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Postgraduate Thesis

"Risk stratification for ischemic heart disease in patients with asymptomatic carotid stenosis"

by

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Nikolaos A. Vryzas

Abstract

Atherosclerosis is a systemic inflammatory vascular disease, involving multiple arterial beds and is associated with the progressive accumulation of lipids, calcium, blood components, carbohydrates and fibrous tissue on the intimal layer of greater and medium-sized arteries, leading to the invasion of leukocytes and smooth muscle cells into the intima, a process that leads to the formation of atherosclerotic plaques. Despite the fact that improvement of pharmacotherapy and revascularization have significantly optimized the prognosis of patients with atherosclerotic vascular disease, myocardial infarction and stroke remain the major causes of mortality worldwide.

Patients with symptomatic atherosclerotic disorder on a certain organ, e.g. heart - ischemic heart disease (IHD), are not only on a risk of acute myocardial infarction (AMI) but also on high-risk of clini9cal manifestations from the brain e.g. transient ischemic attack (TIA) or ischemic stroke mainly due to carotid artery stenosis, or appearance of clinical manifestations from the limbs (Peripheral arterial disease). Patients with history of TIA or ischemic stroke due to carotid artery stenosis (CAS) show two or three times higher risk for AMI compared to the general population. Likewise, patients with IHD have three times higher risk for TIA or ischemic stroke, while patients with PAD have three or four times higher risk for developing ischemic heart failure compared to the general population.

The asymptomatic carotid artery stenosis is associated with increased prevalence of IHD and the annual risk of AMI is high, ~ 3-5%. The prevalence rate of asymptomatic CAS >50% is estimated to be around 2-8% and that of asymptomatic CAS >80% between 1-2%. Correlation between several (vascular) risk factors and CAS has been demonstrated by many studies. The evaluation of the cardiovascular risk factors, classical either new markers like carotid intima-media thickness (cIMT), the coronary artery calcium (CAC) score and the evaluation of morphological characteristics of the atherosclerotic plaque, will help us to detect and stratify patients in high risk for cardiovascular disorders like IHD, especially those who are still asymptomatic.

In this review, are discussed the major studies regarding the risk stratification for cardiovascular disorders and especially for IHD in patients with asymptomatic carotid stenosis, providing the readers with an insightful analysis, in order to assist in selecting potential candidates for cardiovascular intervention. It is very important the establishment of a diagnostic method that can accurately extract the group of patients who have the highest future risk of developing ischemic heart disease. Thus, early recognition of patients at higher risk would maximize the potential benefits of revascularization or optimal medical therapy (OMT), as well as would ameliorate the prognosis.

Key-words: Risk stratification, ischemic heart disease, asymptomatic carotid stenosis, intima-media thickness, carotid plaque

List of abbreviations

ACAS: Asymptomatic Carotid Atherosclerosis Study

ACS: Asymptomatic Carotid Stenosis

ACSRS: Asymptomatic Carotid Stenosis and Risk of Stroke

ACST: Asymptomatic Carotid Surgery Trial

CAS: Carotid Artery Stenting

CDI: Colour Doppler Imaging

CEA: Carotid Endarterectomy

CEMRA: Contrast Enhanced Magnetic Resonance Angiography

CEUS: Contrast-Enhanced Ultrasonography

CTA: Computed Tomography Angiography

CVR: Cerebrovascular Reserve

DSA: Digital Subtraction Angiography

DUS: Duplex Ultrasonography

ECST: European Carotid Surgery Trial

GSM: Gray-Scale Median

JBA: Juxtaluminal Black Areas

NASCET: North American Symptomatic Carotid Endarterectomy Trial

PSV: Peak Systolic Velocity

RI: Resistance Index

TCD: Transcranial Doppler

TIA: Transient Ischemic Attack

Contents

1. Introduction

1.1 Atherosclerosis

Nowadays cardiovascular diseases (CVDs) are one of the major mortality causes in both developed and developing countries. In particular, Alexopoulos [1] notes that cardiovascular disease is the most common cause of death among European men under 65 years old and second most common in women. In addition, Tutuzas [2] observe that atherosclerotic disease is the main cause of death especially in developed countries. CVDs are characterized by the presence of atherosclerosis in the body's vessels, also known as atherosclerotic disease consisting of atherosclerotic plaques.

Initially, it is necessary to define the word atherosclerosis. The word atherosclerosis is etymologically derived from the ancient word "athyroma", which means "powdered cereal". Hippocrates used this word to describe the fatty core of atherosclerotic plaques. Later, Filis [3] highlights that atheromatous disease was previously described as a degenerative disease, inevitable of ageing. However, recent research has shown that the hypothesis of old age is obsolete and atherosclerosis is now described as a chronic inflammatory condition that is preventable.

More specifically, atherosclerotic disease according to Grigoriadou-Manousaki is a chronic disease which leads to the formation of atherosclerotic plaques on the inner layer of the arteries in combination with hardening and loss of elasticity of the arterial wall [4]. Atherosclerotic disease has the ability to affect large and medium-sized arteries. Thus, atherosclerotic plaques cause stenosis or even obstruction of the arterial lumen resulting in tissue and organ ischemia. Atherosclerotic plaques consist of lipids, mainly cholesterol, mostly in complexes with proteins, cholesterol esters, inflammatory cells, fibrous tissue and thrombi. Atherosclerosis [5, 6] is a progressive disease that initiates early in childhood but its clinical manifestations appear usually in the middle age and beyond. The basic morphological alteration is the atherosclerotic plaque or atheroma, which is formed in the intima of the artery and develops slowly and silently without

clinical symptoms for many years, is initially asymptomatic. Haztintuntas [7] describes the four stages of atherosclerotic changes in the arterial wall. Stages 1 and 2 include thickening of the tunica intima of the vessel and formation of vacuolar cells-macrophage cells characterized by accumulation of cholesterol, stage 3 is characterized by accumulation of extracellular lipids, stages 4 and 5 are characterized by atheromatous plaque formation, while stage 6 involves complicated lesions.

Finally, according to Tutuzas (2010), the most severe clinical manifestation of atheromatosis of arteries, which are characterized by very high mortality and morbidity, are the manifestations of acute coronary syndrome (ACS), as well as stroke [2]. In particular, according to estimations, by 2030 40% of the overall mortality will be owed to atherosclerotic disease. Kremastinos emphasizes that it is important to investigate any kind of atherosclerosis because it is inevitable that in the future it will cause myocardial infarction (MI), stroke, or rupture of the aneurysm of the arteries or thrombosis of the arteries [8].

1.1.1 Epidemiology of atherosclerosis

Atherosclerosis-related cardiovascular diseases (coronary artery diasese, ischemic heart disease, cerebrovascular diasease and peripheral arterial disease) it is estimated to be the world's leading cause of death by 2020 [9]. Atherosclerotic carotid artery stenosis above 50% is responsible for 15-20% of stroke including Transient Stroke (TIAs) [10-11]. Hemodynamically significant carotid stenosis> 50% has an incidence of 1-3% worldwide. Above 65 years, the average incidence is increased to 6.9% [12]. The incidence of asymptomatic carotid stenosis varies according to gender and age. In a recent study [13] based on population studies, a narrowing of> 50% was observed in 4.8% of men and 2.2% in women below 70 years old. Those rates were increased to 12.5% for men and 6.9% for women when the population age was above 70 years. While severe asymptomatic stenosis of 70% or higher has an incidence of 0-3.1% in the general population [14].

A recent systematic review and meta-analysis [13] estimated the incidence of asymptomatic carotid stenosis as follows: Incidence of 4.2% (95% Confidence Interval (CI) 3.1 to 5.7) for a 50% or greater and incidence of 1.7% (95% Confidence Interval (CI), 0.7 to 3.9), for a stenosis of 70% or greater.

The Cardiovascular Health Study demonstrated a five-year risk of 5% for the occurrence of fatal or non-fatal stroke in a patient with asymptomatic carotid stenosis with a stenosis of 70% or greater [15]. Recent data show that patients with asymptomatic stenosis of the internal carotid arteries of> 50% have stroke at a rate of 0.5-1% annually [16, 17].

As a result of the aging of the population and the increase in the incidence of carotid disease, with increasing age, asymptomatic carotid disease is expected to become a frequent entity in today's clinical practice in the near future [18].

1.1.2 Pathophysiology of atherosclerosis

Atherosclerosis is caused by the development of lesions in the wall of the arteries. Kremastinos (2009) reports that the core of atherosclerotic plaques is mainly composed of oxidized LDL cholesterol with calcium deposition [8]. These plaques are surrounded by a fibrous tissue capsule that progressively grows and narrows the arteries gradually or weakens their wall, causing their wall to be stretched and create aneurysms. Atherosclerosis begins since adolescence or adulthood in the form of lesions of the tunica intima of the arteries. Atherosclerotic plaques are infiltrated by inflammatory cells, thereby weakening the fibrous capsule (FB) and at some point breaking and creating a thrombus that occludes the artery abruptly and causes the MI or stroke. The process of inflammation is signaled by the production of specific proteins and their antibodies circulating in the blood. Hence, if we detect these substances we can suspect the incidence of a potential cardiovascular event.

Concurrently, atherosclerosis is a complex evolutionary and systematic disease of the arteries that primarily affects the tunica intima of the large and middle-sized arteries

of systemic circulation. Chronic inflammatory response plays an important role regarding the activation of the pathophysiology of the disease and the infiltration of the tunica intima from monocytes-macrophages and T lymphocytes in combination with coexisting endothelial dysfunction and the accumulation of oxidized LDL are the dominant findings of atherogenesis [19].

Hypercholesterolemia, hypertension, smoking and oxidative reactions, occurring in all forms of inflammation destroy or injure endothelial cells of the vessel that results in premature atherosclerosis, which starts from the endothelium. LDL cholesterol plays major role in the formation of the atherosclerotic plaque. The early atherosclerotic lesion is called as fatty streak which is formed in the tunica intima of the arteries by circulating lipids. In addition, exogenous and endogenous factors such as smoking, age, hypertension, diabetes mellitus (DM) and dyslipidemia, accelerate the growth of atherosclerotic plaque in size by accumulated lipids, inflammatory cells and fibrous tissue and may cause partial or complete occlusion arterial lumen.

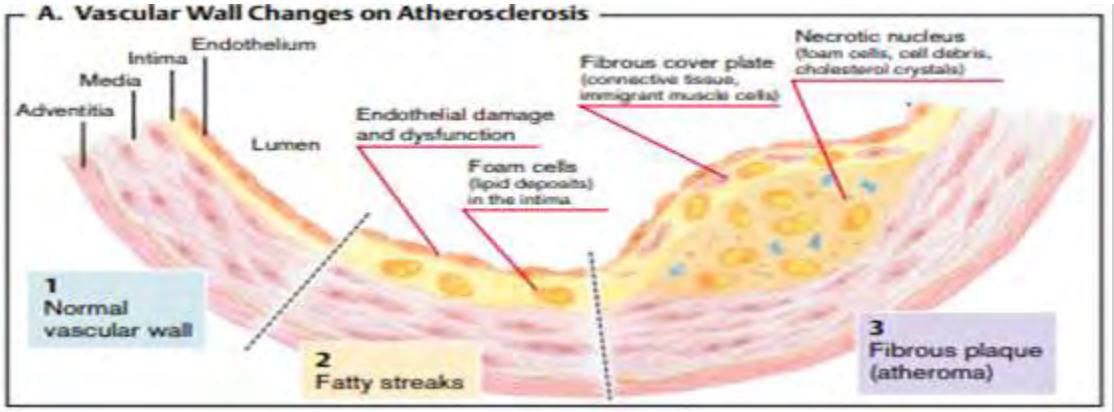


Figure 1."Vascular Wall Changes on Atherosclerosis"

Endothelial cells regulate dilatation of smooth muscle fibers through nitric oxide and contraction through endothelin release. Endothelin acts on platelets and on the subendothelial tissue. In addition, it is necessary for the healing process of small and medium-sized wounds. It also stimulates endothelial cells and monocytes/macrophages. The high-density lipoprotein (HDL) does not penetrate the endothelium. In contrast, low-density lipoprotein (LDL) can be oxidized and penetrate the endothelium in the form of oxidized lipids. Oxidized LDL is toxic to macrophages and it can’t be discarded.

Thereinafter, cells are self-destructed and die - necrosis of the fatty cells. Each dead cell is an additional stimulus for the body which then attempts to self-protect by activation of the immune system. Macrophages and smooth muscle cells migrate to the lumen of the vessel, where they settle beneath the endothelial cells and get multiplied. As a result, the endothelium progressively protrudes into the lumen and loses its smooth surface. This ongoing procedure is known as neoendotheliosis which narrows the vascular lumen and results in turbulent blood flow, which stimulates the endothelium and this causes a vicious cycle.

Furthermore, atherosclerosis results in target organ damage from ischemia and atherothrombosis-atheroembolism. Endothelial injury by platelet aggregation or macrophage necrosis promotes the proliferation of monocytes and smooth muscle cells that migrate to the lesion area. This process continues for many years due to the permanent mechanical or lipidemic loading that is transmitted to the endothelium [8].

Finally, the lipid-rich plates may rupture (unstable atherosclerotic plaque). At the point of rupture, platelets accumulate and a blood clot forms that can completely occlude a previously open arterial lumen. Sudden arterial occlusion due to rupture of the atherosclerotic plaque is now considered to be the predominant mechanism for the manifestation of acute ischemic events, and in particular acute coronary events. In addition, a portion of the ruptured atherosclerotic plaque can detach and cause embolism at peripheral sites (atheroembolism) of the arterial network [4].

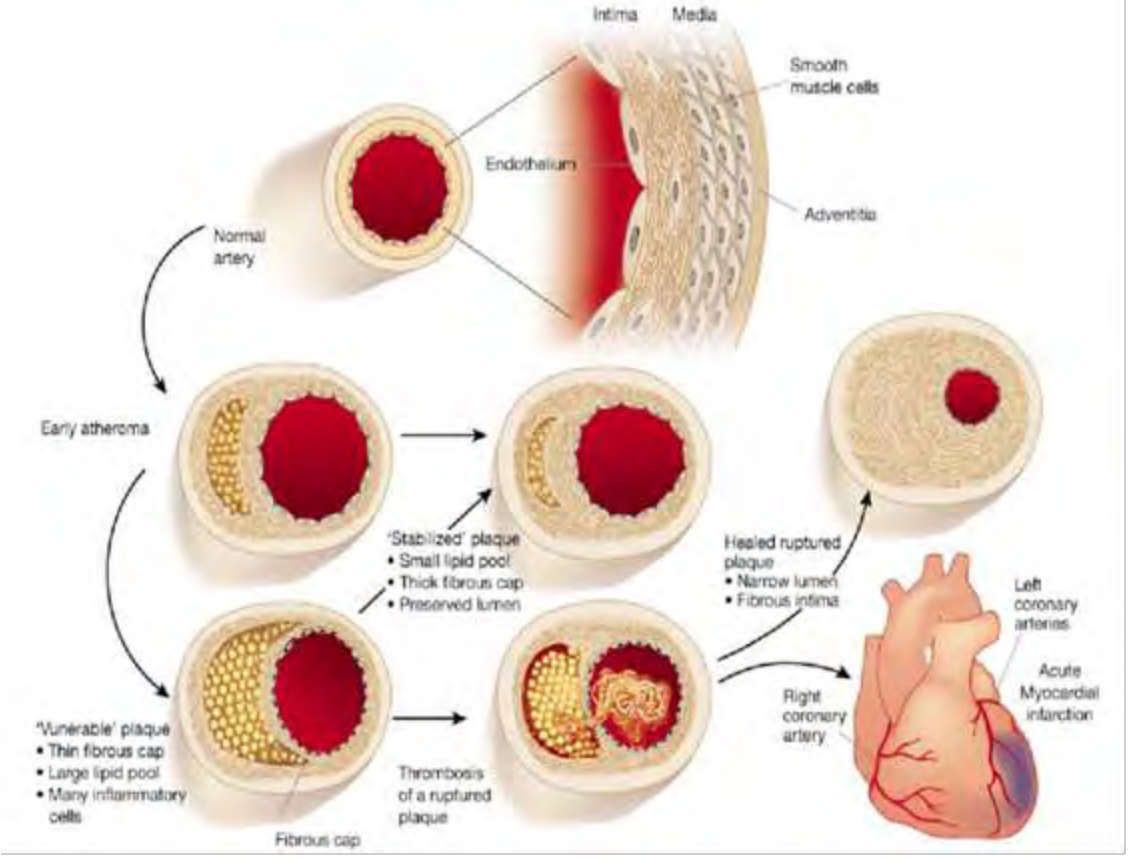


Figure 2. "The progression of Atherosclerosis"

1.1.3 Classical and novel risk factors of atherosclerosis

Parameters and diseases that occur more frequently in people who develop "premature" atherosclerosis than the general population are defined as "risk factors" and are as follows:

1. Hyperlipidemia

2. HDL-cholesterol

3. Arterial hypertension

4. Smoking

5. Diabetes mellitus (DM)

6. The family history of myocardial infarction less than 55 years for men or less than 65 years for women

7. The male sex

8. The history of cerebrovascular disease or PAD

9. Obesity

10. Sedentary lifestyle

11. The high concentration of Lp (a) (> 30mg / dl)

Nowadays, high concentration of fibrinogen has begun to be evaluated as a risk factor, particularly when deciding to treat hyperlipidemia [20]. The co-existence of risk factors of more than one greatly increases the level of risk. The result is not cumulative but multiplicative [20].

However, early diagnosis and treatment, avoiding the parameters established as risk factors, especially when treated from an early age [21], there is no doubt that it will help to prevent and reduce the mortality of cardiovascular disease.

The severity of classical risk factors for the development of atheromatosis varies across the arterial beds and the coexistence of risk factors beyond one, greatly increases the level of risk for premature atherosclerosis [22]. Hypertension is one of the most important risk factors for atherosclerosis. According to the studies of Delker et al., and Grouse et al., there was a remarkable relation between hypertension and hypercholesterolemia with carotid atherosclerosis and IHD [23, 24].

DM is considered equivalent to coronary artery disease (CAD) and vice versa many patients with CAD have already had diabetes [25]. DM has been suggested by several researchers as an independent risk factor for atherosclerosis of carotids and coronary arteries [26, 23]. However, it was demonstrated moderate correlation of DM in

the general population, with both CAD and atherosclerosis of the carotid arteries. In addition, the correlation was strong in women with DM with CAD and atherosclerosis of carotids. Thus, diabetes is the more important risk factor for CAD in women than in men. This risk certainly becomes even greater when other risk factors, such as arterial hypertension, obesity and smoking [27] coexist. Smoking also has been shown that increases the risk of cardiovascular disease. Based on the data provided by the WHO, 80% of premature deaths that were caused by heart disease and stroke could be avoided with healthy eating, systematic physical activity and smoking cessation [25].

According to Dandoulakis the risk of CAD is rising with a positive family history in first-degree relatives as the number of family members with coronary artery disease increases and as younger is the age at which family members developed CAD [25]. Early atherosclerosis often occurs in members of the same family. In many cases, this can be attributed to the hereditary transfer of risk factors such as hypertension, hyperlipidemia and DM. In the studies of Hamby et. Al., and Ten Kate et., Al demonstrated families with severely premature vascular disease, where none of the known risk factors showed any impact. Family history is one of the most important factors regarding the clinical evaluation of the patients. A positive family history is significantly associated with carotid and coronary atherosclerosis [28, 29].

In addition, according to many studies it is well known that physical exercise has a wide range of beneficial effects on the atherosclerosis progression, resulting in 20% -25% reduction in overall cardiovascular mortality [25].

1.2 Carotid disease

1.2.1 Epidemiology of carotid disease

It is estimated that 5-10% of people over 65 have a carotid stenosis over 50% that maybe asymptomatic. Among those suffering from CAD or PAD, the percentage of those

with carotid disease is 20-30%. According to bibliography, ultrasound screening of carotid arteries is indicated after 50 years of age in individuals who have at least one of the risk factors for atherosclerosis. Men under 75 have a higher risk of developing a carotid disease than women in the same age group, while, women are at greater risk than men are over 75 years [7].

According to clinical studies, mostly atherosclerotic plaques in the carotid artery are located in the carotid bifurcation and approximately 40% at the beginning of the ICA [30]. In addition rupturing an atherosclerotic plaque is more often seen in the left CCA.

1.2.2 Anatomy of carotid arteries

The right common carotid artery arises from the anonymous artery, while the left common carotid arises from the aortic arc. Each common carotid artery is directed in the cervix and divided into two other branches, the internal carotid artery (ICA) and the external carotid artery (ECA). The ECA blood supplies most of the face, throat, larynx and lower jaw through its lateral branches. The ICA is the continuation of the common carotid pathway after the split. It crosses the base of the skull with the carotid canal, advances into the cavernous sinus and divides into four branches, the anterior cerebral artery, the anterior choroidal artery, the posterior communicating artery and the middle cerebral artery. The ocular artery is a collateral branch of the ICA. The most important part of the brain vessels comes from the ICA. ICA consists of four main sections: the cervical, the petrous, the cavernous and the supraclinoid.

The two ICA are supplying most of the anterior brain circulation. The two vertebral arteries that protrude from the subclavian arteries through the basal artery, supply most of the posterior circulation of the brain. The cerebral branches of the carotid arteries and the spinal arteries communicate at the base of the brain at Willis arterial circle.

At the bifurcation of common carotid artery, the enlarged final end of the common carotid artery forms the carotid sinus, while the enlarged initial end of the ICA forms the carotid bulb. In the outermost carotid layer of the carotid sinus, there are many nerve fibers, which act as baroreceptors for the reflex regulation of blood pressure.

1.2.3 Pathophysiology of carotid disease

Carotid arteries and spinal arteries are branches of the aorta directing from the cervix towards the sculp, carrying blood rich in oxygen and nutrients to the brain. Carotid arteries belong to the class of elastic arteries and it is a large diameter vessel. The wall of the common carotid consists of three layers from inside towards outside, tunica intima, tunica media and tunica adventitia. The intima consists of an endothelial layer and a thin basement membrane. It is noted that in young people with a healthy carotid wall, the intima is thin enough and its contribution to the mechanical properties of the arterial wall is insignificant and with the progress of age, the thickness of the intima increases with the contribution of the mechanical behavior of the wall to become more important. The tunica media contains smooth muscle cells as well as a water matrix containing proteoglycans. Finally, the tunica adventitia consists of a dense network of collagen fibers along with elastin, nerves and fibroblasts, a layer that restricts the acute overdilation of the vessel.

Pathological changes of the tunica intima components are associated with the development of atherosclerosis. Atherosclerotic disease affects large and medium-sized arteries and is characterized by endothelial dysfunction, vascular inflammation, lipid accumulation, cholesterol and calcium as well as cellular debris within the tunica intima. The deposition of these materials causes the formation of atherosclerotic plaque that was described in a previous chapter in details, which may cause stenosis or obstruction in the lumen of the vessel. As more and more material accumulates, the arteries narrow and harden and this atherosclerotic process may extend to such an extent that decrease or

disrupt blood flow through the carotid, then this is called carotid artery disease or carotid obstructive disease.

The presence of atherosclerosis in the carotid arteries may cause disturbances in normal blood circulation and decreased blood supply [31]. This results in reduced blood supply to the brain and therefore increases the risk of stroke [32]. Stroke is the third cause of death in the developed countries and the first cause of disability in Europe. Carotid disease is responsible for 25% of cerebrovascular events. Studies and clinical data demonstrate that the probability of incidence of ischemic stroke is significantly increased when the carotid stenosis is over 60-70%. According to Sacco et al., the degree of carotid stenosis does not always predict which patients will develop symptomatic disease [33]. Patients with severe carotid stenosis and especially symptomatic patients are at high risk for stroke, in particular the likelihood of an individual suffering from ischemic stroke increases significantly when the carotid stenosis is over 60-70% [34]. However, even low grade carotid stenosis can also lead to stroke.

Regarding the causes of carotid disease: 90% of carotid damage is due to atherosclerosis, while the remaining 10% is due to aneurysms, arteritis, carotid artery dissection, fibromuscular dysplasia, radiation and vasospasm.

1.2.4 Clinical manifestations of carotid disease

When atherosclerosis affects the carotid arteries, it may be revealed by a lot of symptoms, mainly by neurological conditions such as transient ischemic attack (TIA) or stroke. The main symptoms-manifestations are the followings: syncope, sudden loss of vision, blurred vision, or difficulty seeing one or both eyes, tingling or numbness on one side the face or one side of the body, sudden confusion and/or dizziness, aphasia, difficulty in speaking, sudden severe headache and memory problems, or even death [35].

Patients with neurological and ophthalmic symptoms, with audible though auscultation carotid murmur or with atherosclerotic disease in other areas of the body, the patient should be referred for ultrasound examination of carotid arteries [36].

1.2.5 Diagnostic approach of carotid disease

• Color Doppler Ultrasound (CDU)

High-resolution ultrasound scanning of blood vessels using B-scan and Doppler ultrasound provides information not only on the grade of stenosis but also on the characteristics of the arterial wall including the size and composition of atherosclerotic plaques [37]. The sensitivity and specificity of CDU for detection of stenosis > 60% is 94% and 92%, respectively [38]. CDU scanning in a certified diagnostic laboratory is the initial imaging method for estimating the degree of stenosis in symptomatic and asymptomatic patients and the method of screening for the screening control of high-risk asymptomatic patients. The recognition of a 50-99% stenosis in symptomatic neurologic patients or 70-99% in asymptomatic patients is sufficient to make a therapeutic decision for surgery [39].

• Axial Angiography (CTA), Magnetic Angiography (MRA), Digital Abstracted Angiography (DSA)

When CDU is non-diagnostic or demonstrates of intermediate grade stenosis (50-69%) in an asymptomatic patient, additional visualization with (MRA, CTA or DSA) is required prior to any kind of intervention. When it is required pre-invasive control of proximal or intracranial carotid segments in order to decide the type of treatment, further (CTA, MRA or DSA) control is indicated. CTA is preferred compared to MRA due to its superiority in the detection of calcifications. The sensitivity and specificity of CTA for detection of 70-99% stenosis is 85% and 93% respectively, while for detection of total obstruction is 97% and 99% respectively [40]. In a study of 2005, MRA showed 100% sensitivity and 99.3% specificity to detect >70% stenosis and total obstruction [41]. When there is a deviation between two minimally invasive diagnostic methods (US, MRA, CTA), it is indicated to perform DSA in order to clarify the results. DSA is

important when there are ambiguities about the grade of stenosis from the minimally invasive methods, or if it is scheduled a transcatheter opening of carotid artery [39].

1.2.6 Treatment of carotid disease

Carotid Disease is predominantly treated by modifying risk factors, essentially by changing a person's lifestyle, such as stopping smoking, limiting alcohol, controlling and regulating blood pressure and cholesterol, weight loss and daily exercise in order to decelerate the progression of atherosclerosis and thereby decelerate the increase in carotid stenosis.

In the treatment of carotid disease, antiplatelet therapy is mandatory in order to inhibit platelet function by reducing adherence of platelets to the atherosclerotic plaque, thereby reducing the chance of rupturing the atherosclerotic plaque and detachment of its fragments transporting it towards brain causing potential athero-embolic events in brain. Another very importan weapon in order to treat carotid disease are statins, which retard atherosclerosis and reduce LDL [35].

Another way to treat carotid disease is surgical intervention and carotid endarterectomy (CEA), which is the most common procedure for carotid opening and it has very good and long-term results. In addition, carotid artery angioplasty with stent placement, in which the carotid artery stenosis is opened with a balloon under radiological control [35]. Surgical treatment is the most prevalent method in patients with carotid disease especially if they have a significant degree of stenosis, usually more than 70%.

1.3 Novel and classical ultrasonographic markers with diagnostic and predictive value

1.3.1 Characteristics of atheromatous plaque of the carotid bifurcation (degree of stenosis, morphology of carotid plaque)

Severity of stenosis

The analysis of the results of two large randomized clinical trials (ECST and NASCET) according to which the grade of stenosis has been established as the key factor regarding therapeutic decisions in carotid disease, demonstrated that the percentage of stenosis (but not> 99%) was predictive of increased risk for stroke in patients treated with medication [42]. However, studies regarding endarterectomy for asymptomatic carotid artery stenosis, like ACAS [43] and Carotid Surgery Trial (ACST) [44] did not indicate that a) the increase in the grade of stenosis, b) bilateral severe stenosis, and c) severe stenosis and heterolateral obstruction were predictive of stroke in patients treated with medical therapy [45].

In order to limit the number of purposeless surgical interventions in patients with asymptomatic stenosis> 70%, with the only criterion to be the grade of stenosis, the last decades several imaging tools have been developed for the effective morphological description of atherosclerotic plaques and accurate prediction of the overall atherosclerotic "load" of each patient.

Carotid Intima-Media Thickness (cIMT)

B-mode ultrasound is a widely used and important tool for examining the vessel wall and assessing atherosclerotic plaques of the carotids. Intima Media complex consists of endothelial cells, connective tissue and smooth muscle cells and is a part of the vessel where the atherosclerotic plaque develops [46].

Pathological thickening of tunica intima of the arteries is the most common and most commonly detectable clinical manifestation of atherosclerosis [47, 48]. The thickness of

the intima-media is not only an early marker of atherosclerosis but also a marker of hypertrophy/hyperplasia of the smooth muscle tissue that may be associated with genetic factors, hypertension and age-related vascular wall hardening [49].

The effect of arterial hypertension on the IMT of common carotid artery (CCA-IMT) was indirectly studied in the RADIANCE study, which showed that CCA-IMT is more influenced by BP and less than atherosclerosis [50].

The CCA-IMT measurement has multiple advantages in monitoring atherosclerosis as it can be performed without side effects and without radial overload for patients. At the same time, it is a low-cost method and provides accurate information about atherosclerotic ‘’load’’ of vessels, in addition to traditional risk factors. In addition, CCA-IMT measurements have been found to conform to microscopic pathological studies [51, 52].

The cIMT measurement includes the estimation of the combined thickness of the intima and media wall of the carotid artery. This combined measurement, as the existing technology in ultrasonographic devices (using standard probes) provides insufficient longitudinal resolution for the discrimination of tunica intima and media (20% is intima and 80% is media) [53]. In case of healthy intima-media complex, 97.5% consists of the tunica media, while when there is atherosclerotic disease, 80% of the IMT consists of the tunica media [54]. Ultrasonographically, IMT is defined by a double line that is depicted at the proximal and distal wall of the common carotid arteries in longitudinal view. It is delineated by two parallel lines consisting of the edges of two anatomical boundaries: the border lumen-tunica intima and the border tunica media-adventitia[55].

Technique of measuring IMT

When measuring, the various parts of the arterial wall (common carotid, carotid bulb) should be displayed in a longitudinal section perpendicular to the ultrasound beam. Both vascular walls (proximal and distal) should be clearly displayed so that measurements of the diameter to be feasible. The ideal diameter of the vessel lumen should be calculated during diastole of the heart in a sequence of pictures (cine-loop). At

the recorded area it should be clearly distinguished the borders of lumen-intima/media-adventitia layers. cIMT should be measured at the distal wall of the CCA at a distance of 0.5 cm from the carotid bulb and for one centimeter longitudinally [56]. (figure 3)

Ultrasonographic definition of atheromatous plaque

Atherosclerotic plaques are defined ultrasonographically as focal structures that project within the arterial lumen, at least 0.5 mm or 50% relation to the adjacent IMT value or if they have a thickness of> 1.5 mm [56]. (Figure 4)

The thickness of Intima-Media (IM) in clinical practice

Endothelial thickness and presence of atherosclerotic plaque are recommended for the initial assessment of total cardiovascular risk in asymptomatic patients of intermediate risk with two or more cardiovascular risk factors according to the NCEP and coexisting metabolic syndrome with a family history premature cardiovascular disease, a known CAC score 0 and Framingham Risk Score (FRS), equal to 11-12% [56].

The predictive value of cIMT

The Kuoppio Ischaemic Heart Disease study was the first to show a correlation between cIMT and future coronary events. In this study, each 0.1 mm IMT increase was accompanied by an 11% increase in risk for MI during follow up [57]. A meta-analysis [58], which included data from eight studies (31,197 patients) where patients were followed-up on average for 5.5 years, showed that the risk of MI and stroke was 1.26 (95% confidence interval [CI] 1.21-1.30 based on age and gender).

For each 0.1 mm difference in IMT, the probability of manifestation MI and stroke was 1.15 (1.12-1.17) and 1.18 (1.16-1.21) respectively. Even after taking into consideration all the cardiovascular risk factors, IMT remained an independent prognostic factor for the manifestation of cardiovascular event. Recently studies have shown that the combination of conventional risk factors for IHD with IMT improves the prognosis for IHD in diabetic patients and that endothelial thickness is useful for identifying high-risk patients for macrovascular complications of diabetes [59].

Other major clinical trials such as:

- ARIC (Atherosclerosis Risk in Communities) study [60]
- *CHS (Cardiovascular Health Study) [61]*
- CAPS (Carotid Atherosclerosis Progression Study) [62]
- MDCS (Malmo Diet and Cancer Study) [63]
- Rotterdam Study [64]

showed that CIMT can be used to assess the imminent cardiovascular risk.

A recent meta-analysis of a large population (45828 patients) that assessed only the endothelial thickness of the CCA excluding the presence of carotid plaques or IMT measurements in the bulb demonstrated that measurement of the CCA-IMT does not add substantial information to the existing cardiovascular prognostic models risk [65]. Based on the results of this meta-analysis, the 2013 ACC / AHA International Prevention Guidelines downgraded IMT as a measurerement [66].

Measurements of CCA-IMT have a stronger prognostic value regarding stroke prognosis, while the endothelium of ICA (ICA-IMT) appears to predominate in the prognosis of cardiovascular events of atherosclerotic aetiology [53].

The echogenicity of Intima-Media (IM)

Ultrasonographic IMT measurement is established in the clinical and research level, however the utility of measuring the echogenicity of the IM complex is under investigation [67]. Echogenicity measurements that have been performed on atherosclerotic plaques, have shown that echogenicity is associated with different histological characteristics of the plaque, such as elastin, calcium and the size of the lipid-necrotic nucleus [68]. In study [69], IM's echogenicity was found to be associated with multiple cardiovascular risk factors, including inflammation and oxidative stress. In the

same study, the carotid IM morphology was found to be correlated with the echogenicity of the brachial artery's endothelium. IMT of the brachial artery's is associated with different cardiovascular risk factors comparesd to its echogenicity, fact that indicates that the measurement of the echogenicity of IM involves different diagnostic information compared to the IMT measurement [70].

The measurement of atheromatous plaque echogenicity of the carotid artery may be a superior prognostic marker for stroke, however, the measurement of the echogenicity of IM can be an overall marker of vascular wall composition and of the instability of atherosclerotic plaques in other vascular compartments, having an impact on the total cardiovascular mortality [71]. A study published in 2009 included elderly men> 75 years old demonstrated that IM echogenicity can predict total cardiovascular mortality irrespective of IMT, the presence or absence of atherosclerotic plaque and its echogenicity. In addition, the predictive power of IM was also highlighted as independent of cardiovascular risk factors. This means that the measurement of the echogenicity of IM provides innovative predictive information on cardiovascular mortality at the age group above 75 years. In the same group of patients, the IM echogenicity was found lower in patients with a history of stroke compared to asymptomatic ones [72].

Morphological characteristics of atheromatous plaque

- *Irregular edge - Ulcerations*

Multiple ultrasound imaging parameters have been studied, indicative of the characteristics and composition of the atherosclerotic plaque. Some of these, such as the abnormality of the edge, echogenicity and heterogeneity (a combination of echolucency and echogenicity) have been associated with histopathological features of the vulnerable atherosclerotic plaque [73].

Regarding the irregularity of the edge, the ulcerations and the possibility to be detectable through B-mode ultrasound, the European carotid plaque study group revealed sensitivity and specificity 47% and 63%, respectively[74]. The presence of an abnormal edge in ultrasound can predict intraplaque hemorrhage with sensitivity and specificity 81% and

85%, respectively [75]. However, ultrasound analysis is limited (150-200 μm) to detect abnormalities at the edge of the atherosclerotic plaque; therefore, multiple studies compared the available imaging methods for the designation of ulcerations, and among them computed tomography angiography (CTA) proved to be the most effective one [76, 77]. Saba et al demonstrated that CTA had a significantly higher sensitivity compared to ultrasound (93% versus 37.5%) [73]. Furthermore, MRI can detect the presence of ulcers with sensitivity similar to CTA [78].

In a recent study [78], MR using intravenous contrast was found to have significantly superior sensitivity compared to Time Of Flight (TOF) for the detection of ulceration (81.5% vs. 55%) [79].

- *The texture of atheromatous plaque*

The classification of atherosclerotic plaques in homogeneous and heterogeneous, showed that the heterogeneous plaques contain more calcifications, without variations of the ‘’soft’’ tissue concentration [80]. Homogeneous plaques have a uniform texture and smooth surface, while heterogeneous have a smooth or uneven surface [81].

The evaluation of heterogeneity of the atherosclerotic plaque improved the sensitivity of 76% and the specificity of 85% regarding the detection of intraplaque hemorrhage compared to echolucency, while it predicts the thickness of the fibrous capsule of the atherosclerotic plaque (<80μm) as well as the location of the lipid nucleus with 77% and 74% sensitivity and 22%, 17%, respectively [75].

- *The fibrous capsule*

The fibrous capsule (FB) plays an important role in the possible instability of the atherosclerotic plaque, as its thickness and morphology comprise major determinants of potential rupture. Histologically, FB consists of smooth muscle cells in combination with an extracellular matrix that is associated with the presence of macrophages and T lymphocytes [82]. Inflammatory cells have also been found between the surface and the lipid nucleus [83].

According to histological studies, vulnerable atherosclerotic plaques have a thin fibrous capsule and a large lipid-necrotic nucleus containing macrophages and collagen. Rupture of the FB and the "exposure" of thrombogenic subendothelial constituents of the plaque into the bloodstream leads to thromboembolic complications. The ideal imaging method for assessing the fibrous capsule is MRI, which classifies the fibrous capsule into normal, thin or eroded-ruptured. The thick fibrous capsule is depicted as a low signal region in the TOF sequences, which is not visible when the capsule is thin [84]. When the fibrous capsule is broken, the absence of the low signal band between the plaque and the lumen is foolowed by bleeding and/or a thrombus thrombus formation, represented as a region of high signal.

Using MRI, Demarco et al [85] found a strong and statistically significant correlation between the ruptured fibrous capsule and ipsilateral stroke. The application of CT has been tested for the characterization of the fibrous capsule but without satisfactory results due to blurring effects, limiting the distinctive ability of the method [86].

Due to the low resolution of ultrasonography, its use is limited regarding the designation of the FB and therefore there are no relevant studies in the literature [79].

- *Constitution and echogenicity of atheromatous plaque*

The echogenicity of the atherosclerotic plaque characterizes its morphology through the reflection of the ultrasound signal. Multiple studies have shown that vulnerable atherosclerotic plaques are composed of a large lipid core covered by a thin fibrous capsule. They also contain macrophages, a characteristic found in plaques of symptomatic patients and may also contain bleeding features. These plaques appear to be echolucent (with low echogenicity) in ultrasound (Figure 5). Plaques depicted as echogenic (with high echogenicity) have a higher content of collagen and fibrous tissue and are often calcified (Figure 6).

Echolucent atherosclerotic plaques with prominent lipid or necrotic content are characterized by a greater risk of stroke or cardiovascular events compared to echogenic ones and are considered more prone to rupture [87, 88]. Follow-up studies of the history

of atherosclerotic carotid disease have shown that echolucent plaques are often associated with ipsilateral stroke [89,90]. The echogenicity associated risk of an atheromatous plaque has been found to be independent of the degree of stenosis, sex, age and other cardiovascular risk factors [91], while the combined study of echogenicity with IMT has been demonstrated to contribute more to the conventional prognostic models [92].

The assessment of echogenicity was initially proposed as a simple method for the prognosis of cardiovascular events during the performance of percutaneous treatment with stent placement. The Carotid Angioplasty and Risk of Stroke Study (ICAROS) showed that carotid atherosclerotic plaques were associated with an increased risk of stroke during percutaneous treatment [91]. A recent study [93] histologically confirmed the findings of the ICAROS study, as echolucent atherosclerotic plaques were found to release more embolic material during stent placement compared to echogenic ones.

Finally, the increase in the atheromatic plaque echogenicity over a period of 6-9 months has been shown to have a predictive value for medium-term cardiovascular events in asymptomatic patients with a stenosis of> 30% [87].

Qualitative evaluation of echogenicity

The qualitative evaluation of the echogenicity of carotid atherosclerotic plaques is a visual categorization of their sonic reflections, largely dependent on the observer.

Initially, in 1983 Reilly et al introduced the structural characterization of the carotid plaque into homogeneous (characterized by uniform, medium and high level reflexes) and heterogeneous (characterized by high, medium and low-level reflections) [81].

In 1988, Gray-Weale described four different types of plaques, based on echogenicity:

Type 1: Echolucent

Type 2: Predominantly echolucent

Type 3: Predominatly echogenic

Type 4: Echogenic atherosclerotic plaque [94].

In 1990, Widder et al applied an inverse classification with the most echolucent atherosclerotic plaques to be classified in category IV and the most echogenic in class I [95].

Finally, Geroulakis and his colleagues in 1993 introduced a modified version of the Gray-Weale scale, adding a fifth category of atherosclerotic plaque or otherwise the "unclassified" atherosclerotic plaque, that due to its intense calcification, presents bands of acoustic shadow that blur the arterial lumen and the deepest arterial wall, rendering ultrasonographic imaging difficult [96].

Quantitative evaluation of echogenicity

- *GRAY SCALE MEDIAN (GSM)*

Elzatory in 1998 announced a method of computational image analysis, the system analysis of median scale of gray, the Gray Scale Median (GSM) [97]. This method allows a more objective and reproducible assessment of the atheromatic plaque echogenicity compared to visual categorization [98].

The analysis is performed in digitized ultrasound images, which have been "normalized" to GSM of the blood (GSM 0-5) and GSM of the tunica adventitia (180-200). The echogenicity in the area of interest is expressed as 256 different tones of gray, where 0 is equivalent to black and 255 to white. Hence, atherosclerotic plaques with low GSM values are depicted echolucent, while plaques with high GSM values look echogenic. A strong correlation has been found between GSM and the concentration of fibrous-calcified tissue within the atherosclerotic plaque while no correlation has been found between GSM and lipid core size, and various associations have been found with other plaque components [73].

Typically, atherosclerotic plaques with GSM values <25 have been associated with decreased elastin content, increased cellular load and increased DNA content [99, 100].

In study [101], 87 patients with a grade of carotid stenosis > 50% were analyzed and was demonstrated that atherosclerotic plaques with a GSM value of <32 had an incidence 55% of stroke, while atherosclerotic plaques with GSM> 32 had a stroke incidence of only 11%. Similar results were demonstrated in another study [102] where the incidence of stroke was 40% when GSM values were <50 and only 9% for GSM values > 50. These findings lead to the conclusion that echolucent plaques (plaques with low GSM values) that cause a narrowing of> 50%, are associated with an increased risk of stroke in asymptomatic patients.

In conclusion, the measurement of echogenicity by using GSM, could improve the criteria for selection of asymptomatic patients who are selected for operation [103].

- *GSM ANALYSIS WITH COLOUR CODE*

The analysis using GSM is a mean value of the gray scale of the atherosclerotic plaque, without reflecting individual features of the plaque with prognostic significance, while at the same time it has low sensitivity (range 40-60%) for the detection of ‘’soft’’ (GSM <35), mixed (GSM 35-65) and calcified (GSM> 65) atherosclerotic plaques [104].

Sztajzel [105] and his colleagues added color code to the GSM analysis with encouraging results. In particular, they studied each millimeter of the atherosclerotic plaque using three GSM bandwidths (GSM 50 = red, GSM 50-80 = yellow, GSM> 80 = green). The above analysis had a sensitivity of 84% and a specificity of 75% regarding the localization of the lipid nucleus.

The GSM analysis combined with the color code, adapts GSM scales from various tissues (fat, muscle, blood, bone) in order to calculate the area occupied by each tissue in the atherosclerotic plaque. However, there are no analyzes regarding sensitivity and specificity of this method [106].

- *INTEGRATED BACKSCATTER ANALYSIS (IBS)*

The GSM analysis of the atherosclerotic plaque involves the risk of systematic error in quantification of its echogenicity, as the image evaluation depends to a large extent on

the settings of the ultrasound machine, image compression techniques and ultrasound beam focus [107]. An experimental method designed to overcome the above mentioned problems and does not depend on the user of the ultrasound device, it is the integrated backscatter analysis (IBS), which is based on the processing of the primary electromagnetic signals (RF) resulting from the reflected energy of the ultrasound beam [108]. Quantitative methods based on the primary (RF) analysis override the processing that is subject to, the reflected signal by the signal processor of the ultrasound device. This reflected signal contains information about the structural components of the atherosclerotic plaque and tissues, through which it is transmitted, providing useful diagnostic information [109]. The echogenicity of the atherosclerotic plaque as it results from the IBS analysis, it has been found to predict the lipid content of the plaque, and the echolucent plaques, with low IBS values, are recognized as lipid-rich, vulnerable atherosclerotic plaques [110].

In addition, IBS analysis has been found to distinguish "soft", fibrous and calcified tissue in the atherosclerotic plaque. However, conflicting results have been published regarding the ability to separate individual "soft" characteristics from the healthy wall of the vessel. This may be due to the different methods of calculating the reflected energy [111].

Neovascularization – quantitative analysis with contrast-enhanced ultrasonography (CEUS)

Intraplaque neovascularization is another indicator of vulnerable atherosclerotic plaque [77, 73]. Intraplaque neovascularization, originating from vessels of the vessels (vasa vasorum), is critical regarding the enlargement of the plaque. Vasa vasorum are functional, terminal arteries inside the wall of the aorta and large arteries that supply the vessel wall with nutrients and eliminating catabolism debris. They also promote inflammation in the atherosclerotic plaque. The new vessels are characterized by limited structural stability and their presence increases the risk of intraplaque bleeding and rupture of the atherosclerotic plaque [112]. These vessels are immature, thin-walled, and lipids, glucose and erythrocytes can escape from their walls, which in turn attract

macrophages, which can lead to the development of the atherosclerotic plaque [113]. Atherosclerotic plaques with high density of neo-vessels have increased risk of intraplaque bleeding and consequently rupture, which may lead to clinical events [114].

The possibility of detecting neovascularization in the atherosclerotic plaque by non-invasive methods is of major clinical interest. CEUS is a promising tool for imaging neovascularization. This technique exploits both the high spatial resolution as well as the high-time analysis of vascular ultrasound and the properties of the microbubbles as a contrast medium [115].

Clinical [116] and experimental [117] studies have shown that the degree of atherosclerotic plaque enhancement is correlated with the density of neo-vessels in histological examination. Extensive neovascularization is associated with symptomatic and pathological "vulnerable" atherosclerotic plaques [118, 119, 120].

In a series of surgical endarterectomy preparations, a higher degree of neovascularization was found in symptomatic compared to asymptomatic plaques [119], while in ischemic stroke and/or TIA patients, the atherosclerotic plaque showed increased enhancement compared to asymptomatic patients [121]. A recent study also found increased carotid plaque enhancement in patients with acute coronary events compared to patients with stable cardiovascular disease, while at the same time enhancement of atherosclerotic plaque was an independent predictor of risk for future coronary events [122].

Total plaque area (TPA) and total plaque volume (TPV)

The measurement of TPA, such as IMT, is associated with future risk for manifestation of stroke and MI. Although these two measurements are closely related, they probably reflect different biological pathways and different stages of atherosclerosis. TPA measurement has been found to have a greater prognostic value than IMT for stroke. Repeated TPA measurements has been applied to monitor the effects of preventive and therapeutic measures on patients with known cardiovascular risk factors [123]. TPA monitoring can determine whether the effects of therapeutic intervention are satisfactory

or whether further investigation and intensive treatment of new cardiovascular risk factors, such as homocysteine and lipoprotein-α {Lp(a)}, is required in patients with a rapidly evolving atherosclerotic plaque who are already treated for the usual cardiovascular risk factors [124].

An interesting fact is that when patients see by their own eyes ultrasound images and TPA measurements, they are often motivated and are making changes in their lifestyle with beneficial effects (exercise, smoking cessation, strict diet, etc.). On the other hand, the gradual reduction of the plaque size encourages them to maintain these changes [125].

A major disadvantage of ultrasound is the two-dimensional mapping of the three-dimensional carotid anatomy, which is responsible for the high degree of variability in diagnosis. For this purpose, the research interest has been focused on the development of three-dimensional ultrasound techniques that have the ability to reconstitute the conventional ultrasound imaging diagnostic information into three-dimensional images that can be studied on any computer later on. In addition, with the development of three-dimensional ultrasound techniques, it is now possible to quantitate the total volume of TPV carotid atherosclerotic plaques and their surface morphology [126].

Changes in atherosclerotic plaque volume are more closely related to CAC than IMT. The three-dimensional measurements of the TPV of atherosclerotic plaque is the most sensitive method in terms of plaque changes from medical therapy compared to TPA [127].

Compared to IMT, TPV measurement significantly reduces the sample population and the follow-up duration required to study the effects of antiatherosclerotic drugs [128].

Elasticity index

- *Applanation tonometry*

With modern high-resolution ultrasound devices, it is now achievable to record the changes in carotid diameter during the heart cycle. Arterial distensibility reflects mechanical stresses and is a measurement of the elasticity and ability of the artery to

stretch and contract during the cardiac cycle. Reduction of arterial distensibility leads to an increase in arterial stiffness and appears to be a common pathological mechanism for many factors that lead to the onset and progression of vascular changes associated with cardiovascular disease [129].

Arterial stiffness occurs as a consequence of increasing age, hypertension, DM, hypercholesterolemia and smoking [130].

Measuring pulse wave propagation velocity (PWV) with applanation tonometry is the most commonly used method of assessing arterial stiffness as it is simple on its application and also multiple studies have associated it with cardiovascular disease. Mathematically PWV is calculated by the Moens-Korteweg equation

$$PWV = \sqrt{\frac{E \cdot h}{2r\rho}}$$

E is the coefficient of elasticity of the wall, h depicts he thickness of the arterial wall, r depicts the diameter of the vessel and p depicts the density of the blood.

Measurement of PWV is a potentially very potent bio-indicator of atherosclerosis since arterial wall stiffness manifests well before the structural changes of the vessel occur [131].

Early diagnosis of this dysfunction can lead to more effective strategies in order to prevent cardiovascular disease [129].

- *Flow-mediated dilation (FMD)*

The normal healthy endothelium regulates vascular tone by producing anticoagulants, antiplatelet and fibrinolytic agents. Vascular tone is maintained by the release of vasoconstrictors and vasodilators. Nitrogen monoxide (NO) is the major vasodilator and endothelial dysfunction occurs when the bioavailability of NO is reduced. FMD measurement is the most widespread non-invasive method for assessing endothelial

dysfunction. FMD reflects the ability of the brachial artery to distend after provocative reactive hyperaemia and is highly dependent on NO secretion. FMD measurement is based on the reactive hyperaemia caused by transient blockage of the brachial artery with the cuff of a sphygmomanometer. This reactive hyperemia is then studied by using Power Doppler Ultrasound. Traditional cardiovascular risk factors, such as smoking, obesity, glucose or lipid metabolism disorders, and hypertension have been associated with FMD disorder. In addition, disturbed FMD predicts the risk of future cardiovascular events and is a complementary indicator of total atherosclerotic burden [132].

Virtual histology with intravascular ultrasound (VH-IVUS)

VH-IVUS has been widely used in percutaneous coronary interventions for the accurate placement of stents. However, it is not a routine examination for carotids. VH-IVUS can recognize four subtypes of tissue including fibrin, fatty, necrotic, and calcified tissue.

The Carotid Artery Plaque Intravascular Ultrasound Evaluation (CAPITAL) [133] studied the types of atherosclerotic plaque in relation to the outcome of the patient after stent placement in the carotid artery and classified the different types of atherosclerotic plaque based on the localization and distribution of these tissues within the atherosclerotic plaque. In this study, the outcome of the operation was not correlated with the findings of VH-IVUS. VH-IVUS may characterize the morphology of the atherosclerotic plaque prior to stent placement, but its value in predicting microembolism as a complication of the intervention, is limited. However, it can be a useful method for identifying the morphology of the atherosclerotic plaque, contributing to the correct placement of the stent by improving the results of the interventional procedure. VH-IVUS may also reveal areas of stenosis and calcification which are difficult to assess by angiography [134].

New ultrasonographic indices with predictive value

More sophisticated computational techniques of atherosclerotic texture analysis based on methodologies such as multiscale analysis and multiresolution analysis, can be effective methods in order to distinguish symptomatic from asymptomatic plaques. An interesting

finding in the case of wavelets analysis was that the dominant texture features were characterized by horizontal direction within the atherosclerotic plaque, highlighting the importance of mechanical effects (shear forces) on the texture [135].

In a recent study, the statistical features of the atherosclerotic plaque texture were found to be more sensitive to the effect of statins compared to TPV of the atherosclerotic plaque [136].

A recent approach to risk assessment for stroke is the combination of ultrasonographic markers associated with atherosclerotic plaque instability. A characteristic example is a combined study [137] of the echogenicity of the atherosclerotic plaque with the microembolic signals in the cerebral parenchyma recorded by transcranial Doppler ultrasound, demonstrated encouraging results regarding the improvement in the prognosis of stroke risk.

Finally, quantification of the total plaque's risk score by taking into consideration the degree of stenosis, edge irregularity, echogenicity and textural characteristics, has been proposed as the most potent predictor of cardiovascular events compared to FRS [138]. Necessary is the enhancement of the above findings by histological preparations of endarterectomy, as only a few studies have made a histological confirmation of the above risk assessment models [139].

Multiscale transforms (wavelets, ridgelets, curvelets) who are used for image analysis

The distribution of materials within the atherosclerotic plaque determines the spatial distribution of the gray in the ultrasound image. Such distributions can be characterized as:

A) Low spatial frequencies namely slow changes in grayscale, where they may represent large areas occupied by a particular type of material.

B) High spatial frequencies rapid, changes in grayscale, where they can represent different materials randomly distributed within the plate.

The texture can be defined as the distribution of gray levels in the image. The texture analysis in ultrasound images can describe the spatial distribution of the different gradientsvpf gray and hence the underlying distribution of materials. It is known that the effect of speckle due to multiple small randomly distributed reflections limits analysis and blurs the image, reducing the quality and reliability of ultrasound images. Although speckle is considered as noise (a high frequency component of the image), it is not standard random noise and may contain useful information.

Texture analysis using multiple scales transformations such as: Gabor Filters (GB), Discrete Wavelet Transform (DWT), Stationary Wavelet Transform (SWT), wavelet packets (WPs) that appropriately decompose the image frequency content can reveal textural features of the atheromatous plate free from the effect of speckle noise.

Whilst wavelet-based algorithms have been used in medical images for texture characterization, that they have disadvantages such as: limited texture information, and inaccurate information about the mid-range content of the image. In 2011, the prevailing texture characteristics were found to have a horizontal orientation, indicating that texture analysis can be influenced by biomechanical factors (shear forces exerted on the p;aque) [140]

Recently multiscale geometric techniques such as transformations: ridgelets and curvelets were proposed for image processing. The above are an extension of wavelets and can capture geometric structural information of an image. Unlike wavelet methods where they can detect focal structures, the above can detect discontinuities along a line or curve of the image, often found in ultrasound carotid images.

In particular, it was shown that curvelets (97.90%) exceed ridgelets (94.80%) as well as wavelets (89.90%) in correct tissue categorization of five living organs (heart, liver, spleen, kidneys and vertebral column). In the digital tomography of normal, benign and malignant cases the features extracted through the curvelet transforms lead to a better ranking (94.07%) compared to the characteristics extracted from the wavelets (90.05%).

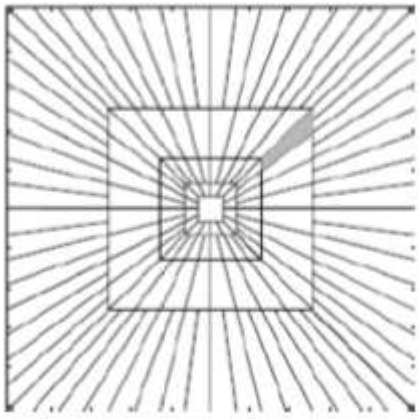
Transformation of curvelets (CT) has been defined as the internal product of a bivariate.

Function f (x) and curvelet ψα, b, θ (x):

CT (α, β, θ) = ∫R2 ψα, b, θ (x) f (x) d (x) (6)

where ψ, b, θ = a-3/4 ψ (DαRθ (x-b), Dα = (1/a

it is a parabolic escalation and R 0 is an alternation of th radians. The parameter a is equal to 2-j, where j = 0, 1 ,. . . is the scale. The parameter θ = 2πl · 2-j / 2 is the angle of rotation where for l = 0, 1 ,. ., such that the location is defined by the sequence of the translation parameters. The function of the curvelets resembles a parabolic "wedge" (Figure 7).



The first generation of discrete curvelet transforms (DCT) concerned an algorithm that was completed by entering zeros into the decomposition filters. The results of the decomposition (detailed sub-images) were parsed in squares and each was analyzed by the discrete ridgelet transforms (DRT). This is actually a local ridgelet transformation that suffers from the blocking effect.

The second generation of DCT, ie the Fast Discrete Curvelet Transform (FDCT), has been shown to be direct and accurate [141]. It is based on a method of separation of frequencies, which comprises a) applying an FFT two-dimension to the image b) paraphrase image in a parallelogram for each scale and angle c) wrapping around the origin and d) applying the inverse two- FFT.

In the FDCT the number of angles for the second level was set to 20 (multiple of 4) and the combination of curvelets was used for coefficients in the first level. For each level only the first half of all coefficients was taken into account because the curvelets produce symmetric coefficients for the angles θ and $\theta + \pi$. The total number of coefficients obtained was 22, resulting in 44 texture characteristics.

The performance of the multiscale transformations was compared to that of the wavelets. The result of the comparison showed a clear superiority of the multiscale transformations with each form of wavelets (Gabor filters (GB), discrete wavelet transform (DWT), stationary wavelet transform (SWT) [140].

2. Methodology

The study is based on bibliography search relating to the subject, via computerized database Pub Med-MEDLINE, using keywords. The review included single-center and multi-center investigations concerning carotid artery stenosis emphasizing on asymptomatic one and its correlation with cardiovascular comorbidities, especially with ischemic heart disease. The key-words that were used: risk stratification, ischemic heart disease, asymptomatic carotid stenosis, intima-media thickness, carotid plaque

The selection of the studies is based on the risk stratification for development of ischemic heart disease patients with asymptomatic carotid stenosis. This review is referred to studies that were published from 1981 until 2016. The aim of this systematic review of the bibliography is to stratify the risk for cardiovascular disorders, especially for IHD in patients with asymptomatic carotid stenosis, in order to assist in selecting potential candidates for cardiovascular intervention. As the early recognition of patients at higher risk would maximize the potential benefits of revascularization or optimal medical therapy (OMT), as well as would ameliorate the prognosis.

3 Results

Asymptomatic carotid stenosis as one of the major and most important consequences of generalized atheromatosis, often coexists with coronary artery disease. In addition, in a significant rate, an acute coronary event occurs in the background of asymptomatic carotid disease, therefore, the immediate diagnosis of carotid stenosis leads to the diagnosis of severe stenotic lesions of coronary arteries, preventing a potentially lethal coronary event.

The correlation of these two conditions (asymptomatic carotid disease and coronary artery disease) varies according to the characteristics of the study population, the degree of carotid stenosis, the presence of symptoms or not, as well as to the selected study method and investigation. It is estimated that the coexistence of these two conditions range from 2 to 22% and comprise manifestations of the same disease, concretely of atherosclerosis with manifestations from different organs.

Occasionally, several studies have been carried out in order to detect the degree of correlation between carotid stenosis and coronary artery disease, to identify risk factors, for stratifying patients to low, intermediate and high risk, and for the prediction of a future vascular event or coronary episode in particular.

Among the oldest and most purposeful studies was that of Norris et al (1991) where the risk of vascular event was assessed in patients with asymptomatic carotid stenosis. A sample of 696 patients (369 women and 327 men) with a range of age between 45-90 years was studied for a period of 6-95 months. Patients were screened by physical examination as well as by ultrasound study of the carotid system. Risk factors such as age, sex, obesity, smoking, family history, arterial hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), peripheral artery disease (PAD) and total blood cholesterol levels were taken also into consideration and evaluation in the course of the study. These factors showed correlation with the degree of carotid stenosis, but not with the risk of cardiovascular events. This study demonstrated more men who were in older age with moderate-severe carotid stenosis. In addition, high levels of total cholesterol were recorded in patients with severe carotid stenosis, while men had a higher rate with severe

carotid stenosis compared to women. Finally, a large subgroup of patients with arterial hypertension and PAD belonged to the group with severe carotid stenosis [142].

The degree of carotid artery stenosis was classified by ultrasound scan findings categorizing it into mild to <50% stenosis, moderate with 50-75% stenosis, and severe stenosis> 75%. During the follow-up, 73 cardiac events (mainly myocardial infarction) occurred, from which a large group of 28 patients had mild carotid stenosis and out of a total of 59 deaths of cardiac etiology, the majority (42) were patients with mild-moderate carotid stenosis (Table 1.)

TABLE A

TABLE 2. Annual Percentage Rate of Vascular Events Over Period of Follow-up

Degree of stenosis	TIA	Stroke	Cardiac	Vascular death
<50% (mild)	1.0	1.3	2.7	1.8
50–75% (moderate)	3.0	1.3	6.6	3.3
>75% (severe)	7.2	3.3	8.3	6.5

TIA, transient ischemic attack.

Norris et al Vascular Risks Stroke Vol 22, No 12 December 1991

Table 1."Vascular Risks Stroke, Norris et al., 1991"

The results of this study demonstrated that the annual risk of a cardiac event increases as the degree of stenosis increases, in particular 2.7% for stenosis <50% and 8.3% for severe stenosis> 75%. We should emphasize on the fact that these rates are significantly higher than those corresponding to transient ischemic attack (TIA) or stroke.

The study of Nadareishvili et al (2002) was one of the most extensive researches on the long-term risk of stroke and MI in patients with asymptomatic carotid stenosis. In particular, it was evaluated the long-term risk for stroke and other vascular events such as MI and death of vascular etiology but not ischemic stroke and during the course of the follow-up. The screening of the patients included CDU of the carotid system and clinical evaluation annually. The study included 106 participants (44 men and 62 women) aged 56-72 years who were screened for approximately 10 years, 50% of the patients for 10

years and the rest for 5 years. In the course of the follow-up were recorded cardiovascular events such as MI, ischemic stroke, TIA, death due to MI, PAD and heart failure (HF). It should be noticed the fact that 70% of the patients had arterial hypertension, 25% had DM and 11% were active smokers.

Taking into consideration the results it is concluded that during the follow-up 10 patients died from cardiac events and 10 had AMI. Overall, the 10-year and 15-year risk of MI was determined to 10.1% and 24% respectively, and the risk rate was significantly higher in patients with 50-99% stenosis of the internal carotid artery (ICA). The long-term risk for MI in these patients was greater than the risk of cerebrovascular event or other vascular events. Age, gender, DM and carotid stenosis were important predictors of MI. In contrast, the long-term risk for cerebrovascular event was approximately 1% per year in asymptomatic carotid stenosis (Fig. 3)

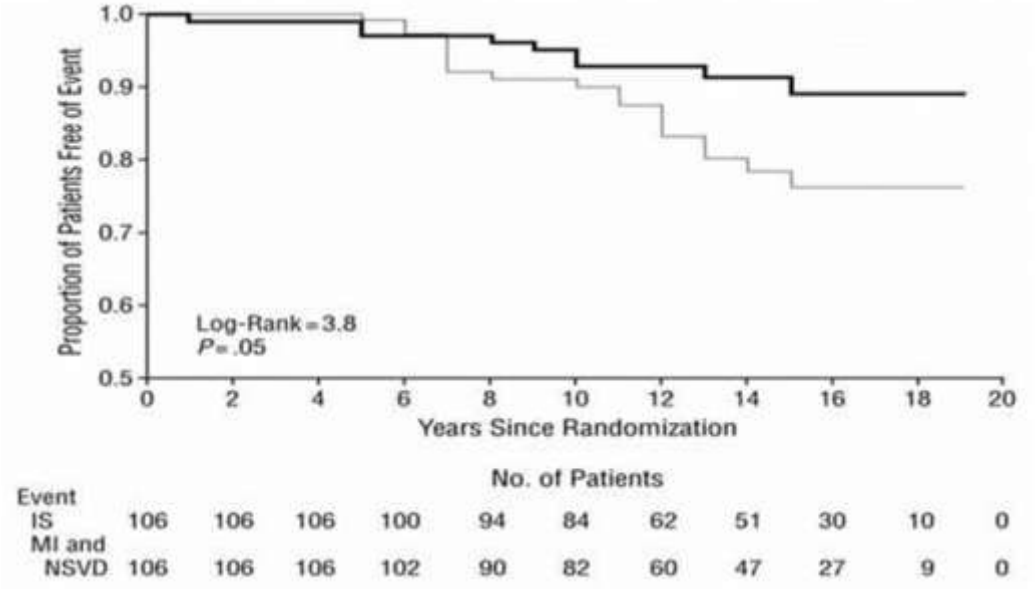


Figure 3." Survival without stroke and survival without myocardial infarction and death of non-cerebrovascular stroke origin in asymptomatic carotid artery stenosis"

Thus, from this study it is concluded that in the future, the therapeutic approach of the asymptomatic carotid artery stenosis should primarily emphasize on the prevention of acute coronary events compared to the risk of ischemic stroke [143].

SMART study (2007) tested the relation between asymptomatic carotid stenosis and the risk of vascular events in patients with known arterial disease. The study included 2684 patients aged 18-79 years with clinical manifestations of arterial disease or DM type II, but without history of cerebral ischemia. It should be noticed that none of the patients underwent surgery for carotid disease. The degree of asymptomatic carotid stenosis was associated with a variety of vascular risk factors such as age, smoking, arterial hypertension and blood lipids levels. Blood glucose level, blood lipids levels, creatinine and homocysteine were recorded and the degree of carotid disease was determined based on the ultrasound findings of both carotids and the peak systolic velocity measurements.

The results manifested that patients with asymptomatic carotid stenosis were older, smokers, with higher recordings of systolic arterial pressure, with higher levels of total cholesterol and LDL cholesterol and history of PAD. In the course of the follow-up, 239 patients (9%) died, 49 (2%) experienced ischemic stroke, and 165 (6%) developed MI. The study showed direct correlation of the extent of carotid stenosis with the risk of developing MI. 172 patients with 30-49% asymptomatic carotid stenosis had an increased risk of AMI (1.2%), stenosis of 50-69% (74 patients) showed 1.5% risk, while stenosis of 70-99% (96 patients) had 1,7% risk and total occlusion (51 patients) 1% risk (Table B).

TABLE B

TABLE 5. Risk of Any Vascular Event in Relation to the Extent of Asymptomatic CAS

	HRs Adjusted for Age and Gender With 95% CIs			
Asymptomatic CAS Extent*	All First Vascular Events (n=253)	Vascular Death (n=147)	Ischemic Stroke (n=49)	MI (n=165)
30–49% (n=172)	1.0 (0.6–1.5)	0.8 (0.4–1.4)	0.7 (0.2–2.1)	1.2 (0.7–1.9)
50–69% (n=74)	1.4 (0.8–2.5)	2.1 (1.1–3.8)	0.6 (0.1–4.1)	1.5 (0.7–3.0)
70–99% (n=96)	1.4 (0.9–2.2)	1.5 (0.9–2.5)	0.7 (0.2–3.0)	1.7 (0.9–2.8)
100% occlusion (n=51)	1.5 (0.8–2.7)	1.5 (0.7–3.2)	2.6 (0.8–8.4)	1.0 (0.4–2.5)

*No carotid artery stenosis is reference category

Stroke May 2007
Goessens et al Asymptomatic Carotid Artery Stenosis

Table 2. "Risk of Any Vascular Event in Relation to the Extent of Asymptomatic CAS"

Totally, asymptomatic carotid stenosis equal or greater than 50% was recorded in 8% of patients and was associated with an increased risk of vascular event and MI occurred in 8% of patients after 5 years. In conclusion, asymptomatic carotid stenosis is an

independent risk factor for vascular events in patients with clinical manifestations of arterial disease or DM type II without having history of cerebral ischemia [144].

Correlation of coronary artery disease with that of atheromatosis of carotid arteries was confirmed by studies such as Kato et al., and Steinvil et al. In Steinvil's et al., study participated 1405 patients aged 54-76 years old (77.2% men and 22.8% women) from January 2007 to May 2009, who underwent scanning with coronary angiography and CDU. The assessment of atherosclerosis of the internal carotid arteries was based on the diameter of the vessel by using B-MODE ultrasound, as well as by recording Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV) values by CDU. The classification of carotid disease was done as follows: a) Normal carotids were defined those with PSV <125 cm/s, without detectable atherosclerotic lesions, b) Mild carotid stenosis, with PSV <125 cm/s and luminal stenosis <50%, c) Moderate carotid stenosis, with PSV 125-230cm/s and luminal stenosis 50-70%, d) Severe carotid stenosis with PSV> 230cm/s and >70% stenosis. IHD was defined as the finding of atherosclerotic lesion that causes luminal stenosis above 70% in one of the epicardial coronary arteries (LAD, Lcx or RCA) while disease of the Left main coronary artery (LMD) was defined as stenosis of the lumen above 50%.

From the results, as it shown in Table D, only 5.9% of patients with normal coronary arteries or without major stenosis, have carotid artery stenosis above 50%, while patients with 1 vessel disease (VD) have 6.6% rate, 13% is the rate for patients with 2VD, 17.8% in patients with 3VD and 31.3% in patients with LMD. Furthermore, it is important to note that in severe CAS (stenosis > 70%), coexist one or even more VD in a rate of approximately 24.5% (Table 3).

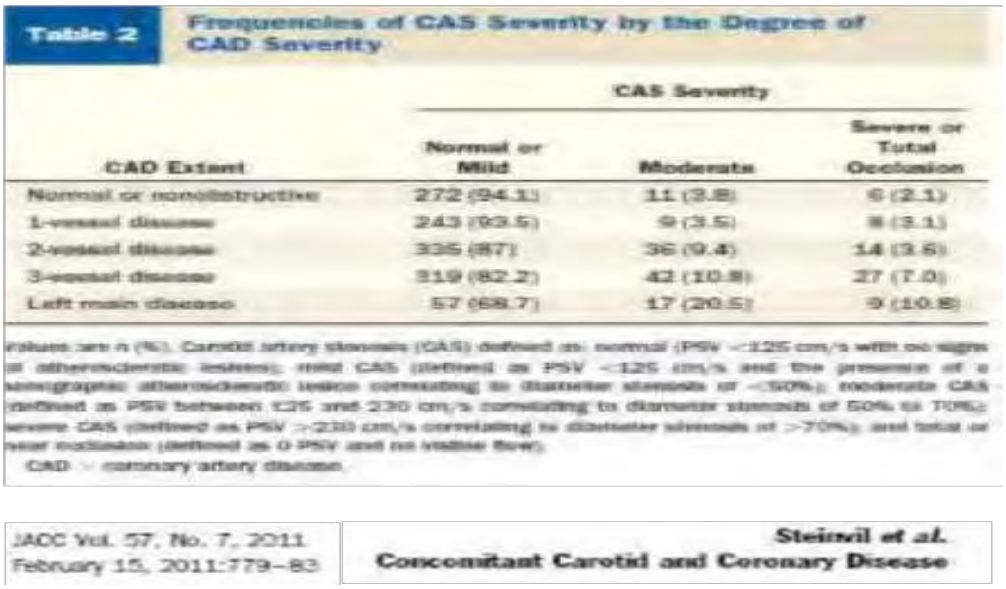


Table 2 Frequencies of CAS Severity by the Degree of CAD Severity

CAD Extent	CAS Severity: Normal or Mild	Moderate	Severe or Total Occlusion
Normal or nonobstructive	272 (94.1)	11 (3.8)	6 (2.1)
1-vessel disease	243 (93.5)	9 (3.5)	8 (3.1)
2-vessel disease	335 (87)	36 (9.4)	14 (3.6)
3-vessel disease	319 (82.2)	42 (10.8)	27 (7.0)
Left main disease	57 (68.7)	17 (20.5)	9 (10.8)

Values are n (%). Carotid artery stenosis (CAS) defined as: normal (PSV <125 cm/s with no signs of atherosclerotic lesions); mild CAS (defined as PSV <125 cm/s and the presence of a sonographic atherosclerotic lesion correlating to diameter stenosis of <50%); moderate CAS (defined as PSV between 125 and 230 cm/s correlating to diameter stenosis of 50% to 70%); severe CAS (defined as PSV >230 cm/s correlating to diameter stenosis of >70%); and total or near occlusion (defined as 0 PSV and no visible flow).

CAD = coronary artery disease.

Table 3." Frequencies of CAS Severity by the Degree of CAD Severity"

The statistical analysis of the results demonstrated that there is a strong correlation between the severity of the carotid stenosis and the extent of IHD. Notably, it is concluded that monitoring the progression of carotid disease can be really important regarding prognosis of future ischemic cardiac events or even death [145, 146].

In another study of Kato et al, participated 125 patients aged 53-73 years old with risk factors for vascular disease (smoking, DM, dyslipidemia, hypertension), who presented with ACS and underwent carotid ultrasound (morphological analysis of atherosclerotic plaque, measurement of IMT) and coronary angiography study within 24 hours of the ACS. The classification of the patients was based according to the number of vessel disease with critical lesions. The first class (50 patients) included those with single lesion, and the second class (75 patients) those with multiple lesions in the vessels.

In patients with multiple coronary artery lesions, IMT values were higher than those in patients with single lesions, and likewise the percentage of atherosclerotic plaques with a large lipid core was higher, 28% in patients with multiple lesions, versus 12% in patients with single lesions. It is worthy to note that 72% of those patients with ACS were diabetic and had multiple lesions in the vessels (Table 4).

Table 2. Coronary Angiography Findings in ACS Patients With Single and Multiple Coronary Plaques

	Single-Plaque Group	Multiple-Plaque Group	p Values
Acute myocardial infarction (%)	90	89	0.90
Culprit vessel (%)			
RCA/LAD/LCx	22/74/4	41/45/13	< 0.006
Number of diseased vessels (%)			
1/2/3	78/22/0	21/48/31	< 0.0001
Number of simplex plaques (%)			
0/1/2/3/≤4	74/22/2/2/0	49/47/1/1/1	0.06
Number of complex plaques (%)			
1/2/3/≤4	100/0/0/0	0/35/28/37	< 0.0001

ACS = acute coronary syndrome; LAD = left ascending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Kato *et al.*
Carotid Artery Remodeling in ACS
JACC Vol. 42, No. 6, 2003
September 17, 2003:1026–32

Table 4." Coronary Angiography Findings in ACS Patients With Single and Multiple Coronary Plaques"

In this study we see that in patients with ACS the existence of multiple and complex atherosclerotic plaques in coronary arteries is related to positive remodeling of carotid arteries (i.e. mean IMT> 1.1mm diameter and diameter of tunica intima is above 8 mm), therefore, the vulnerability of atherosclerotic plaque may be a systemic phenomenon.

In conclusion, we should remark that Kato's et al study establishes the correlation of carotid and coronary artery disease (CAD) by investigating the correlation in morphology of atherosclerotic plaques of carotid arteries and coronary arteries following an acute coronary syndrome (ACS) [145].

Several studies were designed to detect the degree of correlation of IMT of the carotid atherosclerotic plaque and CAD, in particular regarding the prediction of ACS. Kuopio Ischemic Heart Disease study demonstrated that every increment of cIMT by 0.1mm was associated with 11% increased risk for MI. This one was the first study that highlighted the correlation of cIMT with future coronary events.

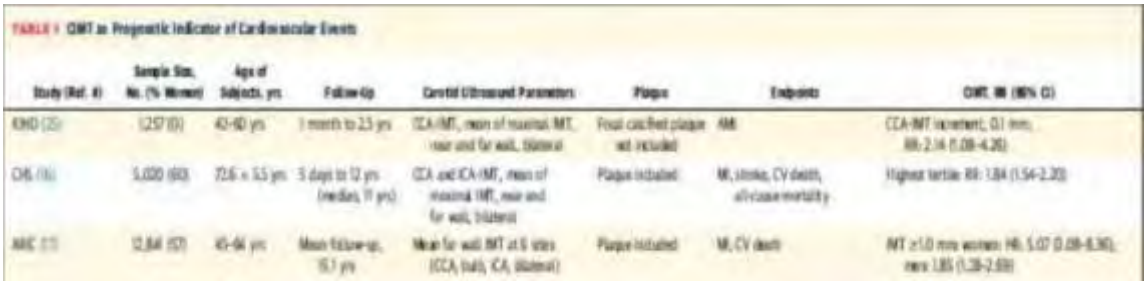
In TROMSO study of Herder et al., where 2743 patients (1307 men and 1436 women) participated, were established the risk factors that play an important role in the progression of IMT as well as in the total plaque area (TPA) of the atherosclerotic plaque.

In addition, we should remark that in this study was measured the IMT in regions without atheromatous plaque. Total plasma cholesterol levels, high-density lipoprotein (HDL) levels, smoking, blood pressure, DM, body mass index, and the presence of cardiovascular disease were included as parameters in the study. The subjects of this study underwent ultrasound scanning of the right carotid artery and got a follow-up for 13 years.

The results of this study revealed a higher percentage in the presence of plaques in men (41.6%) compared to women (32.6%), as well as a higher extent of atheromatosis, as the mean TPA and IMT was higher in men and in the course of the follow-up, the progression of IMT and TPA was also greater in men. In particular, another finding of the study was that the total cholesterol level, systolic blood pressure and smoking are stronger predictive factors for TPA progression than for IMT, whereas age and gender play a more important role in IMT progression. In conclusion, the carotid atherosclerotic plaque shows a stronger correlation with the existence of generalized atherosclerosis in comparison to the thickening of intima-media complex [149].

In several studies like ARIC, CHS and Coskun et al., highlighted the use of IMT as a non-invasive marker of IHD. In ARIC study was established the correlation of increment of cIMT with increased risk of IHD, in a study population of 15792 subjects where, carotid IMT (cIMT) was measured and a repeat measurement was recorded in a time interval of 4-7 years [148]. Likewise, in CHS study where involved 4476 subjects <65 years of age for 6 years, confirmed the correlation of high cIMT values with increased risk of MI and cerebrovascular event [149].

Coskun et al., included in a study 100 patients with stable IHD and confirmed ischemia by stress test, in order to investigate the correlation of IMT with the extent of coronary vessel lesions by coronary angiography imaging. The patients were divided into 2 groups, The first one comprised 39 patients with non-critical coronary artery stenosis, and the second group (with more risk factors) included 61 patients with> 50% coronary artery lesions.



Naqvi and Lee

IMT, Plaque, and Cardiovascular Risk

TABLE 2 Carotid Plaque as Prognostic Indicator of Cardiovascular Events

Study (Ref. #)	Sample Size, No. (% Women)	Age of Subjects, yrs	Follow-Up	Definition of Plaque	Endpoints	Plaque RR (95% CI)
Tromso Study (54)	6,226 (44)	25-84	6 yrs	Localized protrusion of the vessel wall into the lumen	MI	Highest plaque area tertile, RR: 1.56 (1.04-2.36) in men and RR: 3.95 (2.16-7.19) in women
APSIS (100)	558 (33)	60 ± 7	Median, 3.0 yrs	Distinct area with IMT more than twice that of neighboring sites	CV death, MI	Presence of plaque, RR: 1.83 (0.96-3.51)
KIHD (25)	1,288 (0)	42-60	1 month to 2.5 yrs	Area with mineralization or focal protrusion into the lumen, measured at the carotid bulb	MI	Small plaque, RR: 4.15 (1.51-11.47); large plaque, 6.71 (1.33-33.90)
Rotterdam Study (15)	6,389 (61.9)	69.3 ± 9.2	7-10 yrs	Focal widening relative to adjacent segments with protrusion into the lumen	MI	HR for severe plaque: 1.83 (1.27-2.62)
ARIC (50)	13,145 (57)	54.0 ± 5.8	Mean, 15.1 yrs	Plaque defined as meeting 2 of 3 criteria: 1) CIMT >1.5 mm; 2) protrusion into the lumen; and 3) abnormal wall texture	MI, CV death, revascularization	HR varied depending on risk factors. Model with plaque and CIMT improved area under the curve from 0.742 to 0.755

Table 5." OMT & Carotid Plaque as Prognostic of Cardiovascular Events"

Finally, the recordings showed that the IMT value in group 2 (mean IMT: 0.78 ± 0.21) was statistically higher compared to group 1 (mean IMT: 1.48 ± 0.28). (TABLE ST) In conclusion, in this study, the increase in IMT is related to the presence and extent of IHD according to angiographic measurements. [150]

Epidemiological studies have demonstrated that non-invasive atherosclerotic markers such as coronary artery calcium (CAC) score and IMT are major predictive markers of future cardiovascular events. There is a significant number of studies supporting the role of CAC score regarding the prognosis of MI and cardiac mortality. In combination with already existing risk stratification algorithms such as the Framingham Risk Score, European Systematic Risk Assessment and ProCAM studies, CAC score use is getting increasingly widespread (Table 6).

Table 1 Risk factors contributing to 10-year risk of CHD

- For patients with multiple (2+) risk factors
  - Perform 10-year risk assessment
- For patients with 0–1 risk factor
  - 10-year risk assessment not required
  - Most patients have 10-year risk <10%

Major risk factors

- LDL cholesterol
- Cigarette smoking
- Hypertension (BP 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD
  - CHD in male first-degree relative <55 years
  - CHD in female first-degree relative <65 years
- Age (men 45 years, women 55 years)
- HDL cholesterol 60 mg/dL counts as "negative" risk factor; its presence removes one risk factor from the total count
- In ATP III, diabetes is regarded as a CHD risk equivalent

Abbreviations: ATP III, Adult Treatment Panel III; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure.

Sharma et al Vascular Health and Risk Management 2010:6 603–611

Table 6." Risk factors contributing to 10-year risk of CHD"

According to the guidelines of the major societies of cardiology worldwide, there is a strong recommendation to modify risk factors especially in high-risk patients for an acute coronary event, while patients of intermediate risk may need further risk stratification based on CAC score. Several studies have been performed on investigating the value of CAC score in order to predict MI incidence, such as Greenland et al., Kondos et al. and Lamond et al., that approved the strong predictive value of CAC score concerning MI, in

combination with the classical cardiovascular risk factors. In particular, it was determined the risk of IHD based on the CAC score as follows: a) 1% for CAC score: 0, b) 1.9% for CAC score: 1-99, c) 4.3% for CAC score: 100-400, d) 7.2% for CAC score: 400-999, and e) 10.8% for CAC score: > 1000. Thus, we can remark the importance of CAC score in evaluating patients with asymptomatic carotid stenosis and high risk for coronary event [151, 152].

MESA study in an average follow-up of 3.9 years (maximum 5.3 years) included 6698 patients (3,161 men and 3,537 women) aged 45-84 years, investigated the predictive value of IMT measurement compared to Agatston score (CAC score) regarding the occurrence of cardiovascular events. Agatson score was determined by CT scan, as well as IMT was measured in common and ICA bilaterally. The end-point of the follow-up was defined by recording the first cardiovascular event.

Overall were recorded 222 cardiac events (61 AMI, 81 episodes of Angina, 3 succesful resuscitations from cardiac arrest and 13 deaths), 59 strokes (3 of them with concurrent cardiovascular event) and 7 deaths of other cardiovascular origin. For patients with moderate CAC score and high IMT, the annual cardiovascular event rate was 1-2%, while for patients with a high CAC score and moderate or high IMT, the rate was >2%. Results showed that CAC is a better prognostic marker for cardiovascular events than IMT values [153].

Also was confirmed the predictive value of CAC score and additionally, approved that the estimation of TPA of the atherosclerotic plaque is an even stronger prognostic marker compared to CAC score. One more important note from those studies is that IMT measurement was a better prognostic marker for stroke.

IMT of carotid artery and Agatson score are associated with classical cardiovascular risk factors and play an important role in the progression of atherosclerotic disease of the peripheral but also of the coronary arteries. A significant number of studies recommends Agatson score and IMT measurement in asymptomatic patients >50 years old for the detection of high-risk individuals for cardiovascular events as a guide for clinic decisions.

In ROTTERDAM study was studied the contribution of IMT in predicting IHD and in detecting high-risk individuals, when this is added to other classical risk factors such as plasma lipids levels, smoking, arterial hypertension and DM, compared to the predictive power of the IMT when it is used alone. The study included 385 subjects over 55 years old with a follow-up period of 0.1 to 6.5 years. Parameters of the study: medical history, blood pressure recordings determination, lipid profile determination, ECG monitoring, as well as IMT measurements (the mean of 3 measurements in the right and left carotid arteries). During follow-up, 174 patients manifested MI, 165 stroke and 11 presented both with MI and stroke.

Despite the strong correlation between IMT values and future coronary events, the analysis of the results revealed that the independent measurement of IMT has the same prognostic value for the detection of high-risk patients for IHD with the other classical risk factors and its use, as a screening tool for identifying these patients adds nothing more [154].

In addition to the studies with regard to the risk of cardiovascular event in asymptomatic carotid stenosis, several studies had as a subject of investigation the risk stratification in patients with asymptomatic carotid stenosis who are treated either pharmaceutically or invasively (endarterectomy or stent placement).

Wallaert et al. in 2013 attempted to provide a predictive model based on the 5-year survival rate of patients (taking into consideration patient's benefit) with asymptomatic carotid disease who underwent endarterectomy, regarding the decision-taking for the appropriate time of the invasive treatment. For 8 years follow-up 4114 subjects with a mean age of 70, with asymptomatic carotid disease and with no prior history of any vascular event originating from the carotid disease were subjected to selective CEA. 89% of the patients had arterial hypertension, 80% were smokers and 33% had IHD. Patients were classified according to the risk of mortality as low, intermediate and high risk.

Overall, 27% of the patients were classified as low-risk, 65% as intermediate-risk and only 5% were of high-risk. The results demonstrated 5-year survival rate of 82%, the perioperative mortality rate was extremely low at 0.4% in the first 30 days, and the stroke

rate was 0.6%. The 5-year survival rate for low-risk patients was 94%, and for the other two classes was 80% and 51%, respectively. Aggravating factors such as smoking, increased age, severe grade of renal failure, DM, HF, chronic obstructive pulmonary disease (COPD) and bilateral internal carotid artery stenosis were directly correlated with worse 5-year survival [155].

In conclusion and based on the latest guidelines, the candidate-patients for endarterectomy should have a life expectancy of at least 3 years with perioperative risk of vascular event/death below 3% in order to benefit the patient from the operation. In addition, high-risk patients do not show benefit from endarterectomy and maybe, the most appropriate treatment is medical therapy. Hence, this study highlighted the fact that there are high-risk patients with asymptomatic carotid disease who do not benefit from preventive CEA and concurrently provided a tool for selecting appropriate patients.

In 2012 Prateek Gupta et al., investigated the probability of elicitation AMI, stroke or death within 30 days after CEA for asymptomatic carotid stenosis, in order to make easier the preoperative assessment of patients, as well as the selection of appropriate patients for CEA. In this study, participated 17692 patients with a mean age of 72 years (57.9% men), who were operated electively for CEA.

Patients were classified into three categories (low, moderate and high-risk) based on the later parameters: 1) Age, 2) Shortness of breath, 3) Angina pectoris within 1 month, 4) History of PAD and 5) History of COPD. The majority of patients (86.2%) were in the low-risk category, while only 1.2% of them were at high-risk. The exclusion criteria of the patients were: a) Cerebrovascular event with or without neurological manifestation, b) History of TIA, stroke c) tumor of CNS, d) Mobility disorders (hemiplegia, paraplegia, quadriplegia), e) Esophagitis, ascites, cancer, open trauma, transfusion, f) Chemotherapy 30 days ago, radiotherapy 90 days ago, g) Sepsis.

Within 30 days of CEA, 167 patients (0.9%) were diagnosed with stroke, 108 patients (0.6%) were diagnosed with MI and 72 patients (0.4%) died. The overall risk for the aforementioned events was 1.8%. Remarkable fact from the results is that patients <60

years of age had a higher risk of stroke compared to those aged 60-79 years, and those aged> 80 years were at higher risk for stroke, MI and death after CEA.

Finally, this is one more study focusing on the proper selection of patients with asymptomatic carotid stenosis to perform CEA, taking into consideration, the comorbidities of the patients [156].

In another study of Cohen et al. in 1993 [157], was demonstrated that a group of patients with asymptomatic carotid disease benefits most from the conservative treatment of the disease with medication. In this investigation, 444 male patients of a mean age of 64 years were followed-up for 4 years, in order to study the risk factors for mortality in patients with asymptomatic carotid stenosis that were treated with either medication or CEA. Eight clinical risk factors were associated with increased mortality: IHD, history of angina pectoris, congestive heart failure (CHF), peripheral vascular disease, intermittent claudication, DM, arterial hypertension history and abnormal ECG on admission. Three risk factors were associated with increased mortality rates: intermittent claudication, DM and abnormal ECG. While, angiographic prognostic factors of increased mortality included intracranial vascular disease and bilateral carotid stenosis.

The total mortality in both groups (conservative treatment, CEA) was 37%, 61% of deaths were due to IHD, while no difference was observed in mortality rates among patients who were treated with either medication or surgically. We should also observe that the patient group treated with antiplatelet agent had a lower percentage of MI incidence, but not lower overall cardiovascular mortality rate [157].

In another study by Reed et al. in 2003, risk stratification was based on the presence of parameters such as CHF, coronary artery bypass graft (CABG) over 6 months, COPD, renal impairment (serum creatinine levels > 2mg/dl) and age > 80 years. The study reveald that in the absence of these factors the annual mortality is 5.6%, while the existence of one, two and three factors is associated with an annual mortality of 10.2%, 10.6% and 13.2%, respectively [158]. In addition, parameters such as IHD, COPD and DM were associated with an increase in the overall mortality rate, while statin treatment and female sex were protective agents.

Nowadays, a new field of research is the incidence of anemia in CVDs. In the area of HF studies have proved that the existence of anemia in these patients significantly affects life expectancy and its correction may lead to improvement in symptoms and exercise capacity. Similar investigations have been attempted regarding the effect of anemia on total and cardiovascular's origin mortality in patients with asymptomatic carotid stenosis.

In the study of Goliasch et al., participated 1065 patients for a mean follow-up of 6.2 years was attempted to define hemoglobin (HB) as a predictor of long-term mortality in patients with asymptomatic carotid disease. The protocol of the study included ultrasound study of the carotid arteries, detailed medical history taking, and a measurement of blood hemoglobin levels.

According to the results of the study, 275 patients (25.8%) died, out of them, 66.2% (182 patients) died from cardiovascular cause, 27.6% (76 patients) from cancer, 1.8% (5 patients) from chronic renal impairment and 4.4% (12 patients)) died from other causes. The analysis of HB values and their correlation with the cardiovascular events of the study population showed a significant increase in overall mortality by decreasing HB values. The 6-year overall survival of the patients was 61% for HB values <12.9gr/dl, 79% for HB values 12.9-13.9gr/dl, 80% for HB values 14-15gr/dl and 81% for HB values above 15gr/dl.

In conclusion, there is a strong correlation between HB levels and the long-term mortality of patients with carotid disease and in addition it was observed that patients with low HB levels were at increased risk for cardiovascular events and death [159].

As mentioned above, in the studies of Wallaert et al., and Gupta et al, the correct selection of those patients with asymptomatic carotid stenosis that will be subject of CEA and simultaneously will benefit from that, it is an issue that requires consideration of many factors. The necessity for a diagnostic algorithm that might improve making-decision has led to the search of new factors that could predict possible complications. Since MI is the major cause of perioperative and postoperative mortality and is much higher than the risk of stroke, risk stratification for CEA patients was attempted, by using homocysteine serum levels as a predictive marker [155, 156].

In the single-centered study of Duschek et al (2013), the homocysteine (a known cardiovascular risk factor) levels was evaluated as a prognostic tool in patients with asymptomatic carotid stenosis who underwent CEA. The study population was 214 patients, 126 men, 88 women, 130 of them above 75 years old and 84 subjects below 75 years old, who underwent CEA and were followed-up annually for 8.5 years. Homocysteine plasma levels were determined in patients over 14 days prior to CEA.

According to this study the rate of perioperative stroke and death was 0.93%, a total of 22 stroke and 57 cardiac events were recorded and out of the 114 deaths overall, 32 were cardiac, 15 of vascular cause and 47 of other etiology.

This study observed also that the use of homocysteine levels in addition to other cardiovascular risk factors significantly increases the rate of risk assessment in patients with asymptomatic carotid stenosis, in an attempt to specify more accurately those patients who will benefit from CEA. On the other hand, patients with asymptomatic carotid disease and elevated levels of homocysteine undergoing CEA are at increased risk of cardiac death and maybe conservative treatment in these patients is more appropriate [160].

As a final comment, from the aforementioned studies and the meta-analyzes performed, while in patients with asymptomatic carotid stenosis who already receive optimal medical therapy (OMT), the percentage of stroke was significantly reduced to 1% per year, it is not observed proportional reduction in the percentage of total mortality. Overall, 5-year mortality in patients with asymptomatic carotid stenosis > 50% is 23.6% (2.9% annually), while the mortality rates of cardiac origin ranging between 42-82%. In particular, in patients with asymptomatic carotid stenosis who are already on OMT, mortality rate is estimated approximately 24.35%, while in patients who underwent CEA the mortality rate is 22.7%. CEA's contribution to asymptomatic carotid stenosis is to reduce the annual risk for stroke - as demonstrated in ACAS 1995 and ACST 2004 - and not so much in reducing total and cardiac mortality [161].

Atherosclerosis is a systemic inflammatory disease of the vessels and despite the progress in medicine the last years, both in the field of pharmaceutical treatment as well as in interventional therapies, MI and stroke are the main causes of death due to the disease.

The incidence of asymptomatic carotid stenosis increases with age by 0.5% in subjects <50 years to 5-10% in patients >65 years in the general population. In addition, the incidence of asymptomatic carotid stenosis >50% was higher in patients with concomitant PAD

4 Conclusions

Carotid artery disease as a part of the group of the clinical manifestations of atherosclerosis, has a strong correlation with the ischemic heart disease. The presence of atheromatous plaques on carotid arteries amplifies the risk of myocardial infarction about 3-5% annually. Approximately 25% of patients with carotid stenosis >70% simultaneously have ischemic heart disease, and about 12-15% of them show 3 vessel disease, while totally patients with asymptomatic carotid stenosis independently of the grade of stenosis, in approximately 40% of them coexist carotid artery disease.

The classical cardiovascular risk factors influence and determine partly the extent of carotid disease, while its evaluation in combination with markers like carotid intima-media thickness (cIMT), coronary artery calcium (CAC) score and the atheromatic plaque, are useful tools regarding prognosis of future cardiovascular comorbidities, especially for myocardial infarction. The vulnerability of the atheromatic plaque is a systematic phenomenon, its study through specific non-invasive techniques and algorithms can provide a reliable assessment concerning future acute coronary events. Furthermore, despite the initial assumptions, carotid artery disease looks to be a precursor of myocardial infarction on a statistically significant grater rate compared to ischemic stroke. It should be mentioned that the lately, while it is observed significant reduction of the annual risk for ischemic stroke, mortality due to coronary artery disease in patients with asymptomatic carotid stenosis is higher in comparison to the healthy population.

Concerning the selection of appropriate therapy for patients with asymptomatic carotid stenosis, the risk of provocation iatrogenically of an acute cardiovascular event intraoperatively or postoperatively constitutes a key-decision making criterion. Carotid endarteriectomy (CEA) as well as carotid artery stenting (CAS) present both high rates of ischemic cerebrovascular events and acute coronary syndrome as side effects, especially in high-risk patients with life expectancy less than 3 years, which ones eventually optimization of medical therapy would be more appropriate. It should be noted that the all-cause and cardiac mortality in patients with asymptomatic carotid artery stenosis is still high despite its decrement in the general population. The majority of patients with asymptomatic carotid stenosis are categorized as high risk for coronary comorbidities and the aim for those patients is the maximum benefit that by modifying the risk factors and adding to the therapy statin. Furthermore, from guidelines of AHA/ACC of 2013, statin therapy in patients without symptoms of coronary artery disease and LDL levels between 70-189mg/dl, causes reduction of all-cause mortality approximately 17% and about 28% of acute coronary comorbidities (fatal or non-fatal) [162].

Despite the remarkable progression that has been achieved during the last decades concerning the diagnostic approach of atheromatous disease in general, the ischemic heart disease still needs to become further investigated. The total evaluation of patients, taking into consideration the past medical history, physical examination findings, cardiovascular risk factors, cardiovascular imaging findings (invasive and non-invasive), provide to the medical practice important tools regarding diagnosis, management and treatment of all clinical manifestations of atheromatous disease and especially ischemic heart disease. Group of patients who are on higher risk e.g. those with diabetes mellitus (DM), for whom regular follow-up in order to exclude possible existence of latent myocardial ischemia to achieve a better prognosis.

Taking into consideration results from meta-analyses regarding mortality rates in patients with asymptomatic carotid stenosis - the latest one Giannopoulos et al., 2015 – above 50%, 5-year mortality is approximately 23%, while 10-year mortality is 52,5%. In addition, 63% of all deaths were cardiogenic. Taking into account all the previously mentioned it is concluded that patients with asymptomatic carotid stenosis should be

considered as a high risk group for cardiovascular comorbidities, as the evolvement of atherogenic activity is already in advanced level. Special attention should be dedicated for patients with many risk factors and comorbidities like, smoking, age, sex, DM, renal failure, chronic obstructive pulmonary disease (COPD), hypertension, dyslipidemia [161].

In addition, we should emphasize that the above mentioned group of patients should be part of a regular follow-up program in order to control the progression of carotid pathology, as well as for the detection of premature signs of myocardial ischemia, aiming to avoid fatal cardiac events, in combination with the modification of risk factors and the appropriate medical therapy. The future of research possibly is based on the gene approach of each disease and on the fully personalized diagnosis and treatment.

Furthermore, it is necessary for the discovery and application of diagnostic non-invasive methods with low cost and with minimal side effects for predicting future cardiovascular events, as well as the identification of high-risk patients and their proper management with an integrated follow-up program based on personalized treatment, aiming the reduction of cardiovascular mortality.

While angiography remains the "gold standard" for the decision regarding the therapeutic management of carotid disease, studies are trying to prove the adequacy of the CDU and the clinical characteristics of the patient for the choice of treatment. The reason for the above mentioned sentence is because better results have been recorded with immediate (within 14 days since the neurological event) surgical or endovascular treatment. Obviously, CDU fulfills these conditions as it provides a convenient, immediate and uncomplicated result. Improvement on the accuracy and applicability of the CDU while avoiding neurological complications during the implementation of classical angiography, guided many health centers in taking a therapeutic decision relied only on CDU findings. Combination of MRA and CDU may be the most harmless and low cost preoperative imaging approach [163].

The European Carotid Plaque Study Group having as a project-leader Henrik Sillesen, publishes [164] the first major preoperative comparison study of CDU evaluation of the

atherosclerotic plaque and its histological findings after endarterectomy. From the results in 270 patients, they conclude and suggest the therapeutic approach of asymptomatic patients with echolucent atheromatous plaque as potentially symptomatic and recommend endarterectomy.

Fifteen years later, in 2009, [165] the European Vascular Surgery Society recommends the pre-invasive assessment of the carotid atherosclerotic plaque as a prerequisite for assessing its impact on successful outcome of therapeutic techniques and especially in CAS. Reliably now this can be achieved by using CDU and its classification according to GSM based on the analysis of the results with the assistance of electronic computer. It is the most common and at the same time the most reliable method of assessing Atheromatous plaque, as it is characterized by its easy applicability and wide range of availability. Really important fact is the examiner's experience as well as the quality of the ultrasound device. The thin and ulcerative fibrous capsule, the intense inflammatory process, neovascularization and the presence of a large fatty necrotic and hemorrhagic nucleus, characterize an atheromatous plaque as "unstable" and potentially symptomatic, which is delineated as echolucent and definitely more dangerous for neurological complications, especially in symptomatic patients.

PARISK study [166] is expected interestingly, in patients with recent neurological event and stenosis <70%, will evaluate with non-invasive methods the constitution of the atheromatous plaque and the recurrence rate of stroke, in order to select earlier than relapse, the invasive treatment approach.

The role of the fibrous capsule (FB) thickness of the atheromatous plaque regarding its stability has already been established. Nowadays MRI is the most sensitive method for the measurement of FB. Important is the evaluation of the plaque before applying the above mentioned high cost methods and 3D-CDU's development is expected interestingly regarding the imaging of FB [167]. Thus the therapeutic selection henceforward will depend on the parameter of FB.

CDU and CEUS are the most documented methods for the selection of patients undergoing CEA or CAS [168]. More studies are expected to document the findings of

ultrasonography and in reference to the candidacy of patients for CEA in patients with a low degree of carotid stenosis.

Ultrasound in all its forms, as analyzed above based on the International Bibliography, is the most widespread, low-cost, applicable to the majority of patients in order to evaluate the extent of carotid disease, especially at the bifurcation. Accepting as a disadvantage, the subjectivity of the ultrasound technique, simultaneous efforts should be noted for development of common ways of its evaluation, that is a powerful decision-making tool for the therapeutic choice in both symptomatic and asymptomatic atherosclerotic disorder of the carotid bifurcation [169, 170].

The disease is characterized as asymptomatic or symptomatic depending on the clinical picture and patient's history and the treatment decision is formally based on the degree of stenosis of the internal carotid artery. Concerns about the constitution of the atheromatous plaque, where CDU plays major role for its assessment, as well as the interest of completing some of the most promising studies, is expected to be lead the international scientific community to review the guidelines. The patient remains objectively asymptomatic or symptomatic, but the atherosclerotic plaque can now be considered as "potentially symptomatic" and treatment can be adapted according to the findings of the CDU and other methods.

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