evros Prefecture, a closed geographical area in the North-East of Greece, documented the highest incidence of stroke in South Europe (703 strokes /100,000 Person-Years)(32)(Figure 6). Incidence of stroke was more prominent in males, in smokers and in patients suffering from atrial fibrillation. Interestingly, a high number of strokes occurred in patients reported high alcohol consumption, especially as regard as the hemorrhagic ones. Of the total number of strokes, 297 /100,000 Person - Years were infarction, of any severity and location, and a small proportion (7/100,000 Person - Years) were classified as undefined. One-month mortality was found to be higher in patients with hemorrhagic strokes, compared to those with ischemic ones (40.4%, 95% CI, 31.3%–49.4% versus 16.2%, 95% CI, 13.2%–19.2%). In another similarly designed study, conducted in the Greek island of Lesvos, the annual incidence rates of stroke was 227.9 (95% CI 196-260) per 100,000. Following age- and gender-standardization to the 'European' population, FES incidence rates were 117 (95% CI 99-136). Early case fatality was 20.81% (95% CI 16-27%) (33).

Comparing all three studies, one can identify significant variation between stroke incidences, with the higher noticed in the Evros area, which represent one of the highest in the Southern Europe. Several factors may be responsible for this discrepancy, like differences in socioeconomic status and dietary patterns between those relatively closed regions, as well as differences in population access to primary healthcare system, due to disparities in cultural habits and structural variations in local health system. In any of those cases, all epidemiology facts raise awareness for the current status of stroke incidence and prevention in Greek population.

SIMILARITIES AND DIFFERENCES BETWEEN STROKE AND MYOCARDIAL INFARCTION.

Stroke and myocardial infarction are the devastating conditions of two major modern epidemics, carotid and coronary artery disease. They both share great similarities and important differences, which make their acute and long-term management challenging (Table 2).

Both conditions are of acute onset and require emergent management, with pharmacological or mechanical means. Notably, both conditions share strict timelines as regard as the immediate transfer from primary healthcare center to a specialized center for acute treatment, and strict time-periods within the reperfusion therapy must be delivered (34) (35). Therefore, application of similar logistics in terms of out-of-hospital transfer along with in-hospital-management is required, to ensure quick access to reperfusion therapies (“door-to-balloon” and “door-to-needle” times) and achieve the most of the benefits and reduce the burden of acute and long-term mortality and morbidity.

Occlusion of the main artery supplying an important territory and causing ischemia in a precious organ, is another important similarity between both conditions; acute myocardial infarction is caused by an occlusion of a coronary artery in

the heart, while ischemic stroke is caused by an occlusion of an artery in the brain. However, contrary to the fact that myocardial infarction is typically caused by a thrombotic occlusion on a ruptured atheromatic plaque inside the coronary artery *in situ,* ischemic stroke usually may caused by either thrombosis of relatively small vessels, or embolization of thrombus and/or plaque from the proximal arterial tree (carotid disease), or from the heart (cardio-embolic stroke). This is an important factor affecting treatment strategies in those patients. In acute myocardial infarction restoration of flow is mainly achieved with balloon ± stent angioplasty, whereas in acute embolic stroke, reperfusion is achieved with i.v. thrombolysis and thrombectomy/thromboaspiration. In both conditions though, prompt delivery of each therapy, within strict time periods, is essential to restore as early as possible blood flow and save as much as possible of the tissue in ischemia of heart and brain, respectively, as both conditions share high rates of mortality and morbidity. Interestingly, similarly to the primary angioplasty to treat acute myocardial infarction, urgent mechanical thrombectomy or thrombo-aspiration, have been proven more effective to pharmacological treatment in selected stroke patients(36-39).

Table 2 : Similarities and Differences between Acute Stroke and Acute Myocardial Infarction (CTA: Computer Tomography Angiography, PPCI: Primary Percutaneous Coronary Intervention, ECG: ElectroCardioGram)

Similarities		Differences	
Stroke	Myocardial infarction	Stroke	Myocardial infarction
Acute onset		Embolization of thrombus or atheromatic plaque fragments	In situ thrombosis on a ruptured atheromatic plaque
Emergent management within strict time-windows		Patients eligible for intravenous thrombolysis if within 0-4.5 hours	Patients eligible for reperfusion within 0-12 hours
Thrombotic occlusion of a main artery supplying an important territory		Simple criteria are sufficient to initiate intravenous thrombolysis. CT-angiography is necessary to perform mechanical thrombectomy	Simple criteria, like clinical symptoms (chest pain) and ECG are sufficient to perform PPCI
Immediate reperfusion is the only salvage treatment		Multidisciplinary medical team is needed	"Single operator" procedure
Mechanical interventions have proven more effective		Thrombectomy - stent retrieval ± thromboaspiration in Stroke	Balloon ± stent angioplasty in AMI
Both have devastating consequences including death and/or severe disability		Morbidity and Disability more severe in stroke patients	Mortality more severe in AMI patients.

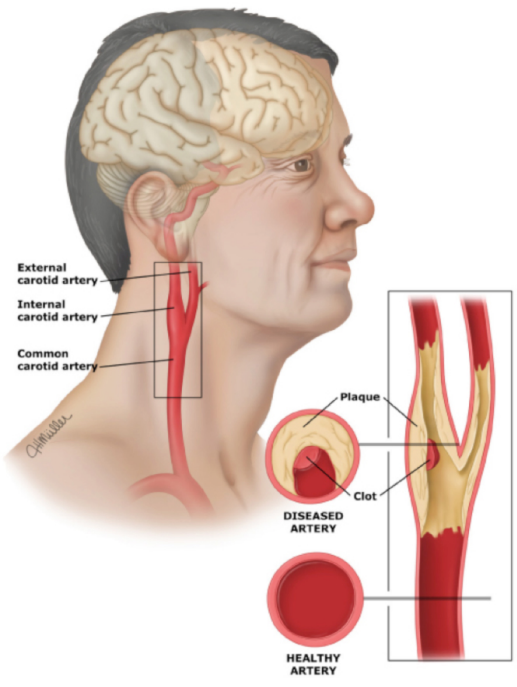
Preprocedural exams, necessary to initiate treatment with thrombolysis or/and thrombectomy/thromboaspiration, are more complex in stroke patients comparing to the myocardial infarction ones. A simple electrocardiogram is most of the times is enough to proceed to mechanical primary coronary angioplasty, while a set of more complex examinations, including complete clinical neurology evaluation, computer tomography cerebral angiography (CTA) and occasionally brain perfusion imaging tests, are required to measure the penumbra and the ischemic /necrotic area(40, 41). Moreover, In most of the cases, a single operator (i.e interventional cardiologist) is needed to perform a successful reopening of an occluded coronary artery and restore blood flow in the setting of myocardial infarction. This not the case, in the setting of acute

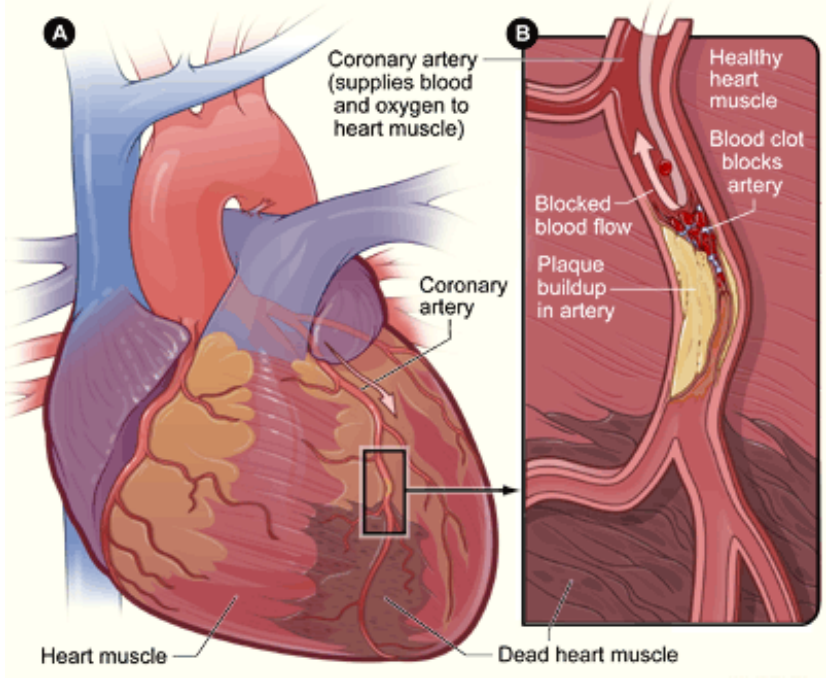
stroke, where a multidisciplinary team is needed to perform thrombolysis and/or acute thrombectomy, including the stroke physician, an anesthesiologist, and the interventional operator to perform the procedure. All these, specific parameters and characteristics along with the similarities in acute management and treatment, make these two important conditions - myocardial infarction and stroke - so alike, yet so different. Being one of the most important, acute diseases to treat, in the Western world, the early identification of individuals at high risk for acute stroke or myocardial infarction is more important than ever.

ASSOCIATION BETWEEN ASYMPTOMATIC CAROTID DISEASE, STROKE AND MYOCARDIAL INFARCTION

Despite the differences between the presentations and management of Acute Stroke and Myocardial infarction, both diseases have a common origin: the occlusion of an artery in a precious and sensitive to ischemia organ, mainly due to atherosclerotic plaque rupture with thrombus formation or embolization (Figure 7).

Indeed, there are accumulative data showing strong association between asymptomatic carotid disease, stoke occurrence and future risk for myocardial infarction. Given the fact that both diseases, share common pathophysiology pathways, it would be rather logical that all three of them, may have common clinical endpoints and therefore it would be of great importance to identify patients in higher risk for future stroke or myocardial infarction events. For that reason, a complete and thorough search of the international literature was performed in order to explore data and concentrate evidence to identify and stratify patients with asymptomatic carotid disease who at high risk.





From ttp://www.victorianvascular.com.au/home/arterial-disease/carotid-artery-disease-stroke/. *From www. nejm.org*

Figure 7. *Schematic representation of acute ischemic / embolic stroke and acute myocardial infarction. Both share common pathophysiology pathways.*

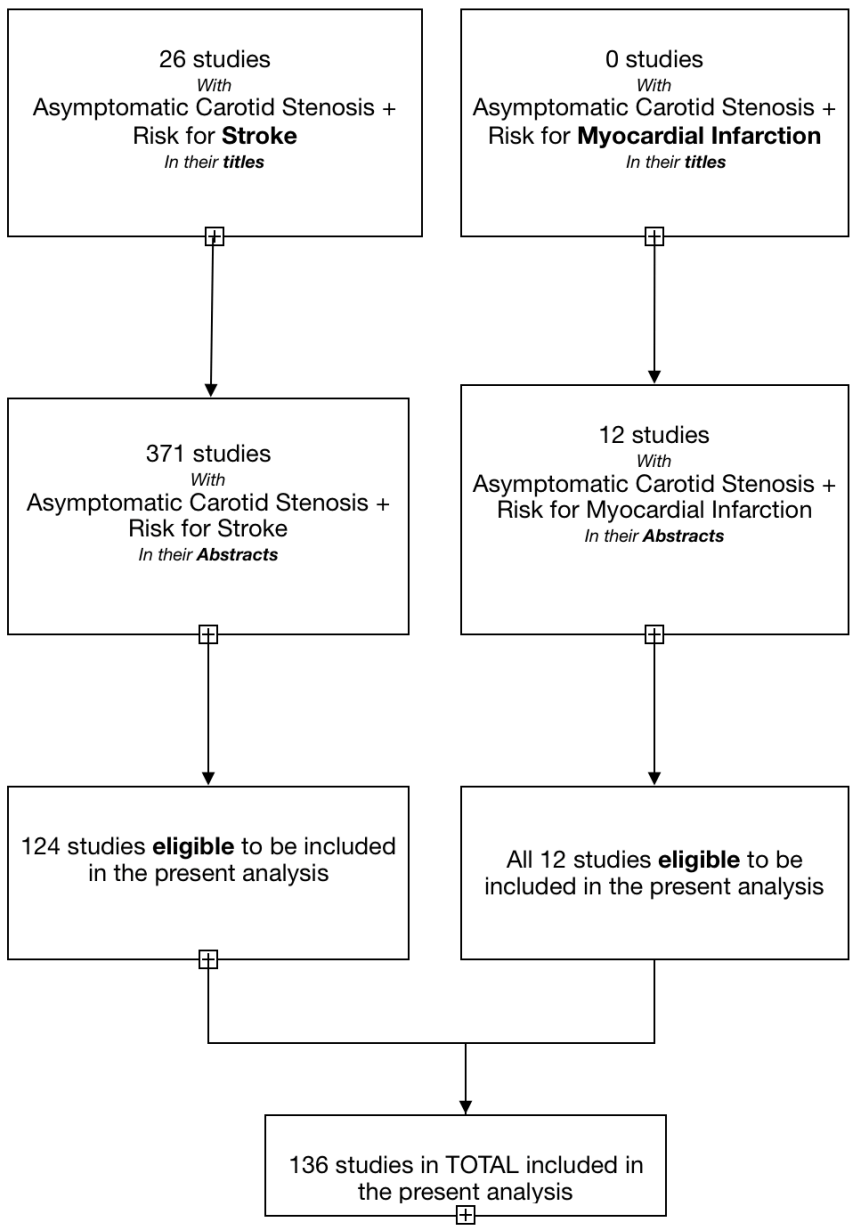
METHODS

All studies conducted to address the risk stratification of patients suffering from asymptomatic carotid disease for having a future stroke and /or myocardial infarction were reviewed. As "Asymptomatic" were defined all patients with the presence of carotid stenosis >50% in any or both of the internal carotid arteries, without the occurrence of any stroke, transient ischemic attach (TIA) or amaurosis fungal in the last 180 days. The current definition is in accordance to the definition used in all major trials examining the prognosis, outcome and implications of treatment strategies in asymptomatic carotid stenosis (42, 43).

Medline/Pubmed was searched for studies published and investigating the association of asymptomatic carotid disease and future stroke occurrence with the terms: "asymptomatic carotid disease.tw", "asymptomatic carotid stenosis.tw", "carotid disease.tw", "asymptomatic carotid disease AND stroke", "asymptomatic carotid disease AND cerebral infarction", "asymptomatic carotid stenosis AND stroke", "asymptomatic carotid disease AND stroke". For the association and risk stratification of patients with symptomatic carotid disease and myocardial infarction the following terms were used: "asymptomatic carotid disease AND myocardial infarction", "asymptomatic carotid stenosis AND myocardial infarction", "asymptomatic carotid disease AND myocardial ischemia", "asymptomatic carotid stenosis AND myocardial ischemia", "asymptomatic carotid disease AND acute coronary syndrome", "asymptomatic carotid stenosis AND acute coronary syndrome", "carotid stenosis AND risk of myocardial infarction", "asymptomatic AND carotid stenosis AND myocardial infarction", "asymptomatic AND carotid disease AND myocardial infarction", "asymptomatic carotid stenosis myocardial infarction.tw", "asymptomatic carotid disease myocardial infarction.tw". To limit the possibility of low quality data and enhance the scientific application of the present thesis, only studies with the above specific queries and published from 1990 up to 2019 were included. In that way, a modern and therefore, more practical interpretation of the available knowledge could be performed. All studies were investigated if they met all search criteria and had adequate scientific power and quality to provide clear and sufficient conclusions. Search engines, like Google, Pubmed as well as available software applications like Papers3, Digital Science & Research Solutions Inc, and EndNote X9.2, Clarivate™ Analytics, was used to facilitate searching. Initial search was done with those terms searched in the studies' titles, and if no results appeared, additional searches was done for the same terms in the abstract and the text of the studies. As expected, several hundreds studies may appear to match all those criteria. To comply with the scope of the present manuscript, a thorough review was done in all studies in order to identify those with high quality data, like those including large number of patients, prospective rather than retrospective studies, and those published in the most highly appreciated international and national journals. Those were considered more suitable for inclusion in the present analysis, in order to maintain the coherence and the quality of the present paper.

RESULTS

After detailed review of the available literature a total 136 studies, which looked in the relation between asymptomatic carotid disease and the occurrence of stroke or myocardial infarction, were identifying. Detailed representation of the number and the selection between those studies is provided in the graphic below:



All of the studies were separately and thoroughly examined in order to verify its scientific relevancy, accuracy and credibility to the main purpose of the present analysis. Therefore, only studies published in exceedingly respectful journals are included, which enrolled sufficient number of patients with specific definitions and clinical endpoints, were included. Important information was found regarding the risk of stroke and myocardial infarction in patients with asymptomatic carotid disease. Special attention was paid to identify group of patients at high risk for stroke and / or myocardial infarction and to determine factors, either, laboratory, anatomical or clinical, that contribute to higher incidence of stroke and / or myocardial infarction, in patients with asymptomatic carotid disease. Several group of patients may exceed higher probability of having a stroke in the future, like those suffering from cardiac disease, specifically coronary artery disease and had already undergone coronary artery bypass grafting (CABG) and elderly populations. Similarly, specific group of asymptomatic carotid patients with several clinical characteristics may experience higher incidence of myocardial infarction. Along with them, certain factors, like specific inflammation markers or particular lipid profile may also

contribute in higher risk for future cardiovascular events, including stroke and myocardial infarction, in patients with severe asymptomatic carotid disease. In the following pages, the general risk for future stroke and myocardial infarction events for patients having asymptomatic carotid disease, as well as the particular groups of patients and specific factors that may contribute to this risk.

DISCUSSION AND ANALYSIS

ASYMPTOMATIC CAROTID DISEASE & STROKE

Management of asymptomatic Carotid disease regards one of the biggest debates of modern medicine, especially as regard as the conservative or interventional management of those patients. It is widely known that the presence of atherosclerotic carotid disease is one of the most important factor for future cerebrovascular events, with probability proportionally increased to the degree of the stenosis. Nicolaides A et al. showed a relationship between ICA stenosis and event rate which was proven linear when the stenosis was expressed as percentage of the carotid bulb (ECST definition), and S-shaped when expressed as percentage of the distal internal carotid artery (NASCET definition)(Figure 8)(44-46). In addition to the degree of the stenosis, authors identified that history of contralateral TIAs and reduced renal function, defined as creatinine >85μmol/l, were also strong predictors for stroke. All three factors (degree of the stenosis, impaired renal function and history of previous contralateral TIAs), consist a group of high risk of patients, with almost double event rate of stroke comparing to the rest of the patients (7.3% vs. 0.7%). On the other hand, the annual rate for stroke was quite low in the rest of the carotid patients. Given the fact that the perioperative risk of stroke in patients undergoing, interventional repair of carotid stenosis, either with carotid endarterectomy (CEA) or carotid stenting (CAS), is ranging between 1.6-3.0%, creates a big dilemma as regard as the final management of asymptomatic patients (47) (48).

Large epidemiology studies have shown that the annual stroke rate is relatively low. In the very early studies the annual stroke rate for patients having carotid stenosis of >50% was ranging from 4.0 - 7.2% (49, 50). However, all those studies were lacking of large number and good follow-up of the patients. In the first well conducted study with 242 patients from Bock et al. the annual stroke rate was calculated in 2.7% while the combined endpoint of stroke / TIA was 3.6%, numbers well beyond the initial estimations (51). That was the first time, where the plaque constitution was shown to play important role in stroke incidence (echolucent plaques had much higher incidence of stroke compared to the echogenic ones - 5.7% vs. 2.4%, $p = 0.03$). Notably, patients with total occlusion of the internal carotid artery, had significantly lower risk for future stroke events (1.0%), but high total death rate (7.7%), indicating that carotid occlusion is not a risk factor for stroke, bur rather an indicator of advanced cardiovascular disease leading to premature death (52).

Improvement of modern medical therapy, and strict adherence with current guidelines in prevention and treatment of risk factors (hyperlipidemia, hypertension and life styles modification), played a pivotal role in stroke risk reduction in patients with asymptomatic carotid stenosis. Recent data for Sato et al., demonstrated very low risk for stroke in patients with carotid stenosis treated with optical medical treatment (0.46% or 1/249 patient-years)(53). Of note, those rates where significantly lower compared to that of patients underwent CEA for severe stenosis (4.7% or 5/107 patient-years, p=0.016 for comparison with medical treatment group), which questions the need for surgical intervention in asymptomatic patients. It is important to notice that carotid stenosis is associated with large embolic stroke. Data from the SMART study (Second Manifestation of ARTerial disease), den Hartog et al, showed that most of the major, embolic type strokes, were associated with large-vessel atherosclerotic carotid disease, whereas lacunar type of strokes were associated

with hypertension and other risk factors (54). Those data are in accordance to previously published data where, Tsiskaridze et al. shown that carotid stenosis <90% were mostly led to large embolic type strokes, while severe or sub-occlusive stenosis (90-99%) led to border zone strokes, which may implicate hemodynamic disturbance rather embolic mechanism in those patients (55).

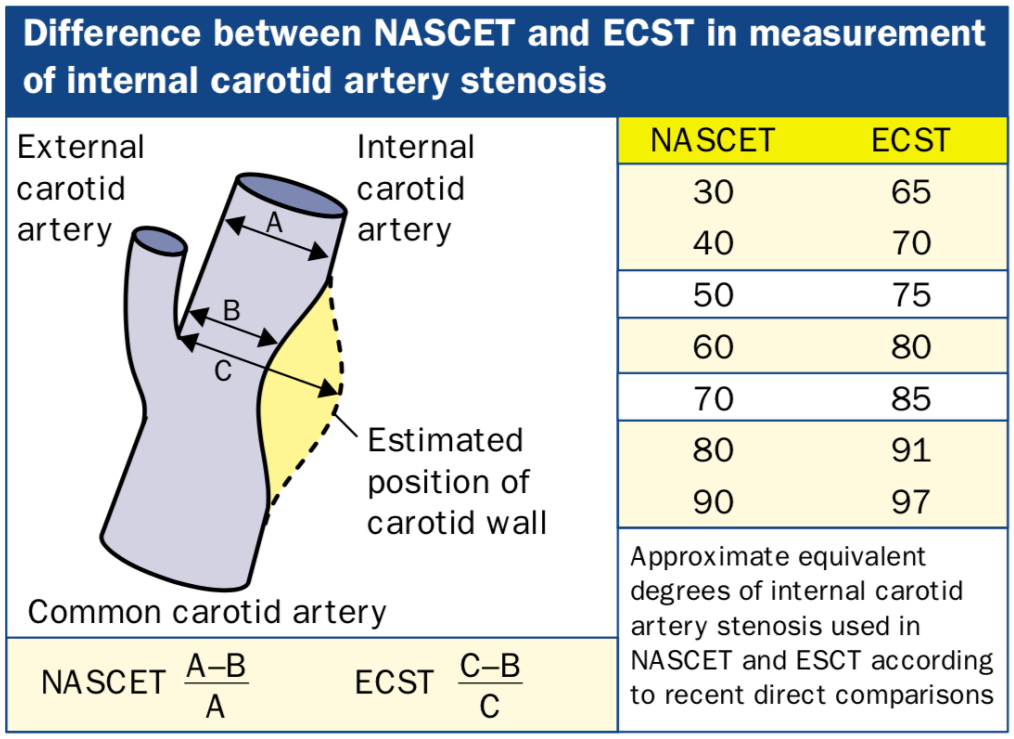


Figure 8. *Differences between the two widely acceptable methods for carotid stenosis severity estimation: The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST).*

IDENTIFICATION OF PATIENTS AT HIGH RISK FOR STROKE

As medical treatment reduced significantly the risk for stroke in patients with asymptomatic carotid disease, the role of interventional treatment, either surgical or percutaneous, is now limited. However, some risk still remains (56). As it was previously discussed, carotid artery disease is may associated with rather large stroke which may lead to severe morbidity and high grade of disability. Therefore, it is important to identify groups of patients that are at higher risk for stroke, in whom possible intervention would have been beneficial.

Several clinical and anatomical factors, associated with plaque "vulnerability", have been recognized to be associated with increased risk for stroke in patients with asymptomatic carotid disease. Additionally, in the recent years, specific diagnostic tools and imaging modalities have been developed to promptly indicate those which carotid atherosclerotic plaques are at higher risk for rupture, thrombosis or occlusion, and therefore suitable for surgical or percutaneous interventional treatment. In the following pages a thorough review of the currently available diagnostic and imaging modalities, along with all the recognizable clinical and anatomical characteristics known to be associated with increased risk for subsequent stroke events, will be discussed. (Table 3).

Table 3. Clinical, anatomical and biochemical markers of increased risk for stroke in patients with asymptomatic carotid artery disease.

Clinical Characteristivcs	Anatomical and carotid plaque characteristic	Biochemical markers
Diabetes Melitus	Plaque echolucency	Increased WBC
Sex	Presence of vasa-vasorum	Inflammation markers (hs- CRP)
Advanced Age	Thin external plaque cap	
Presence of PAD	Extensive lipid core	
Presence of previous CABG	Eterogenous plaque composition	
Previous Stroke		
Mirco-embolic signals on TCD examination		

PAD: Peripheral artery disease, CABG: Coronary Artery Disease, TCD: Transcranial examination, WBC: White Blood Cells, Hs-CPR: high-sensitive C-Reactive Protein.

Diagnostic Tools and Imaging Modalities to identify vulnerable carotid plaques

During the last decade, a significant amount of effort has been given to develop new tools that can be used to look into either the plaque characteristics or sings of previous embolic events which may predict higher chances for subsequent ones. Plaque constitution and structure has been one of the most important ones. For many decades now, plaque characteristics have been the subject of extensive research in effort to identify those who might be the more dangerous ones. Plaque echolucency is one of the most important plaque features which can be easily evaluated with almost all available ultrasound machines. More specialized software applications are needed for accurate measurement of the areas and calculate the total volume of the echolucent plaque, relative to the non-echolucent one.

From the early ‘80s, it has been shown that carotid plaque characteristics may play a role in identify subgroup of patients at higher risk for stroke. That was the principal reason behind the first classification of type of carotid plaques introduced by Gray-Weale et al, according to which, carotid plaques could be categorized in four (4) different types, based on plaque ultrasound morphology and degree of echogenity (57). According to this calcification, carotid plaques could belong in one of the four types, with Type I being the most echolucent, Type 2 being a mixed plaque, predominately more echolucent, whereas Type 3 is a mixed plaque predominately more echogenic. Type IV is most echogenic of all. More recently, an additional category (Type V) has been indroduced, to classify plaques with dense calcification which does not allow characterization of the content (Table 4, Figure 9). Based on this model, special computer software applications have been developed in order to calculate and/or categorize a carotid plaque; the Gray-Scale-Media (GSM) system of analysis is the most popular and widely used for this purpose. Langsfeld et al. showed that in patients who undergone CEA, those

with contralateral heterogenous plaques has significantly higher rates for future stroke events compared to those with homogenous ones (58). These preliminary conclusions were subsequently confirmed by Mathiesen et al. in a large prospective study including 223 patients having asymptomatic carotid disease (The Tromsø Study) (59). In this study, subjects with echolucent atherosclerotic plaques have increased risk of ischemic cerebrovascular events independent of degree of stenosis and cardiovascular risk factors.

Further and modern analysis of the additional characteristics of the plaque using specific computer models, confirmed the notion above. Kakkos et al. used, additional texture analysis of the ultrasound technical parameters, like spatial grey level dependence matrices (SGLDM), grey level run length statistics (RUNL) and Run Percentage (RP), to better plaque constitution and potential instability (60). Authors concluded that additional to GSM usage of those parameters, especially the SGLDM, may better recognize atheromatic plaque which may create embolic events in the future. Giannoukas et al. also demonstrated that echo-lucent plaques (Type I) were more prominent in young and symptomatic patients compared to type IV (61). In their study only carotid stenosis and plaque echolucency were identified as risk factors for cerebral events. Moreover, in patients who underwent carotid stenting with filter protection devices, Giannakopoulos et al. showed that the presence of embolic material particles in 30 filters (56.6%) (62). The presence of embolic material into the filter EPD was 2.38-fold increased for every category change from type IV to type I carotid plaques (OR = 2.38, 95%CI = 1.15-4.93). The association remained the same even after adjustment for the c

Table 4. Types of atherosclerotic plaques, according to the echogeninity calculated with duplex ultrasound.

Type of Plaque	
I	Predominantly echolucent with a thin echogenic cap
II	Intermediate echolucent lesions with small areas of echogenicity
III	Intermediate echogenic lesions with small areas of echolucency (<25%)
IV	Uniformly echogenic lesions (equivalent to homogenous).

linical characteristics and traditional risk factors, indicating a strong relationship between plaque features and risk for stroke. The notion of plaque echo-lucency and the risk for stroke, gained particular importance after the ICAROS study. The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) registry included 418 cases of CAS collected from 11 international centers (63). An echographic evaluation of carotid plaque with GSM measurement was made pre-procedurally. After follow-up completion, there were 11 of 155 strokes (7.1%) in patients with GSM ≤ 25 and 4 of 263 (1.5%) in patients with GSM >25 (P=0.005). The risk was even higher for patients with severe carotid stenosis (≥ 85%). Multivariate analysis revealed that GSM (OR, 7.11; P=0.002) and rate of stenosis (OR, 5.76; P=0.010) are independent predictors of stroke. Authors concluded that apart from severity stenosis, preprocedural evaluation of carotid plaques using the GSM system would be useful to identify patients who might need better protection and specific management prior,

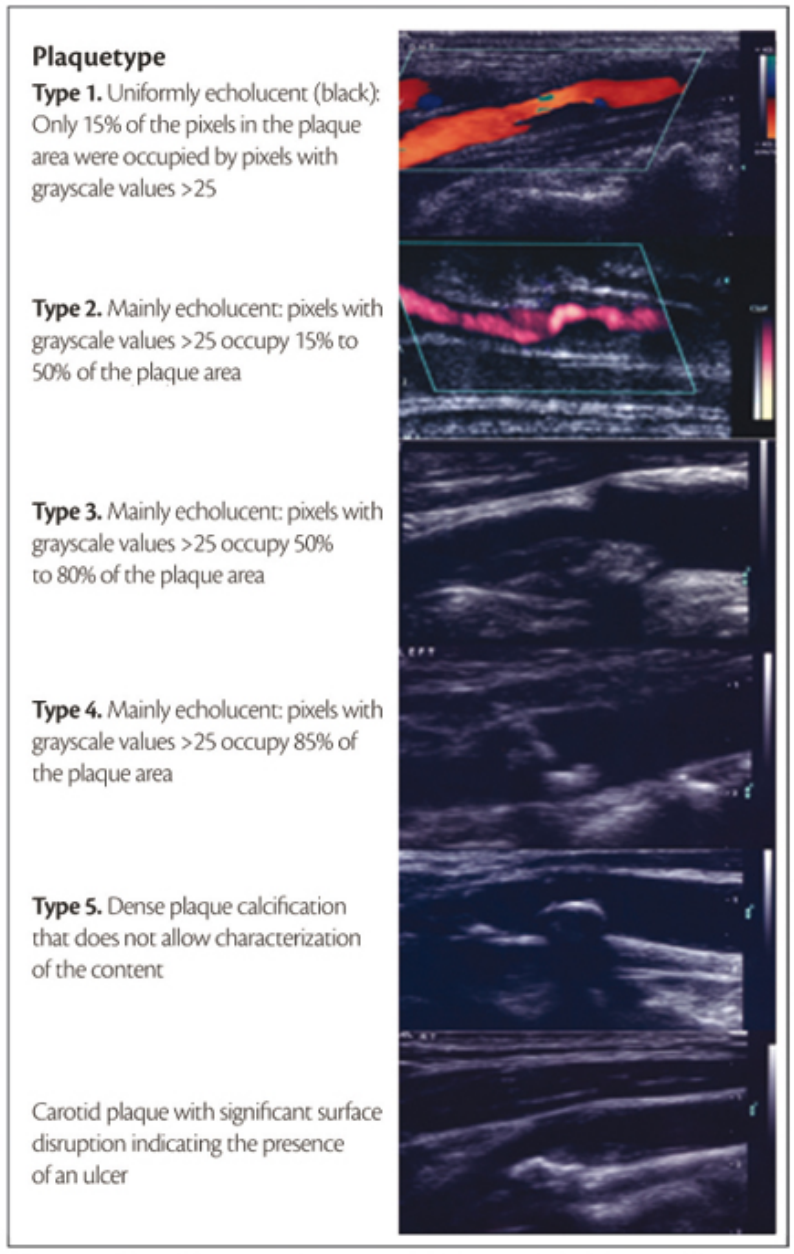


Figure 9. *Different types (I-V) of carotid plaques according to Gray-Weales classification. Duplex Ultrasound images representative of each type.*

during or after procedure, as those patients suffering from higher rates of peri- and post-procedural rates of stroke. It has to be noted that this study, refers to patient who underwent interventional treatment and therefore may not apply for asymptomatic patients managed with optimal medical therapy only. However, it was the first time where a clinical study signals an important finding with significant clinical impact.

Importantly, Reiter et al. strongly opposed these results. In their study examined 698 consecutive patients who underwent carotid scheduled carotid stenting, included in a single-center registry database and had classified the plaque morphology according to GSM levels and the Beletsky and Gray-Weale plaque scores. They found that neither GSM nor Gray-Weale's classification, had any impact on the occurrence of peri-interventional cerebral events. Contrary to ICAROS, this study was a single-center study, in which all imaging data were stored in digital form - and not in analogue, as in ICAROS - and, therefore a computer based analysis mainly done, providing accuracy and excellent repetition in plaque echo-lucency measurements. Authors also discuss that the higher number of patients enrolled in their study (698 in Reiter et al. vs. 418 in ICAROS) may also have played a role in this contradiction as in ICAROS study, high standard deviation in GSM values were noted, while in Reiter et al. study, the sample size was almost double resulting in much higher predictive power.

Gupta et al. looked at the importance of MRI in plaque characterization. Authors performed a metanalysis of nine (9) cohort studies (n = 779 patients) examining intraplaque hemorrhage, the percentage of lipid-rich necrotic core, or incidence of thinning and/or rupture of the fibrous cap. Patients were followed-up for average one (1) month for the occurrence of ipsilateral stroke or transient ischemic attack. All of the parameters checked and analyzed were identified as predictors for stroke events, either minor or major. Interestingly, the thinning or rupture of plaque cap was the strongest among all with an almost 6-fold increase of the future risk [5.93 (95% confidence interval, 2.65-13.20), whereas intraplaque hemorrhage and necrotic core were lower, yet strong hazard risks of 4.59 (95% confidence interval, 2.91-7.24), and 3.00 (95% confidence interval, 1.51-5.95), respectively(64). They concluded that presence of those three important and easy-to-identify markers, can strongly identify patients with high risk for stroke. Further to that, Howard et al. demonstrated, that in carotid plaques extracted surgically in symptomatic patients, the presence of those factors associated with increased future risk for new cerebral events. Moreover, the more of those factors the patient was presenting with, the higher the probability for stroke events, indicating that, in addition to degree of the stenosis, plaque composition may play

an important role in risk stratification in patients with carotid disease (65). Nevertheless, given all available data, plaque constitution and histopathology characteristics play an important role in patients with asymptomatic carotid disease. A recent metanalysis which included seven (7) studies and 7557 patients, found strong relationship between predominantly echo-lucent carotid plaques and the risk for future ipsilateral stroke events, across all stenosis severity. These high-level scientific data, along with the previous registries and observation data, confirms the clinical importance of the plaque structure along with stenosis severity. Apart from the clinical significance, it has been shown that measuring GSM in carotid plaques seems to be cost-effective, as an echo-lucent based strategy in selecting patients to undergo CEA may have an incremental cost-effectiveness ratio of $29.000/quality-adjusted life - years (66).

More detailed analysis on plaque morphology emerged several other characteristics which be associated with plaque instability and subsequent increased risk score, among them the presence of intra-plaque *vasa-vasorum* and presence of intra-plaque haemmorhagic spots. It is known that presence of *vasa-vasorum* play an important role in the pathogenesis of the vulnerable atheromatic plaque. Most importantly, intraplaque mirco-haemorrhages caused or associated with the presence of *vasa-vasorum* have been related to future acute cardiovascular events, among them a variety of cerebral events, as neovascularization and inflammation are thought to precipitate plaque rupture and erosion, and therefore thrombotic and embolic events. In 2004, Kleiner et al., examined postmortem specimens of arterial wall and atheromatic plaques from different vascular territories (carotid, renal and iliac arteries) for presence of inflammation and neo-vascular vessels (67). They found out that patients who had been symptomatic and experienced several cardiac, cerebral and vascular events, had significantly higher intimal macrophage content and neo-vasculatory network, compared to asymptomatic ones. These changes were uniformly present across different arterial sites, indicating for the first time a potential new marker for plaque vulnerability.

Plaque neo-vasculate and presence of intra-plaque *vasa - vasorum,* have been shown to be detected accurately, with the use of normal ultrasound, with or without the use of contrast agents (sonographic means). Apart from ultrasound, intra-plaque neo-vasculatecan be also identified using other imaging modalities like computer tomography angiography (CTA) and Magnetic Resonance Imaging (MRI) (68, 69). Both techniques have resulted in accurate and detailed identification of vasa-vasorum or their consequences i.e. intra-plaque micro-haemmorhages, using modern CTA angiography protocols and specific MRI protocols, like dynamic contrast enhanced MRI (70). As regard as the ultrasound identification of *vasa-vasorum,* it seems that constast-enchanced ultrasound (CEUS) improves imaging of carotid intima-media thickness (IMT) and permits real-time visualization of neovascularization of the atherosclerotic plaque offering high diagnostic accuracy. A recent meta-analysis and systematic review which included 20 studies which conducted to evaluate the accuracy of quantitive and qualitative accuracy of CEUS in detecting intra-plaque neo-vasculate, reported pooled sensitivity 0.80 (95% CI, 0.72-0.87), pooled specificity 0.83 (95% CI, 0.76-0.89), for qualitative measurements. For quantitative CEUS, pooled sensitivity was 0.77 (95% CI, 0.71-0.83), pooled specificity was 0.68 (95% CI, 0.62-0.73), while the pooled diagnostic odds ratio was 7.06 (95% CI, 3.6-13.82), and area under the curve was 0.888. Given the simplicity of the technique, the relative low risk of adverse events and its diagnostic accuracy, looks that CEUS is a promising noninvasive diagnostic modality for detecting intraplaque neovascularization (71).

Even though the hypothesis behind carotid intra-plaque neo-vascularization association with plaque vulnerability is strong, there were not yet sufficient data to justify clinical application of routine measurement in asymptomatic patients. Staub et al. retrospectively analyzed retrospective data from 147 symptomatic patients with carotid disease. The concluded that presence of intra-plaque neovascularization was directly associated with cerebral vascular events (72). Importantly, this association remained strong, even after adjustment with all traditional cardiovascular risk factors. Similarly, in the analysis of 4-year retrospective database, Romero et al., showed that the proportion of symptomatic patients was double in the group with enhanced intra-plaque mirco-vasculate, compared to those patients without (69). Again, this association remained independent form other known cardiovascular risk factors. The same was also proven, using other imaging modalities, like dynamic contrast enhanced MRI or intravascular optical coherence tomography (OCT) (73).

Unfortunately, there are no prospective data to justify preprocedural imaging of intra-plaque neo-vasculate, as it was never proven that any intervention in those patients may result in higher incidence of stroke. More importantly, evidence on whether those patients have to be selected or rejected for interventional treatment, or set in an intensive medical therapy before intervention, are not available. However, recent data demonstrated significant regression of the area and presence of intra—plaque *vasa-vasorum* with intense statin therapy (strictly adhered to modern Primary Prevention Guidelines with target LDL<100mg/dl) and administration of ACEi for hypertension control, which may be a sign of plaque stability and possible reduction in future stroke risk (74). Additional, prospective data, in large patients studies, are required to prove causative relation between presence of intra-plaque neo-vasculate and stroke risk. Accumulative evidence, however, may soon provide sufficient guidance to help clinicians to identify those asymptomatic patients with carotid disease, who may benefit from interventional approach, either surgical or percutaneous.

Further to plaque characteristics, additional investigation has done on plaque performance. In an effort to identify those asymptomatic plaques that may become unstable, and therefore prone to distal embolization and stroke, extensive research has done on the presence of “pre-stroke”, silent cerebral events, that may be premature signs of forthcoming stroke or TIA events. TransCranial Doppler (TCD) has been utilized extensively for this purpose. TCD ultrasonography provides a relatively inexpensive, noninvasive real-time measurement of blood flow characteristics and cerebrovascular hemodynamics within the basal arteries of the brain, obtained via different acoustic “windows” through the skull (Figure 10 a, b). Nowadays, TCD headset devices, which allows continuous monitoring while the patient is standing or lying in the examination or operator’s table, are available (Figure 10 c, d). Currently, more convenient, remote, wireless and portable TCD devices, which can be used for longer monitoring periods, are providing more comfort for both the patients and the doctor (Figure 10 e, f). They can be used in monitoring either asymptomatic patients for MicroEmbolic Signals (MES) detection, or patients undergoing CEA or carotid stenting for periprocedureal MES; in both cases, MES have been associated with increased risk for stroke.

MES are defined as short lasting (<0.01–0.03 s), unidirectional intensity increase, and intensity increase (>3 dB) within the Doppler frequency spectrum; intensity increase is focused around 1 frequency. MESs appear randomly within the cardiac cycle and produce a “whistle,” “chirping,” or “clicking” sound when passing through the sample volume (Figure 11).In retrospective studies, presence of MESs have been identified and been more frequent in patents with carotid stenosis presented as symptomatic, and abolished in those patients, who eventually underwent CEA (75). Accordingly, in patients who selected for CEA, either symptomatic or asymptomatic, who have been monitored for a specific period of time

(20 min - 1 hour), the presence of MES were significantly higher to the symptomatic ones, indicating that MESs were associated with plaque instability and potential impending stroke events (76, 77). In the first prospective study, 202 patients (231 carotid arteries) were monitored at least once for presence of brain MES with TCD (4.3 studies / artery) (78). The authors found out that although there were more ipsilateral carotid cerebrovascular events among ES-positive arteries, this was not statistically significant.

More detailed and with longer monitoring time studies, showed that MES detection is efficacious and feasible method to identify asymptomatic patients with higher risk for stroke. In the first prospective study, The Asymptomatic Carotid Emboli Study (ACES), Markus et al. enrolled 467 patients, from 26 centers worldwide with asymptomatic carotid stenosis >70%, who undergone one-hour TCD monitoring and followed-up for two years (79). In this study, the annual risk of ipsilateral stroke or TIA between base examination and 48 months was 7.13% in patients presenting embolic signals and 3.04% in those without, and for ipsilateral only stroke was 3.62% in those with, and 0.70% in those without embolic

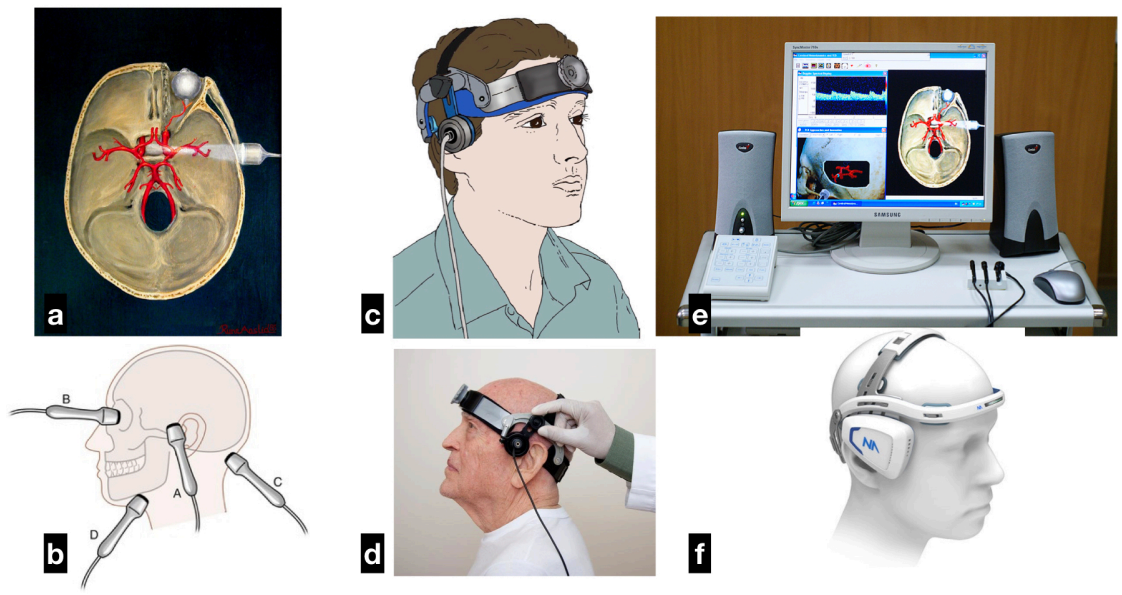


Figure 10. ***a, b:*** schematic representation of the basic principals and acoustic windows for TCD. ***c,d:*** headset TCD device. ***e:*** computer terminal for TCD recording and evaluation, ***f:*** portable TCD device. (*TCD: TransCranial Doppler*)

signals, respectively. The hazard ratio for the risk of ipsilateral stroke and TIA for patients who had embolic signals on the recording preceding the next 6-month follow-up compared with those who did not was 2.63 (95% CI 1.01-6.88; p=0.049), and for ipsilateral stroke alone the hazard ratio was 6.37 (1.59-25.57; p=0.009). Importantly, when the results were adjusted for significant risk factors for stroke, like degree of stenosis and use of antiplatelet therapy, the results remained the same. Further studies and metanalyses confirmed those results and optimized the TCD protocol in order to improve the accuracy and credibility of the method to better detect MESs (80, 81). In conclusion, TCD screening of asymptomatic patients with severe carotid disease, appears an important method to identify patients with who are at a higher risk of stroke and TIA, and also those with a low absolute stroke risk.

Clinical characteristics associated with increased risk for stroke

Further to local and anatomical plaque features, general and clinical characteristics have been demonstrated to be associated with increased risk for stroke, in patient with asymptomatic carotid stenosis. Even from the initial period of surgical treatment of severe asymptomatic carotid stenosis, diabetes, hypertension and older age have been identified as significant predictors for stroke.

It is known that diabetic patients are at high risk to develop carotid stenosis, especially those with long standing diabetes and the elderly ones (82-85). Moreover, diabetes itself has been recognized as an important factor to contribute in stroke occurrence to asymptomatic patients. Inzitari et al. studied the natural history of the asymptomatic carotid stenosis, in patients who suffered contralateral symptomatic carotid stenosis in five-years time, during the NASCET trial. History of diabetes and the degree of stenosis were mainly associated with large-artery stroke, whereas history of myocardial infarction and hypertension were associated with cardioembolic stroke (86). Additionally, in patients, high risk for vascular events, like those with PAD and/or diabetes, the presence of vascular future events, including cerebral ones, were higher in diabetic type II subgroup, comparing to other high risk subgroups (87). Additional studies confirmed those results, showing that diabetes along with anatomical and plaque-based specific features, like presence of intracranial stenosis and "soft" - echolucent carotid plaque, pose a higher risk for stoke (88). However, even though diabetes still regards an

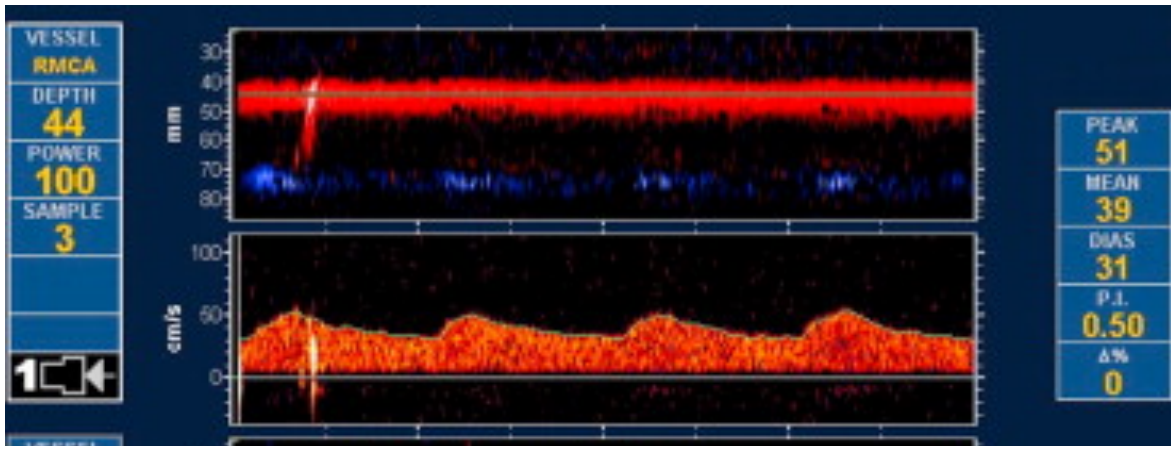


Figure 11. Typical MES detected in an 1-hour monitoring in a patient with asymptomatic severe carotid stenosis (*MES: MicroEmbolic Signal*).

important predictor for future stroke events in patients with asymptomatic carotid disease, the risk of developing a stroke remains low. In the large Second Manifestation of Arterial Disease Study, 4319 patients with clinically manifested arterial disease or specific risk factors, but without a history of cerebrovascular disease, were included and followed-up for more than six (6) years (54). The any territory annual ischemic stroke risk was 0.4% and 0.5% per year in 50% - 99%, and 0.5% per year in 70% - 99% degree of carotid stenosis, respectively, demonstrating a rather low risk for stroke irrespective of its diabetes subtype and degree of stenosis. Importantly, recent data show that treatment of diabetic patients with asymptomatic carotid stenosis with best medical treatment only, may be not enough to prevent future cerebrovascular events in diabetic patients, especially the smoker ones, and therefore it is possible that those patients may be benefit from interventional rather conservative management (89).

Along with diabetes several other, clinically based risk factors have been recognized, among them hypertension, older age, gender, smoking, sleep apnea syndrome, and obesity. Hypertension has been a known factor for cardiovascular disease development, including carotid disease. Even presence of pre-hypertension stage may be associated with higher prevalence of carotid disease, especially in men (90). Hypertension, has never been directly associated with elevated risk for stroke in patients with carotid disease, however, there are sufficient data which support the notion that controlling blood pressure within normal range, may reduce significantly the risk for stroke in those patients. Plaque instability due to intraplaque hemorrhage, and increased shear stress in the carotid plaque have been named as potential mechanisms for both elevated risk for stroke and progression of the disease (91, 92) .

There are significant differences in stroke occurrence between genders in patients with asymptomatic carotid disease. It has been known that male patients with high grade asymptomatic carotid stenosis are at substantially higher risk for stroke comparing to female and have more frequently unstable plaques in contrast to women (93, 94). Moreover, plaque imaging modalities using MRI showed that men present with higher prevalence of thin/ruptured thin fibrous carotid plaques (95). It seems then that women may have less prevalence of carotid stenosis as well as less probability to develop unstable plaque and potentially to suffer an embolic stroke than men, data to support a direct between them are not existing. It is important to mention, that women with asymptomatic carotid stenosis, benefit less from any interventional procedure comparing with men. Data from ACAS and ACST1 showed a benefit of CEA for men, but not women in 5 year risk of any stroke or perioperative death (women OR 0.96, 95% CI 0.63 to 1.45 vs men OR 0.49, 95% CI 0.36 to 0.66) (96, 97) . In contrast however, newer data from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) trial, which included patients treated with carotid stenting and CEA demonstrated equal stroke reduction rate between male and female (98). The low number of female patients included in the trail, and the inclusion of patients treated with stenting, and not with CEA only, may have affected the results.

Obesity, smoking and other important clinical syndromes like sleep apnea have been associated with elevated stroke risk particularly in men. In study where in which 390 carotid plaques, both symptomatic and asymptomatic, examined for instability features, it was shown that those obtained from obese patients were significantly associated with symptomatic status and presented more instability components, compared to those in asymptomatic ones (99). Thus, probably the “obesity paradoxical” is not the case for asymptomatic patients. Another complex relation has been identified between carotid stenosis and sleep-apnea syndrome. Both central and obstructive sleep-apnea have been recently found to be associated with increased prevalence of carotid disease and risk for cerebrovascular events (100, 101). Since sleep-apnea is a treatable disease, screening for patients with sleep-apnea syndrome and asymptomatic carotid disease, may reduce the incidence of cerebral adverse events in the future.

ASYMPTOMATIC CAROTID DISEASE & MYOCARDIAL INFARCTION

As previously discussed, carotid stenosis is part of ACD and therefore its presence would possibly associated with the presence of atherosclerotic disease in other vascular territories, among them the coronary artery tree. It is known that patients suffering from carotid disease have elevated risk for other adverse cardiovascular events like myocardial infarction. Apart from the fact that patients who undergo carotid revascularization may experience myocardial infarction in the early postoperative period, there are accumulative data, although few, that presence of asymptomatic carotid stenosis may be associated with higher risk for future acute coronary events. Even the presence of carotid bruit may be associated with increased risk for cardiac events (Figure 12). In an early prospective observational study included 500 patients with carotid bruits, without evidence of cerebral events, Chambers B and Norris JW demonstrated that 7.0% of the patients experienced coronary ischemic events in a 4-year follow-up period; The risk of cerebral events was higher in patients with severe carotid stenosis (>75%) in doppler ultrasound imaging (102). However, this was not the case for coronary adverse events, indicting that the presence of carotid disease is an independent predictor for future coronary events and myocardial infarction, regardless of its severity .

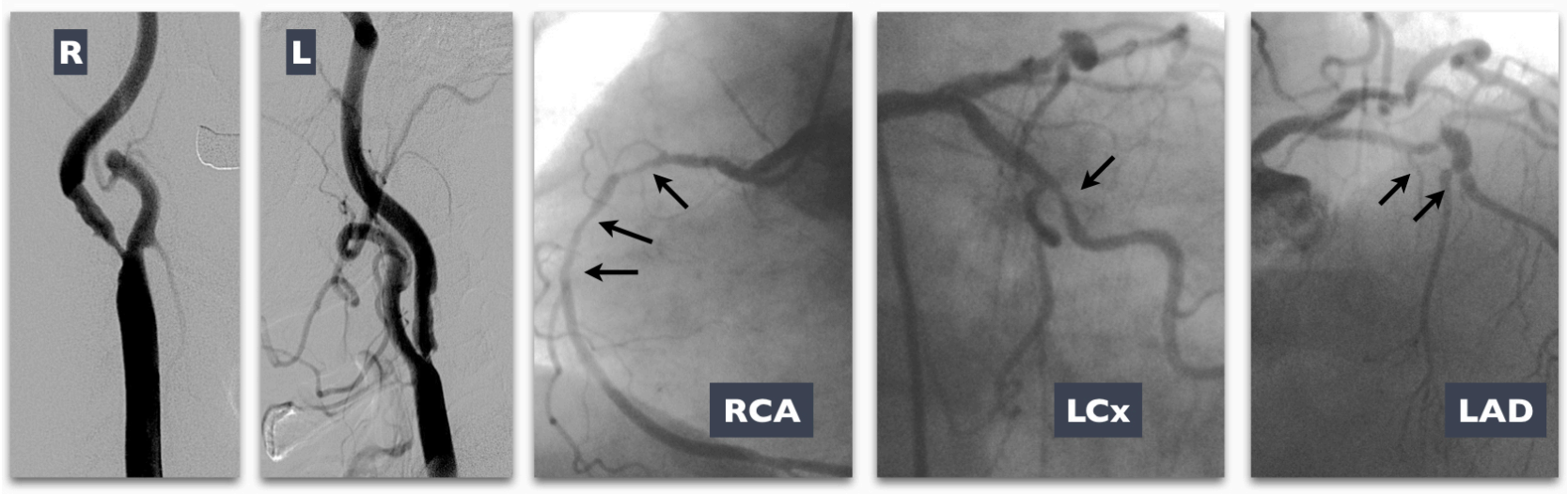


Figure 12: A 72-years-ol patients presented with minor myocardial infarction (NSTEMI) and carotid bruit. Coronary and carotid selective angiography revealed significant bilateral carotid disease and severe triple-vessel coronary artery disease. *R: right, L: Left, RCA: Right Coronary Artery, LCx: Left Circumflex coronary artery, LAD: Left Anterior Descending coronary artery.*

A subsequent large metanalysis of 20 prospective cohorts confirmed those results. The analysis included 17,295 patients with 62,413.5 patient-years of follow-up, and a sample of 273 patients followed up for average 4 years (minimum 2yrs and maximum 7yrs) (103). The risk for MI in patients with carotid bruits was 3.69 (95% CI 2.97–5.40) compared with 1.86 (0.24–3.48) in those without - both calculated per 100 patient-years. Annual rate of cardiovascular death were also higher in patients with bruits than in those without (2.85 [2.16–3.54] per 100 patient-years vs 1.11 [0.45–1.76] per 100 patient-years). In the four trials in which direct comparisons of patients with and without bruits were possible, the odds ratio was doubled for both MI [2.15 (1.67–2.78)] and death [2.27 (1.49–3.49)]. Presence of carotid disease, discovered even with clinically audible carotid bruit, may be sufficient to identify patients at high risk for coronary events, which may benefit from aggressive medical treatment, mainly antiplatelet and hypolipidemic one.

Additional studies confirmed those preliminarily data. Nadareishvili et al. studied 106 patients with asymptomatic carotid stenosis, who had completed clinical follow-up more than 5 years. The 10- and 15-year risks of myocardial infarction and non-stroke vascular death were 10.1% (95% CI, 4%-16%) and 24.0% (95% CI, 14%-34%). Interestingly, along with well-known coronary risk factors like age and diabetes, carotid stenosis was also identified as an independent risk factor for non-stoke death and myocardial infarction (104). In the SMART study (Second Manifestations of ARTerial disease), enrolled 2684 asymptomatic patients with clinical manifestation of carotid and peripheral artery disease or type 2 diabetes; of them 221 patients were identified with asymptomatic carotid disease >50% stenosis (87). None of the patients had undergone any kind of intervention or revascularization. At 5-years follow-up 8.0% of the patients with carotid stenosis experienced myocardial infarction. After adjustment for age and sex, carotid stenosis emerged as an independent predictor for vascular death and coronary events in long-term follow-up. Park et al., studied 1390 pateints who had angiographically proven CAD and scanned them for carotid disease with duplex ultrasound examination one day before or after coronary angio. Those patients who had evident carotid disease (n=433) had higher prevalence of cardiovascular risk factors and acute coronary syndrome (34.2% vs. 24.6%, p<0.001) than those without carotid plaque (n=957). On univariate analysis, carotid stenosis proven as an important predictor of cardiac death, MACE (death, myocardial infarction and stroke), whereas presence of abnormal intima-media thickness identified as a predictor of total cardiovascular events. Multivariate analysis revealed that carotid plaque was associated with cardiac death (HR 6.99, 95% CI 1.88-25.95, p=0.004), hard MACE (HR 1.89, 95% CI 1.18-3.04, p=0.008) and total MACE (HR 1.47, 95% CI 1.13-1.90, p=0.004), whereas CIMT was associated only with total MACE (HR 1.39, 95% CI 1.06-1.81, p=0.017). Those data confirm the notion that carotid artery disease, is a robust marker of advanced coronary artery disease, associated with worse prognosis and indicate that those patients may require intense medical treatment, with close follow-up and possibly early and complete intervention to achieve complete repair of the coronary arteries, either with surgical and/or percutaneous interventions.

Carotid atheromatic stenosis regards an important risk factor for acute coronary events. The Reduction of Atherothrombosis for Continued Health (REACH) Registry enrolled 45227 patents with 4-year follow-up; 10725 patients had documented carotid atherosclerosis (105). After adjustment for cardiovascular risk factors and geographic region, the possibility for cardiac events increased by 22% in patients with carotid atherosclerosis versus without. The relative increase was 18% in patients enrolled with multiple risk factors only, 25% in patients with coronary artery disease, and 46% in patients with history of cerebral disease, and 37% in patients with peripheral disease. An interesting analysis was made, according to the symptomatic status of both coronary artery disease (patients with history of myocardial infarction) and carotid atherosclerosis (patients with stroke). In both groups, carotid atherosclerosis independently predicted coronary future events, with multivariable-adjusted HRs of 1.36 (95% CI, 1.13–1.63) in stroke patients and 1.32 (95% CI, 1.18–1.47) in patients with myocardial infarction for any cardiac events. The corresponding multivariable-adjusted HR for major coronary end points were 1.54 (95% CI, 1.09–2.17) and 1.37 (95% CI, 1.11–1.70), respectively. In conclusion, carotid stenosis was an independent predictor of coronary events in patients with symptomatic coronary artery disease and patients with previous cerebrovascular manifestation of carotid disease (stroke) and no myocardial infarction. Therefore, it appears that carotid disease may again classify patients with any type of vascular disease who at high risk for death and myocardial infarction. Yet, data from a prospective registry showed that asymptomatic carotid stenosis is a predictor of

events in patients without significant coronary artery disease. Patients who had clinically driven coronary angiography, without known carotid disease, underwent concomitant digital substraction angiography (DSA) of the carotid arteries. Carotid artery stenosis were associated with an increased risk of the composite major adverse cardiovascular events among patients without evident coronary artery disease (CAD) (hazard ratio=3.17 [95% confidence interval, 1.52-6.60]; P<0.01; and hazard ratio=1.69 [0.95-3.01]; P=0.07, respectively) though not in patients with CAD (106). These findings emphasize the fact that presence carotid stenosis should be considered as CAD equivalent. This is important especially for those patients in whom severe obstructive CAD has been excluded on basis of coronary angiography, but still retain a high risk for future cardiac events. However, recent analysis of a smaller group of patients (n=395) who had simultaneous coronary angiography and carotid DSA failed to confirm the previous results. In this study, patients with concomitant coronary and carotid disease had significantly higher coronary and cerebrovascular adverse events (MACCEs). Nevertheless, the rate of MI was numerically higher in patients with carotid and coronary disease comparing to those having only coronary artery disease, without reaching statistical significance (5.0% vs. 2.7%, p=0.331, respectively).

Not only the presence of carotid disease, but further the progression of severity of the stenosis may predict myocardial infarction. In a prospective study of 1065 patients with carotid stenosis without previous cerebral event, who had serial of ultrasound examinations within a range of 6-9 months, 93 patients (9.0%) were identified with disease progression (107). Patients with progressive carotid stenosis had a significantly increased risk for cardiovascular events compared with patients with non-progressive disease, with almost 2-fold increase in total MACE and at HRs varied from 1.59 to 1.75 for the rest of cardiac events, including MI, peripheral vascular events and death from cardiac or peripheral disease causes. These results were also confirmed by Balestini et al. who evaluated prospectively 523 patients with asymptomatic carotid disease. All patients had ultrasound re-evaluation at 12-months post initial examination and followed-up for a median period of 42 months (108). During follow-up 96.7% of patients without carotid disease progression remained without clinical events. On the contrary, among the patients with progressive disease, 53.7% experienced a vascular event and 27.1% experienced an ipsilateral stroke. It appears that patients with progression of pre-existing carotid disease, may be at higher risk for cardiovascular events, including myocardial infarction. Therefore, a prospective repeated evaluation of carotid disease severity and its progression, comparing to baseline images, may be considered to recognize patients on potentially higher coronary risk who may benefit from adjective medical treatment or even coronary revascularization, if amenable.

It is known that carotid plaque morphology is an important predictor for stroke events in patients with asymqptomcatid carotid stenosis, even of moderate severity. In addition to the disease progression, the morphology of the carotid plaques may be associated with the severity of coronary artery events. In the study of Komorovsky et al., 337 patients who underwent coronary angiography because of an acute coronary syndrome (ACS) and had additional carotid duplex examination within 15 day's post index event. Both carotid and coronary lesion complexity and structure were recorded (109). Authors found out that the prevalence of hard carotid plaques is higher among patients who have complex coronary lesions than among those who have simple coronary lesions, and this prevalence increases with an increased extent of CAD. Moreover, patients with ACS who presented with hard carotid lesions and complex coronary lesions had significantly worse outcome comparing to other carotid/coronary morphology plaque combinations. Recent studies, tried to explain these finding. Hamada et al. analyzed the carotid plaque composition of 97 patients who admitted for CEA or

carotid stenting, using pre-procedural MRI carotid imaging, by calculating the ratio of plaque intensity to muscle intensity on T1-weighted image (110). They found a clear association of carotid plaques of high-intensity on T1-weighted MRI, with the presence as well as the future development of coronary artery disease. Those carotid plaques could be regarded as "unstable" ones, and may be considered as a clinical phenotype of systemic inflammation and a strong marker for imminent cardiac events.

CONCLUSIONS

Carotid artery stenosis is a part of general atherosclerotic disease. Its presence is strongly associated with increased risk for both cerebral and cardiac adverse events, with the most predominant one; the stroke. As the future risk for stroke in those patients is relatively small, the decision to treat them with either conservative or interventional treatment (surgical / percutaneous) is an important one, with the fact that any intervention carries an inherent risk for periprocedural adverse events. Not all patients with asymptomatic carotid disease have the same risk for future stroke. Significant differences have been found among those patients. Several clinical and anatomical characteristics have been found to be strongly associated with elevated risk for future stroke events. Plaque composition and morphology, asymptomatic micro-embolic signals as detected with TCD, and several inflammation markers have been identified as the most potent among the rest. Patients presenting with those risk factors have significantly increased risk for stroke comparing to others. The more of the them a patient presents with, the higher the risk. It appears that in addition to the degree of the stenosis, plaque composition and morphology, as this can be identified with advanced imaging techniques either using ultrasound or MRI, are the most important features to predict future events. Since carotid disease is a form of generalized atherosclerotic disease, one can expect presence of atherosclerotic disease in other vascular territories, primarily in coronary arteries. A significant proportion of patients suffering from carotid disease, have coronary artery disease as well. The majority of those patients is at high risk for future cardiac events. More specifically, those with advanced carotid stenosis and progression of the severity of the stenosis, appear to be at higher risk for cardiac death and/or myocardial infarction. Importantly, along with future stroke risk, carotid plaque characteristics and morphology, can also predict future cardiac risk, especially myocardial infarction.

Asymptomatic carotid disease regards an important manifestation of generalized atherosclerotic disease. Patients presenting with carotid stenosis, either unilateral or bilateral, are at increased risk for future coronary and cerebrovascular adverse events. Identifying those patients, regards one of the most important tasks of modern cardiovascular medicine, in effort to select those who will benefit from either intensive primary prevention treatment or prompt early interventional therapy. Continuous ongoing research is needed to further increase the accuracy and precision of the current methods and markers, in order to early and precisely recognize patients with asymptomatic carotid disease who are at increased risk, in an effort to prevent them from the potential future catastrophic consequences of disability, myocardial infarction, and death.

BIBLIOGRAPHY

1. Barquera S, Pedroza-Tobias A, Medina C, Hernandez-Barrera L, Bibbins-Domingo K, Lozano R, et al. Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. Arch Med Res. 2015;46(5):328-38.
2. Nowbar AN, Howard JP, Finegold JA, Asaria P, Francis DP. 2014 global geographic analysis of mortality from ischaemic heart disease by country, age and income: statistics from World Health Organisation and United Nations. Int J Cardiol. 2014;174(2):293-8.
3. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1483-92.
4. Nowbar AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. Mortality From Ischemic Heart Disease. Circ Cardiovasc Qual Outcomes. 2019;12(6):e005375.
5. Institute of Health Metrics and Evaluation (IHME) S, WA, USA www.healthdata.org Accessed December 2019. Global Burden of Disease (GBD) Project. 2017.
6. Miller G, Hughes-Cromwick P, Roehrig C. National spending on cardiovascular disease, 1996-2008. J Am Coll Cardiol. 2011;58(19):2017-9.
7. Miller G, Cohen JT, Roehrig C. Cost-effectiveness of cardiovascular disease spending. J Am Coll Cardiol. 2012;60(20):2123-4.
8. 2017 CS. CVD Statistics. http://www.ehnheart.org/cvd-statistics.html. Accessed Dec 2019.
9. Maniadakis N, Kourlaba G, Cokkinos DV, Angeli A, Kyriopoulos J. The economic burden of atherothrombosis in Greece: results from the THESIS study. Eur J Health Econ. 2013;14(4):655-65.
10. Gioldasis G, Talelli P, Chroni E, Daouli J, Papapetropoulos T, Ellul J. In-hospital direct cost of acute ischemic and hemorrhagic stroke in Greece. Acta Neurol Scand. 2008;118(4):268-74.
11. Kritikou P, Spengos K, Zakopoulos N, Tountas Y, Yfantopoulos J, Vemmos K. Resource utilization and costs for treatment of stroke patients in an acute stroke unit in Greece. Clin Neurol Neurosurg. 2016;142:8-14.
12. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139-e228.
13. Ntaios G, Bornstein NM, Caso V, Christensen H, De Keyser J, Diener HC, et al. The European Stroke Organisation Guidelines: a standard operating procedure. Int J Stroke. 2015;10 Suppl A100:128-35.
14. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.
15. Papanagiotou P, Ntaios G, Papavasileiou V, Psychogios K, Psychogios M, Mpotsaris A, et al. Recommendations for Mechanical Thrombectomy in Patients with Acute Ischemic Stroke : A Clinical Guide by the Hellenic Stroke Organization. Clin Neuroradiol. 2018;28(1):145-51.
16. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.
17. Rossello X, Huo Y, Pocock S, Van de Werf F, Chin CT, Danchin N, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. Int J Cardiol. 2017;245:27-34.
18. Degano IR, Salomaa V, Veronesi G, Ferrieres J, Kirchberger I, Laks T, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. Heart. 2015;101(17):1413-21.

19. Kanakakis J, Ntalianis A, Papaioannou G, Hourdaki S, Parharidis G. Stent for Life Initiative--the Greek experience. EuroIntervention. 2012;8 Suppl P:P116-20.
20. Panagiotakos DB, Georgousopoulou EN, Pitsavos C, Chrysohoou C, Metaxa V, Georgiopoulos GA, et al. Ten-year (2002-2012) cardiovascular disease incidence and all-cause mortality, in urban Greek population: the ATTICA Study. Int J Cardiol. 2015;180:178-84.
21. Makaris E, Michas G, Micha R, Gkotsis D, Panotopoulos C, Pisimisis I, et al. Greek socio-economic crisis and incidence of acute myocardial infarction in Southwestern Peloponnese. Int J Cardiol. 2013;168(5):4886-7.
22. Kollia N, Panagiotakos DB, Georgousopoulou E, Chrysohoou C, Tousoulis D, Stefanadis C, et al. Exploring the association between low socioeconomic status and cardiovascular disease risk in healthy Greeks, in the years of financial crisis (2002-2012): The ATTICA study. Int J Cardiol. 2016;223:758-63.
23. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke. 2010;41(6):1294-7.
24. Pilcher JM, Danaher J, Khaw KT. The prevalence of asymptomatic carotid artery disease in patients with peripheral vascular disease. Clin Radiol. 2000;55(1):56-61.
25. Marsico F, Ruggiero D, Parente A, Pirozzi E, Musella F, Lo Iudice F, et al. Prevalence and severity of asymptomatic coronary and carotid artery disease in patients with lower limbs arterial disease. Atherosclerosis. 2013;228(2):386-9.
26. Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. Eur J Vasc Endovasc Surg. 2009;37(3):262-71.
27. Marsico F, Giugliano G, Ruggiero D, Parente A, Paolillo S, Guercio LD, et al. Prevalence and severity of asymptomatic coronary and carotid artery disease in patients with abdominal aortic aneurysm. Angiology. 2015;66(4):360-4.
28. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528.
29. Bots ML, Looman SJ, Koudstaal PJ, Hofman A, Hoes AW, Grobbee DE. Prevalence of stroke in the general population. The Rotterdam Study. Stroke. 1996;27(9):1499-501.
30. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. Eur J Epidemiol. 2012;27(4):287-95.
31. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, et al. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. Stroke. 1999;30(2):363-70.
32. Tsivgoulis G, Patousi A, Pikilidou M, Birbilis T, Katsanos AH, Mantatzis M, et al. Stroke Incidence and Outcomes in Northeastern Greece: The Evros Stroke Registry. Stroke. 2018;49(2):288-95.
33. Stranjalis G, Kalamatianos T, Gatzonis S, Loufardaki M, Tzavara C, Sakas DE. The incidence of the first-ever stroke in a Mediterranean island population: the isle of Lesvos stroke study. Neuroepidemiology. 2014;43(3-4):206-12.
34. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.
35. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.
36. Elgendy IY, Kumbhani DJ, Mahmoud A, Bhatt DL, Bavry AA. Mechanical Thrombectomy for Acute Ischemic Stroke: A Meta-Analysis of Randomized Trials. J Am Coll Cardiol. 2015;66(22):2498-505.

37. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-31.
38. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, et al. Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients: A Meta-Analysis. Stroke. 2017;48(9):2450-6.
39. Xiong YJ, Gong JM, Zhang YC, Zhao XL, Xu SB, Pan DJ, et al. Endovascular thrombectomy versus medical treatment for large vessel occlusion stroke with mild symptoms: A meta-analysis. PLoS One. 2018;13(8):e0203066.
40. Campbell BCV, Majoie C, Albers GW, Menon BK, Yassi N, Sharma G, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol. 2019;18(1):46-55.
41. Phan K, Saleh S, Dmytriw AA, Maingard J, Barras C, Hirsch JA, et al. Influence of ASPECTS and endovascular thrombectomy in acute ischemic stroke: a meta-analysis. J Neurointerv Surg. 2019;11(7):664-9.
42. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. New England Journal of Medicine. 2016;374(11):1021-31.
43. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med. 2016;374(11):1011-20.
44. North American Symptomatic Carotid Endarterectomy Trial C, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445-53.
45. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet. 1998;351(9113):1379-87.
46. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. Eur J Vasc Endovasc Surg. 2005;30(3):275-84.
47. DD DEW, Morris D, GJ DEB, Bulbulia R, Halliday A. Asymptomatic carotid artery stenosis: who should be screened, who should be treated and how should we treat them? J Cardiovasc Surg (Torino). 2017;58(1):3-12.
48. Moresoli P, Habib B, Reynier P, Secrest MH, Eisenberg MJ, Filion KB. Carotid Stenting Versus Endarterectomy for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis. Stroke. 2017;48(8):2150-7.
49. Roederer GO, Langlois YE, Jager KA, Primozich JF, Beach KW, Phillips DJ, et al. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. Stroke. 1984;15(4):605-13.
50. Bogousslavsky J, Despland PA, Regli F. Asymptomatic tight stenosis of the internal carotid artery: long-term prognosis. Neurology. 1986;36(6):861-3.
51. Bock RW, Gray-Weale AC, Mock PA, App Stats M, Robinson DA, Irwig L, et al. The natural history of asymptomatic carotid artery disease. J Vasc Surg. 1993;17(1):160-9; discussion 70-1.
52. Hackam DG. Prognosis of Asymptomatic Carotid Artery Occlusion: Systematic Review and Meta-Analysis. Stroke. 2016;47(5):1253-7.
53. Sato K, Fujiyoshi K, Hoshi K, Noda C, Yamaoka-Tojo M, Ako J, et al. Low Stroke Rate of Carotid Stenosis Under the Guideline-Oriented Medical Treatment Compared With Surgical Treatment. Int Heart J. 2016;57(1):80-6.
54. den Hartog AG, Achterberg S, Moll FL, Kappelle LJ, Visseren FL, van der Graaf Y, et al. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. Stroke. 2013;44(4):1002-7.
55. Tsiskaridze A, Devuyst G, de Freitas GR, van Melle G, Bogousslavsky J. Stroke with internal carotid artery stenosis. Arch Neurol. 2001;58(4):605-9.

56. Conrad MF, Boulom V, Mukhopadhyay S, Garg A, Patel VI, Cambria RP. Progression of asymptomatic carotid stenosis despite optimal medical therapy. J Vasc Surg. 2013;58(1):128-35 e1.
57. Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. J Cardiovasc Surg (Torino). 1988;29(6):676-81.
58. Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. J Vasc Surg. 1989;9(4):548-57.
59. Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromso study. Circulation. 2001;103(17):2171-5.
60. Kakkos SK, Stevens JM, Nicolaides AN, Kyriacou E, Pattichis CS, Geroulakos G, et al. Texture analysis of ultrasonic images of symptomatic carotid plaques can identify those plaques associated with ipsilateral embolic brain infarction. Eur J Vasc Endovasc Surg. 2007;33(4):422-9.
61. Giannoukas AD, Sfyroeras GS, Griffin M, Saleptsis V, Nicolaides AN. Association of plaque echostructure and cardiovascular risk factors with symptomatic carotid artery disease. J Cardiovasc Surg (Torino). 2010;51(2):245-51.
62. Giannakopoulos TG, Moulakakis K, Sfyroeras GS, Avgerinos ED, Antonopoulos CN, Kakisis JD, et al. Association between plaque echogenicity and embolic material captured in filter during protected carotid angioplasty and stenting. Eur J Vasc Endovasc Surg. 2012;43(6):627-31.
63. Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. Circulation. 2004;110(6):756-62.
64. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke. 2013;44(11):3071-7.
65. Howard DP, van Lammeren GW, Rothwell PM, Redgrave JN, Moll FL, de Vries JP, et al. Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk. Stroke. 2015;46(1):182-9.
66. Baradaran H, Gupta A, Anzai Y, Mushlin AI, Kamel H, Pandya A. Cost Effectiveness of Assessing Ultrasound Plaque Characteristics to Risk Stratify Asymptomatic Patients With Carotid Stenosis. J Am Heart Assoc. 2019;8(21):e012739.
67. Fleiner M, Kummer M, Mirlacher M, Sauter G, Cathomas G, Krapf R, et al. Arterial neovascularization and inflammation in vulnerable patients: early and late signs of symptomatic atherosclerosis. Circulation. 2004;110(18):2843-50.
68. Vicenzini E, Giannoni MF, Puccinelli F, Ricciardi MC, Altieri M, Di Piero V, et al. Detection of carotid adventitial vasa vasorum and plaque vascularization with ultrasound cadence contrast pulse sequencing technique and echo-contrast agent. Stroke. 2007;38(10):2841-3.
69. Romero JM, Pizzolato R, Atkinson W, Meader A, Jaimes C, Lamuraglia G, et al. Vasa vasorum enhancement on computerized tomographic angiography correlates with symptomatic patients with 50% to 70% carotid artery stenosis. Stroke. 2013;44(12):3344-9.
70. Sun J, Song Y, Chen H, Kerwin WS, Hippe DS, Dong L, et al. Adventitial perfusion and intraplaque hemorrhage: a dynamic contrast-enhanced MRI study in the carotid artery. Stroke. 2013;44(4):1031-6.
71. Huang R, Abdelmoneim SS, Ball CA, Nhola LF, Farrell AM, Feinstein S, et al. Detection of Carotid Atherosclerotic Plaque Neovascularization Using Contrast Enhanced Ultrasound: A Systematic Review and Meta-Analysis of Diagnostic Accuracy Studies. J Am Soc Echocardiogr. 2016;29(6):491-502.
72. Staub D, Patel MB, Tibrewala A, Ludden D, Johnson M, Espinosa P, et al. Vasa vasorum and plaque neovascularization on contrast-enhanced carotid ultrasound imaging correlates with cardiovascular disease and past cardiovascular events. Stroke. 2010;41(1):41-7.
73. Aoki T, Rodriguez-Porcel M, Matsuo Y, Cassar A, Kwon TG, Franchi F, et al. Evaluation of coronary adventitial vasa vasorum using 3D optical coherence tomography--animal and human studies. Atherosclerosis. 2015;239(1):203-8.

74. Magnoni M, Ammirati E, Moroni F, Norata GD, Camici PG. Impact of Cardiovascular Risk Factors and Pharmacologic Treatments on Carotid Intraplaque Neovascularization Detected by Contrast-Enhanced Ultrasound. J Am Soc Echocardiogr. 2019;32(1):113-20.e6.
75. Markus HS, Thomson ND, Brown MM. Asymptomatic cerebral embolic signals in symptomatic and asymptomatic carotid artery disease. Brain. 1995;118 (Pt 4):1005-11.
76. Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. Stroke. 1999;30(7):1440-3.
77. Stork JL, Kimura K, Levi CR, Chambers BR, Abbott AL, Donnan GA. Source of microembolic signals in patients with high-grade carotid stenosis. Stroke. 2002;33(8):2014-8.
78. Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. Stroke. 2005;36(6):1128-33.
79. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol. 2010;9(7):663-71.
80. King A, Shipley M, Markus H. Optimizing protocols for risk prediction in asymptomatic carotid stenosis using embolic signal detection: the Asymptomatic Carotid Emboli Study. Stroke. 2011;42(10):2819-24.
81. Best LM, Webb AC, Gurusamy KS, Cheng SF, Richards T. Transcranial Doppler Ultrasound Detection of Microemboli as a Predictor of Cerebral Events in Patients with Symptomatic and Asymptomatic Carotid Disease: A Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg. 2016;52(5):565-80.
82. De Angelis M, Scrucca L, Leandri M, Mincigrucci S, Bistoni S, Bovi M, et al. Prevalence of carotid stenosis in type 2 diabetic patients asymptomatic for cerebrovascular disease. Diabetes Nutr Metab. 2003;16(1):48-55.
83. Wang J, Wu J, Zhang S, Zhang L, Wang C, Gao X, et al. Elevated fasting glucose as a potential predictor for asymptomatic cerebral artery stenosis: a cross-sectional study in Chinese adults. Atherosclerosis. 2014;237(2):661-5.
84. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups. Stroke. 2014;45(8):2366-71.
85. Safri LS, Lip HTC, Saripan MI, Huei TJ, Krishna K, Md Idris MA, et al. Older age and duration of exposure to type 2 diabetes in selective screening of asymptomatic carotid artery stenosis for primary stroke prevention-A single institution experience. Prim Care Diabetes. 2019.
86. Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med. 2000;342(23):1693-700.
87. Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der Graaf Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. Stroke. 2007;38(5):1470-5.
88. Lam TD, Lammers S, Munoz C, Tamayo A, Spence JD. Diabetes, intracranial stenosis and microemboli in asymptomatic carotid stenosis. Can J Neurol Sci. 2013;40(2):177-81.
89. Lim S, Mora-Pinzon M, Park T, Yoon W, Crisostomo PR, Cho JS. Medical therapy does not confer stroke prevention for all patients: identification of high-risk patients with asymptomatic carotid stenosis is still needed. Int Angiol. 2019;38(5):372-80.
90. Wang D, Zhou Y, Guo Y, Wang C, Wang A, Jin Z, et al. Arterial pre-hypertension and hypertension in intracranial versus extracranial cerebrovascular stenosis. Eur J Neurol. 2015;22(3):533-9.
91. Yang JW, Cho KI, Kim JH, Kim SY, Kim CS, You GI, et al. Wall shear stress in hypertensive patients is associated with carotid vascular deformation assessed by speckle tracking strain imaging. Clinical Hypertension. 2014;20(1):10.
92. Tuenter A, Selwaness M, Arias Lorza A, Schuurbiers JCH, Speelman L, Cibis M, et al. High shear stress relates to intraplaque haemorrhage in asymptomatic carotid plaques. Atherosclerosis. 2016;251:348-54.

93. Dick P, Sherif C, Sabeti S, Amighi J, Minar E, Schillinger M. Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. Stroke. 2005;36(6):1178-83.
94. Wendorff C, Wendorff H, Kuehnl A, Tsantilas P, Kallmayer M, Eckstein HH, et al. Impact of sex and age on carotid plaque instability in asymptomatic patients-results from the Munich Vascular Biobank. Vasa. 2016;45(5):411-6.
95. Ota H, Reeves MJ, Zhu DC, Majid A, Collar A, Yuan C, et al. Sex differences of high-risk carotid atherosclerotic plaque with less than 50% stenosis in asymptomatic patients: an in vivo 3T MRI study. AJNR Am J Neuroradiol. 2013;34(5):1049-55, S1.
96. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? Lancet. 2004;364(9440):1122-3; author reply 5-6.
97. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. Stroke. 2004;35(10):2425-7.
98. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD, 2nd, Gonzales NR, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol. 2011;10(6):530-7.
99. Rovella V, Anemona L, Cardellini M, Scimeca M, Saggini A, Santeusanio G, et al. The role of obesity in carotid plaque instability: interaction with age, gender, and cardiovascular risk factors. Cardiovasc Diabetol. 2018;17(1):46.
100. Mason RH, Mehta Z, Fonseca AC, Stradling JR, Rothwell PM. Snoring and severity of symptomatic and asymptomatic carotid stenosis: a population-based study. Sleep. 2012;35(8):1147-51.
101. Ehrhardt J, Schwab M, Finn S, Guenther A, Schultze T, Witte OW, et al. Sleep apnea and asymptomatic carotid stenosis: a complex interaction. Chest. 2015;147(4):1029-36.
102. Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. N Engl J Med. 1986;315(14):860-5.
103. Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. The Lancet. 2008;371(9624):1587-94.
104. Nadareishvili ZG, Rothwell PM, Beletsky V, Pagniello A, Norris JW. Long-term risk of stroke and other vascular events in patients with asymptomatic carotid artery stenosis. Arch Neurol. 2002;59(7):1162-6.
105. Sirimarco G, Amarenco P, Labreuche J, Touboul PJ, Alberts M, Goto S, et al. Carotid atherosclerosis and risk of subsequent coronary event in outpatients with atherothrombosis. Stroke. 2013;44(2):373-9.
106. Steinvil A, Sadeh B, Bornstein NM, Havakuk O, Greenberg S, Arbel Y, et al. Impact of carotid atherosclerosis on the risk of adverse cardiac events in patients with and without coronary disease. Stroke. 2014;45(8):2311-7.
107. Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P, et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. Stroke. 2007;38(11):2887-94.
108. Balestrini S, Lupidi F, Balucani C, Altamura C, Vernieri F, Provinciali L, et al. One-year progression of moderate asymptomatic carotid stenosis predicts the risk of vascular events. Stroke. 2013;44(3):792-4.
109. Komorovsky R, Desideri A, Coscarelli S, Cortigiani L, Tonello D, Visonà A, et al. Predictive value of associations between carotid and coronary artery disease in patients with acute coronary syndromes. American Journal of Cardiology. 2005;95(1):116-9.
110. Hamada S, Kashiwazaki D, Yamamoto S, Akioka N, Kuwayama N, Kuroda S. Impact of Plaque Composition on Risk of Coronary Artery Diseases in Patients with Carotid Artery Stenosis. J Stroke Cerebrovasc Dis. 2018;27(12):3599-604.