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Atherosclerotic Plaque Regression and Arterial Reverse Remodelling in Carotid and Femoral Arteries by Statin Use in Primary Prevention Setting: Ultrasound Findings

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1. Introduction

Atherosclerosis is a generalized process which begins early in childhood (first decade of life) and develops silently and more or less rapidly during adolescence and young adulthood (Stary et al., 1994). Recent investigation using whole body multislice computed tomography in 52 ancient Egyptians mummies (mean age 45.1 ± 9.2 years) from the Middle Kingdom to the Greco-Roman period, a time span of more than 2,000 years, Allam et al. (Allam et al., 2011) showed that atherosclerosis (as in contemporary humans) was more evident and extensive with advancig age, and as common and devastating disease as at present time.

Atherosclerotic cardiovascular (CV) disease, which includes coronary artery disease, stroke and peripheral arterial disease, is the most common cause of premature death in the industrialized world thereby constituting an immense public health problem. This disease was formerly considered an inevitable consequence of aging. The Framingham Heart Study, the most important and influential investigation in CV diseases which laid the foundation for preventive medicine and for CV disorders in particular (Greenberg, 2010), enrolled its first patient in 1948. In the following 40 years a large body of scientific evidence from the Framingham cohort and other major epidemiological studies definitely established that multiple CV risks were responsible of the growing CV disease burden, mainly in high-income countries (Mendis 2010). The scientific Framingham Community gave foundation to the risk factor concept providing insights into their prevalence, incidence and prognostic value. Due to variation in prevalence of individual risk factors in different geographic regions specific approaches to CV disease prevention have been implemented in various countries. Accordingly, a WHO survey on CV risk factors in 2002 showed that more than three quarters of the global CV disease burden was attributable to the following 3: tobacco, blood pressure and cholesterol. And the INTERHART case-control study (Yusuf et al., 2004), involving 27,000 subjects from 52 countries representing all inhabited continents, provided

evidence that approximately 80% of the population attributable risk of acute myocardial infarction was predicted by smoking, lipids, hypertension, diabetes and obesity.
As demonstrated in the Karelia Community (Puska, 2010), despite recent attempts to include new CV events predictors, it appears that targeting the already known major risk factors, identified 50 years ago in the Framingham community, remains a priority for the present time and the future. In addition to tobacco the most important modifiable risk factors are hypertension and hypercholesterolemia: due to distinct pathways of atherosclerosis in intracranial versus extracranial disease in patients with hypertension this risk factor has been thought to have major responsibility in the pathogenesis of cerebrovascular diseses whereas the second in coronary artery disese (Napoli et al., 2006). Increasing evidence suggests that atherosclerosis is a diffuse disease with first clinical manifestation in one territory often followed by symptoms coming from other vascular districts. Accordingly, a very high burden of preclinical (silent) coronary artery disease has been recently documented in patients with cerebral infarction (Amarenco, et al., 2010) In recent years, despite the wishful statement by the nobel prize winners Brown and Gldstein "heart attacks: gone with the century? (Brown & Godstein, 1996) CV diseases still remain the undisputed number one killer in most countries and will remain in the next future with an increasing contribution from eastern countries. The well known different gender susceptibility to advanced atherosclerotic lesions observed some 20 years before the occurence of clinical events, supports the pediatrician's view that early preventive measures in young male people can significantly postpone the onset of clinical manifestations (Mc–Gill & McMahan, 2006). Some optimism comes from the percentage decrease (44% to 76%) in death due to coronary artery disease (CAD) during 1980 through 2000 attributed to risk-factor changes in 10 studies in different populations across the globe (Ford et al., 2007). According to Jeremia Stamler (Stamler et al., 2006) an important goal is to increase the population at low risk until it will be the overwhelming majority. He also mentioned the importance of improving life style from the time of preconception to birth and through school age to young adult: a statement in line with studies pioneered by DJP Barker (Barker 1992) on the association between measures of fetal growth and increased risk of CV diseses later in life. Somehow in line with these observations, it has been reported that maternal hypercholesterolemia is associated with enhanced lipid deposition in human fetal arteries (Napoli et al., 2006).
As far as the lipid story is concerned, after early pathological investigations demonstrating that younger hypercholesterolemic people manifest atheroscerotic plaques in their first or second decade of life, it became clear that serum cholesterol was responsible of the intimal atherosclerotic plaque formation laiding the foundation of the science of atherosclerosis as a major research target for the present time and years to come. It has been consistently shown in studies that on average each 1% raise in cholesterolemia is associated with an approximate 3% increase in risk for CV events, and that on the contrary, the HDL cholesterol level is inversely associated with CV diseases in both sexes at all ages ((Barker 1992). At present a great number of experimental, genetic, and epidemiologic papers support the notion that LDL cholesterol is the most important risk factor for atherosclerosis and responsible for clinical events both in men and women (Freeman et al., 2006; Napoli et al.,2006). Moreover, as a relevant finding from the ARIC study it has been shown that a lifelong history of reduced LDL cholesterol levels (by a nonsense mutations in PCSK9) over a 15-year period was associated with 47% reduction of coronary artery disease risk even in presence of multiple risk factors (Cohen et al., 2006), a larger result compared to that predicted from other LDL-lowering trials. These findings strongly support the view that

benefits from cholesterol lowering treatments with statins are expected in relation with the effective duration of treatment along years. According to William Robert (Roberts, 2002) substantial evidence exists that keeping serum total cholesterol <150 mg/dl, LDL-cholesterol <100 mg/dl, and HDL cholesterol at least >20 mg/dl, the chances of forming atherosclerotic plaques are slim. Statins have been available since late-eighties and yet, more than 20 years later, most patients who have had atherosclerotic events or who are at high risk for atherosclerotic events unfortunately are not on statin therapy despite its proven benefit in decreasing first and repeated atherosclerotic events.

2. The atherosclerotic plaque

Atherosclerotic plaques develop over many years. Initiating event is focal subendothelial retention of apoB lipoproteins on extracellular matrix molecules particularly proteoglycans (Tabas et al., 2007). These retained molecules become aggregated and oxidized and induce a series of biological modifications producing a maladaptive inflammatory response by which monocytes enter the subendothelium and become cholesterol enriched foam cells after incorporating the modified lipoproteins. The fibrous cap of such a plaque may become thin and rupture as a result of the depletion of matrix components through the activation of proteolytic enzymes such as matrix-degrading proteinases. It has been shown that lipoprotein retention is amplified and retention continues to accelerate once lesions become established. This implies that lesions are more dangerous when formed early in life and suggests the great gain young subjects can have if don't leave untreated their high blood cholesterol level and other risk factors. Endothelial dysfunction is the first step in atherosclerosis and the combined association of a decreased NO production with an increase of NO inactivation appears to be a marker of this condition. Major responsibility in the formation and progression of atherosclerotic is attributed to reduced adiponectin plasma levels. Adiponectin is thought to be also involved in the regulating of necrotic core development (see 3.4 section of this chapter).

Of note, arterial wall reverse (outward) remodelling is usually associated with vulnerable plaques with higher risk of rupture. Their vulnerability is defined as a relatively large necrotic lipid core, intraplaque haemorrhage, abundant vasa vasorum and/or calcification. They are also covered by a thin, inflamed, fibrous cap that may fissure (Naghavi et al., 2003; Virmani et al., 2005). Collagenous fibrous cap represents a form of scar-like response promoted by smooth muscle cells migration into the intima. Of note, plaque progression (Fig.1) is associated with dying macrophages giving rise to areas of necrosis with cholesterol crystals, extracellular debris, proteases and prothrombotic agents (Tabas et al., 2007). These advanced plaques (Fig. 2) are characterized by fibrous cap thinning, plaque erosion and rupture as a result of the depletion of matrix components through the activation of proteolytic enzymes such as matrix-degrading proteinases (MMPs) that are highly concentrated in atherosclerotic plaques by inflammatory cells (macrophages, foam cells), smooth muscle cells and endothelial cells, ultimately being responsible of clinical thrombotic events such as acute myocardial infarction or stroke. A number of research lines have been identified and a therapeutic window of opportunity appears to exist to selectively block proretentive subendothelial matrix-lipoprotein interaction with a potential for regression of advanced plaques

Great advancement of the knowledge in coronary plaque structure has been obtained in recent years by intravascular imaging modalities which can characterize the plaque according to the presence of thin fibrous cap and other findings such as active inflammation, lipid core disruption and severe stenosis, with high sensitivity specificity and predictive

accuracy (Valgimigli et al., 2006; Hong et al., 2009). Much interest has been recently focused on the role of calcium which is incorporated into the plaque with an active process resembling bone formation preceded by apoptosis of smooth muscle cells and generation of apoptotic bodies acting as calcification sites with further steps ultimately leading to hydroxyapatite deposition (Mamm et al., 2011).

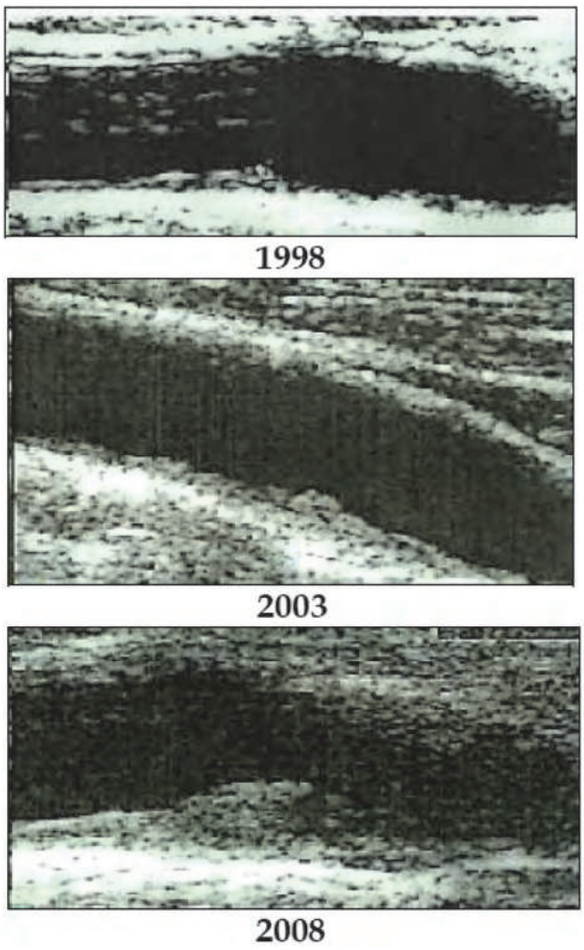


Fig. 1. Plaque formation and progression in the carotid artery. B-mode ultrasound imaging of the left carotid artery in a long-axis during a 10 years period follow-up (1998-2008) in a healthy man from 45 to 55 years of age. Of note, this subject was normotensive and had surprisingly normal blood lipids level (total chol. 165 mg/dl, HDL chol. 71 mg/dl and tryglicerides 64 mg/dl). In 1998, at age 45 y.o., a small plaque was present (maximum short axis diameter: 1.3 mm). In the following ten years a progressive increase in plaque dimension occurred associated with a mild expansive arterial wall remodelling [Glagov phenomenon (Glagov et al., 1987)] in the far field in the year 2003, with a marked step-up increase of the outward arterial remodelling in 2008. The large echo-lucent (black) area within the plaque in 2008 is associated with a thin fibrous cap indicating a high risk of plaque rupture in this subject.

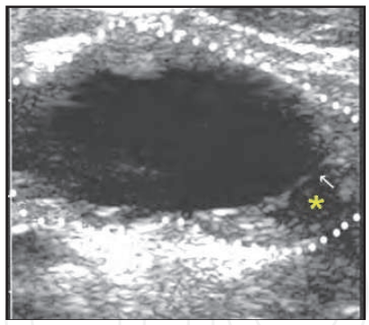


Fig. 2. Vulnerable plaque of the carotid artery bifurcation referring to type VI lesion of the AHA plaque nomenclature. The asterisk indicates the area of the lipid necrotic core covered by a very thin fibrous cap (small arrow) with high risk of rupture. The plaque is associated with a marked outward vessel remodelling keeping intact the lumen of the artery.

Moreover, a recent non invasive ultrasound study of femoral arteries in animals opened a door for clinical application of quantification of adventitial vasa vasorum proliferation, a feature of plaque progression (Moguillansky et al., 2011). But evidence exists that despite core in vivo imaging strategies are promising, their invasive nature and limited spatial resolution, as well as ionizing radiation and poor penetration, limit their possible application in human beings. A future however most exists for hybrid technologies and advanced reconstruction and post-processing techniques.
Summarizing, atherosclerosis has top responsibility in total and CV mortality, either industrialized and in the developing countries, it is a cholesterol dependent disease, progressive in nature and characterized by a very long preclinical period. Total cholesterol plasma level > 130 mg/dl is the necessary causing factor. This process starts in the early decade of life and is accelerated by other major risk factors like hypertension, smoking, diabetes, obesity and male gender. It can be easily identified by B-Mode ultrasound of carotid and femoral arteries during the asymptomatic (preclinical) period long before clinical manifestations do occur, opening a window for early diagnosis and lipid-lowering interventions.

2.1 Plaque regression and stabilization

An ischemic event is usually associated with an advanced atherosclerotic lesion. Early studies in animals showed that removal of atherogenic factors reduced the prevalence of atherosclerotic lesions. As far as the regression studies of atherosclerosis in human beings is concerned, we must first acknowledge those studies pioneered at the University of California in 1978 by David Blankenhorn and his group (Blankenhorn et al., 1978; Blankenohorn 1978). These authors used advanced computer techniques for image processing derived from space-fly technology with a digital array depicting up to 256 shades of gray. This group first demonstrated the regression by treatment of atherosclerotic lesions with serial femoral artery angiograms (two exams at 13 months interval) performed in 25 hyperlipidemic subjects. During the following 15 years nine arteriographic human studies have been conducted by different groups with a total of 2.101 patients and a mean follow-up of 3,3 (1 to 10) years. These studies have been reviewed by Brown et al. (Brown et al., 1993). Despite several diversities among these studies the analysis showed a benefit from treatment: whether by diet, diet plus life style changes, by hypolipidemic drugs niacin and lovastatin, or plus ileal by-pass associated with resins (cholestipol or cholestiramine). The

mean numbers of angiographic outcomes were the following: 53% progression and 8% regression in the control group, versus 26% progression and 26% regression in the treated groups. The authors concluded that this analysis has confirmed the hypothesis that lipid lowering therapy selectively depletes the atherosclerotic plaques lipid content and prevents plaque disruption and the associated clinical events. For what the plaque instability is concerned many factors concur to the phenomenon. The mechanical strength of the cap appears to be one of these and depends on the amount and structure of collagen and other tissue protein determinants of plaque rupture.

Mechanisms by which lipid lowering may stabilize vulnerable plaques in humans have been extensively investigated in recent years. Specific cellular and molecular alterations consequent to lipid lowering have been identified: matrix metalloproteinase (MMP) activity reduction with associated increase of collagen content in plaques appears to have major importance. Smooth muscle cells have a central role in the formation and stabilisation of the fibrous cap because they produce connective tissue matrix proteins. It has been suggested that the combination of lipid lowering and antioxidant agents has a rationale for preserving fibrous cap stabilization (Davies, 1998). On this line it has been shown (Aikawa et al., 1998; Crisby et al., 2001) that pravastatin not only decreases lipid content, oxydized LDL and inflammation, but also MMPs-2 and cell death, whereas it increases collagen content providing the first strong evidence of plaque stabilizing effect by statins in humans.

In 2001 Corti et al. (Corti et al., 2001) using serial black-blood MRI of the aorta and carotid arteries at baseline, 6 and 12 months after lipid-lowering therapy with simvastatin in hypercholesterolemic patients with aortic and/or carotid atherosclerotic plaques, demonstrated that persistent reduction in total and LDL cholesterol levels was associated with a significant inverse remodeling and lumen preservation of both aorta and carotid arteries at 12 months. In the REVERSAL study, published in 2004 by Nissen et al. (Nissen et al., 2005) intravascular ultrasound have been used in 502 patients divided into equal sized groups receiving either pravastatin 40 mg or atorvastatin 80 mg daily dose for 18 months: a complete halting of coronary disease progression was observed in the atorvastatin-treated patients but a continued disease progression occurred in the pravastatin-treated group, thereby suggesting that a very low levels of LDL cholesterol are needed to arrest and stabilize the ongoing atherosclerotic process and that 40 mg pravastatin is inadequate to this end. A step up progression of the results from lipid reducing drugs has been demonstrated by Corti et al. (Corti et al., 2005) in a further study in which a significant regression of atherosclerotic plaques has been obtained by effective and protracted lipid-lowering therapy: moreover and of major importance, the study suggested that the degree of LDL-cholesterol reduction rather than the statin dose was associated with plaque regression. Differently from previous intravascular studies in which statins administration was accompanied only by slowing or halting of the atherosclerotic process, Nissen et al. (Nissen et al., 2006) first demonstrated in 2006 a significant regression of coronary atherosclerosis with serial intravascular ultrasound examinations in the ASTEROID trial: the study was conducted during 24 months period in 349 patients submitted to high-intensity statin therapy with rosuvastatin 40 mg. Of interest, a 10-12 months period appears to be the appropriate time interval for initial appreciation of plaque regression in carotid and femoral arteries during statin treatment also in our experience in the last ten years period (Rusconi C, 2008; Rusconi et al., 2011). Thus, evidence exists allowing us to conclude that with appropriate statin use plaque regression and stabilization do occur. The phenomenon can be assessed non-invasively in patients using ultrasound imaging of carotid and femoral arteries and is further examined and described in details in the last part of this chapter.

3. The 4S trial and the statins story

As far as the story of secondary CV events prevention is concerned, it is worthy to mention the pioneering Scandinavian Simvastatin Survival Study (4S) trial (The Lancet, 1994) and its promoter Prof. Terjie Pedersen who opened the door to evidence based secondary CAD prevention by statin use. In this study it has been shown for the first time that simvastatin reduced mortality in patients with a high cardiovascular risk. Many large outcome trials of statins have been performed during the following years confirming the results of the 4S trial. Further recent confirmation that statin use continues to be useful comes from a double-blind randomised trial (SEARCH Study, 2007) comparing 80 versus 20 mg simvastatin administration in 12,064 men and women 18–80 years old with a history of myocardial infarction. In this study the higher simvastatin dosage has reduced from 25,7% to 24,5% (with 6% proportional reduction) the major vascular events. Consistent with previous trials, this result has been obtained by an average 0·35 mmol/L greater reduction in LDL cholesterol. In this study the risk of statin-related myopathy was low with the 20–40 mg simvastatin dosage (about one per 10,000 patients per year) but increased about ten times (to about one per 1000 patients per year) with 80 mg simvastatin daily. Of importance, the excess risk mainly occurred during the first year and has been largely confined to those people carrying *SLCO1B1* genetic variants which can be otherwise detected before starting treatment and may be useful for tailoring the statin dose in the first year of treatment, especially when certain other drugs are simultaneously used (The Search Collaborative Group, 2008). In this study clear evidence has come out that lowering LDL cholesterol concentrations lowers the risk of major vascular events and that intensive LDL cholesterol lowering reduces the risk even more. Based on these results the authors suggested that "for patients deemed to be at sufficient risk of major cardiovascular events a more appropriate strategy - by contrast with current guidance - could be to consider regimens which involve newer, more potent, statins (80 mg atorvastatin or 20–40 mg rosuvastatin daily) or the combination of standard doses of generic statins (40 mg simvastatin daily) with other agents that can lower LDL cholesterol substantially, without producing such increases in the risk of myopathy". On the subject of the recent statins introduction in the armamentarium of cardiovascular therapy Scott Grundy (Grundy, 2004) wrote the following statement: "lowering low-density lipoproteins by statin therapy to reduce the risk for major clinical events in patients with clinical atherosclerotic CV disease represents a therapeutic triumph of modern medicine". After a seven years period from this statement a surprising sequence of successes has so far characterized the statins story, also extending the positive results to apparently healthy people with preclinical atherosclerosis. According to the extraordinary evidence on the issue and in agreement with the SHAPE Group strategy in USA-Texas State, (Naghavi, M., Libby, P., & Falk, E. 2003) we think that the time has come to go by far beyond such evidence by applying effective preventive measures also to the great group of individuals with preclinical atherosclerosis.

There are now available multiple noninvasive imaging modalities that can identify subclinical atherosclerosis in different vascular beds. They include ultrasonography, coronary CCS assessment by CT, noninvasive CT angiography and MRI. All these methods have advantages and draw backs, but only CCS and ultrasonography have been mostly used. The CCS has provided powerful prognostic information in both sexes of multiple ethnic populations and a systematic review of both symptomatic and asymptomatic populations led investigators to conclude that who have a negative CCS are highly unlikely

to have CAD (Sewer et al. 2009). But discordant results have been also reported. In our view, due to the associated radiation exposure and the need of repeated examination in the course of years also to establish the right moment for an interventional procedure, the coronary CCS should be used to this end only after careful evaluation of risk/benefit ratio. The issue will be later thoroughly treated in this chapter.

3.1 Statins-induced event reduction in primary prevention setting

Patients with established CHD or other clinical manifestation of atherosclerosis, or diabetes, have by definition a substantial risk for future cardiovascular events and premature death. These people should have intensive lipid-lowering therapy because the benefit from these drugs is estimated to largely overweight the risk associated with such a treatment, even if low baseline LDL concentration is present (Cheung & Lam, 2010). On the other side, according to the results of several studies statin treatment appears appropriate in primary prevention setting only in presence of specific risk factors.

The first clinical trial to study the effect of statins in primary prevention setting in patients with a relatively low risk was the WOSCOPS trial (Shepherd et al., 1995) performed in 6.595 hypercholesterolemic patients using 40 mg pravastatin, obtaining a 32% risk reduction in major CV events during a 4.9 years period of follow-up. The following AFCAPS trial (Downs et al., 2001) studied the effects of lovastatin in healthy men and women and was associated with 39% reduction in major coronary events definitely confirming the benefits of statin treatment in healthy individuals. The results of the subsequent PROSPER trial (Shepherd et al., 2002) in 1,585 subjects taking pravastatin raised the question of the potential cancers risk and the problem of side effects with statins. The concern has been subsequently negated by the following studies: ASCOT (Sever et al., 2003) in 5,168 hypertensive patients, HPS (Heart Protection Study Collaborative Group, 2002) in 20,536 patients, CARDS (Colhoun et al. 2004.) in 1.428 diabetic patients, ASPEN (Knoop et al., 2006) in 959 diabetic patients. All the aforementioned studies have demonstrated mostly positive results on the incidence of coronary and cerebrovascular disease without increasing cancer risk.

Recently, in primary prevention setting the MEGA trial (Nakamura et al., 2006) in 3.966 hypercholesterolemic Japanese women during a mean follow-up of 5.3 years, randomly assigned to diet or diet plus 10-20 mg pravastatin, it has been shown that pravastatin reduced coronary events by 23% without any difference in the incidence of cancer or other adverse events between the two groups, suggesting that treatment with a low dose of pravastatin reduces the risk of coronary heart disease in Japan by much the same amount as higher doses have shown in Europe and the USA. In the year 2004 a meta-analysis (Grundy et al., 2004) from the National Cholesterol Education Program Adult Treatment Panel III Guidelines, including 26 randomized trial, 5 of them planned *more vs less statins* and 21 planned *statins vs control* (also including the eight studies just mentioned in previous lines) with a total of 170.000 participants, the authors conclude that further reductions in LDL-cholesterol safely produce definite further reductions in the incidence of heart attack, revascularisation and ischemic stroke, reducing the annual rate of these major vascular events by just over a fifth with each 1.0 mmol/L of LDL-cholesterol reduction. Furthermore, no evidence of any threshold within the cholesterol range studied was found suggesting that by 2-3 mmol/L plasma lowering of LDL-cholesterol would reduce risk by about 40-50% respectively. Of importance, further reduction of LDL-cholesterol did not produce any adverse effects even in those subjects with baseline LDL- cholesterol lower than 2.0 mmol/L. A meta-analyses of more versus less intensive therapy, and of statins versus

control, did not discovered any adverse effects on cancer incidence (CTT Trialists, 2005). A number of other important conclusions for clinical practice have been drawn in this meta-analysis: 1) the primary goal for patients at high CV risk should be to achieve the largest LDL-cholesterol reduction possible, without materially increasing myopathy risk, 2) lowering of LDL-cholesterol further below the limit established by NECP in 2004 (Grundy et al., 2004) of 70 mg/dL (1.8 mmol/L) to achieve additional benefits, without an increased risk of cancer or non-vascular mortality, 3) to achieve these benefits, with newer more potent statins such as 80 mg atorvastatin or 20 mg rosuvastatin daily, 4) to use combination of standard doses of generic statins (40 mg simvastatin or pravastatin daily) with other LDL-cholesterol lowering therapies.

In primary prevention setting (asymptomatic and apparently healthy subjects) statins are used in presence of risk factors and hypercholesterolemia in particular. Prototypic condition in which aggressive LDL-cholesterol reduction is mandatory is familial hypercholesterolemia. General agreement exists that in these patients should be used the highest tolerated statin dosage. In a study on this subset of patients it has been shown that atorvastatin 80 mg treatment was accompanied by regression of carotid intima media thickness whereas conventional LDL-cholesterol lowering was not (Smilde et al., 2001). Similarly, the great number of apparently healthy subjects with documented atherosclerosis, either by 2D-echo of carotid/femoral arteries or by CT scan of coronary calcium, in addition to life style modifications and other risk factors control, statin treatment appears appropriate according to the severity of the atherosclerotic process and the number and weight of risk factors.

Of note, for what the dietary alcohol is concerned, it has been shown that comparing alcohol consumers and abstainers for a 3 years period follow-up after femoral or carotid artery surgery, alcohol consumers had less cardiovascular event rate as well as more stable plaque cores and less macrophage infiltration (Gisbertz et al., 2011) confirming that mild-to moderate alcohol consumption may help to reduce atherosclerosis progression.

3.2 HDL-cholesterol and statins

Clinical, experimental and epidemiological evidence consistently demonstrated the inverse association and causal relationship between low HDL levels and the risk of coronary artery disease (Gordon & Rifkind, 1989). Statin treatment of cardiovascular patients reduces clinical events by 25 to 45%. High-density lipoprotein (HDL) has been proposed as a therapeutic target to further reduce this residual cardiovascular risk. The primary role of HDL and reverse cholesterol transport in the reduction of CHD risk is supported by a considerable amount of experimental data. The mechanism by which HDL can mediate protection from atherosclerosis is complex and multifactorial and evolving concepts of the role of HDL in protection from atherosclerosis have been recently pointed out (Farmer & Liao, 2011).

The HDL particles exert a strong antiatherosclerotic action through several mechanisms. These include a facilitating cholesterol efflux from cholesterol-loaded foam cells, an antiinflammatory action, a positive effect on nitric oxide synthesis, serving as a plasma transport lipoprotein for biologically important proteins and as an antithrombotic agent by improving thrombolytic balance. In addition to their beneficial effects on the coagulation system the HDL molecules have a favorable complex interaction with the protein C and protein S system and have a significant natural antioxidant effect which improves endothelial function and inhibits the oxidative step required for LDL uptake by the macrophage. These properties of HDL have been demonstrated to decreased apoptosis and

promote endothelial repair. Clinical trials with new HDL-raising drugs are currently under way to provide definitive evidence that increasing HDL will reduce cardiovascular events **(**Brewer, 2011).

Low HDL levels are present in about 10% of the general population and represent the most frequent form of dyslipidemia in patients with CAD. Reduced HDL concentrations seem to be unable to eliminate efficiently the cholesterol excess at vascular wall level, contributing to the onset of the inflammatory response that typically occurs in the pathogenesis of atherosclerosis from its earliest stages. In keeping with this evidence the results of numerous studies quite convincingly suggest that HDL is capable of exerting anti-inflammatory activity either directly or by modulating the expression of a number of acute phase reactants. Endothelial repair and reduced apoptosis are other mechanism by which HDLs preserve vascular function (Kera et al., 2011).

In a recent careful examination of 20 randomized control trials (completed in the period from 1991 to 2009) in which statins have been used, for the first time clear evidence emerged that despite statin treatment a low HDL-cholesterol plasma level remains an independent predictor of higher cardiac events (Jafri et al., 2010) A post-hoc analysis of one of these studies, the TNT trial (Waters et al., 2004), showed that low levels of HDL-cholesterol was predictive of high rate of major CV events even at very low level of LDL-cholesterol thus suggesting that low levels of HDL and high levels of LDL cholesterol are indipendently important predictors of cardiovascular disease. Similarly, in another meta-analysis of 23 trials of various lipid-modifying drugs the sum of LDL-cholesterol percentage reduction and the HDL-cholesterol increase better predicted the benefit than the individual lipoprotein changes: it has been calculated that each 0.26 mmol/L (10 mg/dL) decrease in HDL-cholesterol level was associated with 7 additional myocardial infarction and 4 additional CV events/1000 person-years (Brown et al., 2004). It has been also underlined that despite the aforementioned undisputable evidence of the benefit associated with higher HDL-lipoprotein plasma levels, certain drugs (fibrates) do not appear to be associated with clear benefit (Joy et al., 2008).

In a recent and important study Kera et al. (Kera et al. 2011), measured the cholesterol efflux capacity from macrophages (a metric of HDL function) in 203 healthy volunteers who underwent carotid artery IMT assessment and in 442 angiographycally confirmed coronary patients, as well as in 351 patients without angiographic confirmed disease: in this study the authors demonstrated the followings: 1) HDL-cholesterol levels and apolipoprotein A-1 (the major protein component of HDL) were significant determinants of cholesterol efflux capacity accounting for less than 40% of the observed variation, 2) the efflux capacity was inversely related to IMT and was a strong inverse predictor of coronary artery disease status. The authors concluded that this capacity "is not explained simply by circulating levels of HDL-cholesterol or apoliprotein A-I and is independently related to both the presence and extent of atherosclerosis".

Therapeutic options for raising HDL-cholesterol plasma levels still appear inconsistent either in experimental or in preclinical setting and, up to now, in clinical studies the cholesterol efflux capacity has not been enhanced in statins treated patients. Due to inability of statins to further reduce the risk associated with low HDL-cholesterol, a treatment has been suggested (Cziraky et al., 2008) to promote optimal lipid values in several at risk patients-populations based on the association of a statin with extended-release niacin, the most effective agent for raising HDL-cholesterol levels. This approach appears most justified in type 2 diabetes which is characterized by two to three times higher prevalence of

hypertrigliceridemia usually associated with decreased HDL-cholesterol levels and increased small dense LDL-cholesterol particles, forming the powerful risk factor of the lipid triad (Temelkova- Kurktschiev & Hanefeld, 2004). As far as the antioxidant potential of HDL particles is concerned it has been shown that distribution of HDL subpopulations according to their particle mean size has important implication for their antioxidant potential and that HDL3 particles are more resistant to oxidation (Shuhei, 2010).

3.3 Inflammation, C-reactive protein and lipoprotein (a)

Inflammation and inflammatory pathways appear to have a fundamental role in the pathogenesis of atherosclerosis and coronary artery disease in particular (Hansson, 2005). Accelerated atherosclerosis has been described in patients with chronic inflammatory diseases such as rheumatoid arthritis, psoriasis and systemic lupus erythematosus. High sensitivity C-reactive protein (hsCRP), an acute phase reactant produced by the liver is the most studied, although nonspecific, marker of inflammation. In 1997 Ridker et al. (Ridker et al., 1997) gave first demonstration of hsCRP ability to predict future myocardial infarction and stroke in apparently healthy asymptomatic subjects, and several papers have been published in recent years on the subject supporting Ridker's conclusions that hsCRP is a strong predictor of future major cardiovascular events. Moreover, evidence +has been published that the magnitude of this effect is similar to that of cholesterol and blood pressure and that also people with elevated hsCRP levels but without hyperlipidemia might benefit from statin treatment (Ridker et al., 2008).

However, in a recent report of the Heart Protection Study (HPS Collaborative Group, 2002) with 20.536 high risk patients randomly assigned to simvastatin 40 mg versus placebo for 5 years, it has been observed a 29% reduction of major vascular events without any significant difference between the four subgroup (defined by the combination of low or high baseline LDL-cholesterol and CRP) with clear evidence of benefits mainly in those with both low LDL-cholesterol and low CRP. These findings suggested that LDL-cholesterol reduction is the necessary condition to reduce the risk of cardiovascular events, independently of CRP changes. According to the authors, this conclusion appears to be mainly supported by the finding that LDL-cholesterol reduction by simvastatin reduced the event risk to a similar extent irrespective of baseline CRP levels. At present, it appears uncertain whether hsCRP should be considered only a clinically useful disease marker or whether it also may play a causal role in the atherothrombotic process. Of interest, in a recent study in the TNT study population (Arsenault et al., 2011) investigating the effects of atorvastatin 80 mg versus 10 mg in patients with stable coronary artery disease, it has been shown that in contrast to the blood lipid levels almost none among several non-lipid biomarkers predicted recurrent CV events after 1 year of treatment. According to the authors' suggestion the cardiovascular benefits were primarily due to the effects of statins on lipids biomarkers rather than on non-lipid ones. According to 2009 Canadian Lipid Guidelines (Jenest et al., 2009) hsCRP should not performed on everyone but only in selected subjects and in patients with metabolic syndrome for better risk stratification.

More recent data from Molenkampf et al. (Molenkampf et al., 2011) suggest that in primary prevention setting hsCRP may help selecting in the general population those people with highest risk of coronary events but with low coronary calcium score (CCS). In particular they demonstrated that CCS was superior to hsCRP in the discrimination and reclassification of coronary risk and that further improvement in coronary risk assessment was obtained when CCS was added to Framingham risk variables and hsCRP, whereas

adding hsCRP to Framingham risk variables and CCS did not increase risk prediction. In any case, and in complete agreement with the authors, in asymptomatic subjects and for all individuals, the first-line recommendation remains a healthy lifestyle including quit smoking, regular physical activity, healthy diet, blood pressure and weight control. The efforts that are necessary to implement effective lifestyle modification in larger cohorts must be weighed against the costs of extended risk assessment and, for what CCS is concerned, the risk attributable to radiation exposure (see later). Being hsCRP a nonspecific marker of inflammation, it has been suggested that among the other inflammatory markers interleukine-6 may provide valuable additional prognostic information. In conclusion, at present time it appears that hsCRP should not be considered neither a major player in the atherosclerotic process nor a major predictor for future events, but may be thought to better stratify the risk and to support clinical decision in the individual patient.
Finally, as far as the lipoprotein-(a) [Lp(a)] is concerned, the results from the recently published Young Finnish Study [a prospective population-based cohort study of 939 men and 1,141 women followed-up from the mean age of 17 and 38 years with repeated Lp(a) and both carotid IMT and flow-mediated dilation tests] do not provide any support for an early atherogenic effect of increased Lp (a) plasma levels (Kivimaki et al., 2010).

3.4 Adiponectin

Adiponectin is the most abundant adipokine released by adipocytes in response to extracellular stimuli and metabolic changes (Berseghian, 2011). It is predominately, but not exclusively, produced by adipose tissue and recent studies suggest that it is also synthesized and secreted by human cardiomyocytes (Pineiro et al., 2005). It is reduced in obesity and type 2 diabetes and low plasma concentration has been associated with an increased risk of CAD and acute coronary syndrome in several though not all studies. Low plasma levels of adiponectin are also associated with increased NO inactivation combined with decreased NO production, both of which contribute to endothelial dysfunction, the first step in atherosclerosis. Adiponectin is thought to be also involved in the regulation of necrotic core development. In patients with stable CAD and in acute coronary syndrome, a decrease in plasma adiponectin values has been found to be associated with an increase in necrotic core in both culprit and non-culprit lesions assessed by intravascular ultrasounds, suggesting that in this clinical setting lower adiponectin levels reflect plaque vulnerability (Otake et al., 2008). Accordingly, the association of decreased plasma adiponectin level and increased necrotic core ratio has not been demonstrated in patients with stable CAD (Sawada et al., 2010). Although produced by adipocytes, adiponectin exhibits plasma levels inversely proportional to body mass index and visceral adiposity (Bajaj & Ben-Yehuda, 2006). Adiponectin is thought to decrease atherosclerosis progression through inhibition of both neointimal thickening and SMC proliferation and migration into the intima. As recently suggested by Barseghian et al. (Barseghian et al., 2011) direct adiponectin administration in humans is premature and warrants further investigation but indirect methods such as lifestyle modifications and pharmacological interventions may be used to increase adiponectin plasma levels at present time (Hermann et al., 2006). On this line, a meta-analysis of 19 studies confirmed an increase of endogenous adiponectin levels with thiazolidinediones use. Accordingly, pioglitazone exhibited the potential of coronary plaque stabilization in patients with type 2 diabetes by increasing adiponectin levels and reducing the necrotic-core component (Ogasawara et al., 2009; Riera-Guardia & Rothenbacher, 2008).

3.5 Lipids and stroke prevention

The stroke represents the second leading cause of death and is a major contributor to health-care cost. As recently reviewed by Endres et al (Endres et al., 2011) variations have been found between the main risk factors for haemorrhagic vs ischemic stroke and overwhelming evidence suggests that hypertension is a major cause of brain damage and that brain benefits more from high blood pressure treatment. Moreover, it has been indicated (Pischon et al., 2007) that the main modifiable risk factors such as diabetes, smoking, hypertension, and hypercholesterolemia, explain only 55% of variance for stroke events compared to 88% variance for myocardial infarction. In that review (Endres et al., 2011) it has been underlined that actually no randomized clinical trial exists providing a blood pressure target for effective prevention of first strokes. In several studies a close relationship between cholesterol plasma levels and stroke has not been found and hypercholesterolemia is thought to have major responsibility in atherothrombotic stroke only Endres et al., 2011). Although it is still unsettled whether statin use is useful in primary prevention of atherothrombotic stroke in subjects with mild hypercholesterolemia, evidence exists on the other side (Naghavi et al,. 2003) that even mild carotid atherosclerosis in apparently healthy subjects, and independently of lipid plasma values, identifies those subjects with more or less generalized subclinical disease which should be appropriately treated with statins.

3.6 LDL-cholesterol and cancer

Several cancer subtypes (gastrointestinal, hematological, female-specific, urologic and lung cancer) have been observed to be associated with low LDL-cholesterol levels and the mechanisms by which preclinical cancer might induce low LDL-cholesterol plasma levels are largely unknown. The issue of a potential increased risk of cancer in patients treated with hypolipidemic drugs has been already faced in previous pages (see section 3.1) where substantial evidence has been provided on the safety of statin use. The problem of an increased risk of cancer by hypolipidemic drugs has been raised since the late seventhies by the Clofibrate trial, a WHO Cooperative Trial on primary prevention of ischemic heart disease using clofibrate (Oliver et al., 1978). In this study a 47% excess mortality occurred in the treated group during the study period but it has not continued in the follow-up period with only 5% excess mortality after treatment has ended. Recent meta-analyses (Benn et al., 2011) from more than 90,000 patients have lessened the concern, raised in the previous three decades, on risk of cancer using LDL-cholesterol lowering drugs (Rose et al. 1974). However, the pendulum of the potential damage from cholesterol lowering thearpy has been again a little bit forced forward by the results from two studies in Denmark – the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS) on 59,566 and 6,816 subjects respectively– which have shown that, indipendently of statin use, participants with low plasma cholesterol level (<87 mg/dL) were associated with a 47% increased risk of cancer, a finding not observed in those patients with innate low plasma LDL-cholesterol level identified by genetic study of single-nucleotide polymorphisms in PCSK9, ABACG8 and APOE (Benn et al., 2011). This study has left unsettled the issue of the potential cause-effect relationship between LDL-cholesterol lowering by statin use and cancer. However, a recent metaanalysis of data on cancer from 166,000 paricipants in 25 randomized trials, it has been concluded that, at least in the five years treatment period no evidence emerged of any effect of statin therapy on cancer incidence or mortality at any particular site (Emerson et al., 2010). Has the story come to an end?

4. Imaging of atherosclerosis

Atherosclerosis has been generally viewed as a chronic and inevitably progressive disease characterized by continuous accumulation of atheromatous plaque within the arterial wall. In the last 25 years an important step-up progression occurred with the introduction of a variety of anti-atherosclerotic therapies, the most important of which are the so called statins, which rank among the most extensively studied therapies in contemporary medicine, opening the door to an effective anti-atherosclerotic treatment in addition to standard non pharmacologic measures. Almost simultaneously, invasive and non-invasive imaging techniques of atherosclerosis have been attempted in the course of years and an extraordinary development in non-invasive assessment has been realized during the last two decades. X-ray angiography is still considered the gold standard imaging technique for vessel patency studies but it does not usually allow obtaining information on plaque structure as well as differentiating stable from unstable plaques and the risk of rupture. This technique typically suffers from these limitations and even to day many cardiologists unfortunately still behave as if the absence of angiographic abnormalities indicates the normality of coronary artery anatomy and absence of atherosclerosis (Davis et al., 2004) In a decreasing degree of complexity the new imaging modalities are represented by the following: 1) magnetic resonance imaging (MRI), 2) CT angiography, 3) CCS ,4) B-mode ultrasonography of carotid and femoral arteries as well as abdominal aorta. All these methods are used in clinical setting and the type of investigation closely dependent on the clinical problem the individual patient has and on which techniques are locally available. As it has already been discussed in previous pages high-quality studies have demonstrated that a correlation exits between the severity of atherosclerosis in one arterial territory and involvement of other arteries and that these tests can predict the risk of future CAD events (Fowkes et al., 2008). Accordingly, noninvasive atherosclerosis imaging has evolved into a central method in clinical cardiology and both CCS and B-mode ultrasonography have recently become the most used techniques as first line approach for atherosclerosis detection in primary prevention setting (Greenland et al., 2003). Expert recommendations have endorsed the use of these imaging modalities in primary prevention (Stein et al., 2008) allowing a step-up progression towards an individualised CAD prevention through more effective use of drugs. According to 2009 Canadian Lipid Guidelines (Genest et al., 2009) the screening for high risk subjects should include the following as Class I Recommendation Grade, Level of Evidence C:

- All men over 40 and postmenopausal women
- Anyone with atherosclerosis or diabetes regardless of age
- Anyone with family history of premature (< 60 yrs) cardiovascular event
- All patients with hypertension or dyslipidemia
- All patients with inflammatory diseases such as lupus, rheumatoid arthritis and psoriasis
- Children of patients with severe dyslipidemia
- Subjects with xanthomas, xanthelasma or premature arcus corneus
- Erectile dysfunction
- Chronic renal disease.

Moreover, the following test for atherosclerosis are suggested as Class IIa Recommendation Grade, Level of Evidence C :

- Ankle brachial index
- Exercise stress test

- Carotid B mode ultrasonography
- Cardiac Computed Tomography

These guidelines (Genest et al., 2009) indicate that the presence of atherosclerosis in one of these tests places the individual in the high risk category. In the following pages in addition to a brief review on the usefulness of noninvasive techniques the attention will be focused on noninvasive plaque imaging by ultrasound (which is available in every clinical setting) enabling first line study of plaque burden and structure with assessment of potential regression during statin treatment.

4.1 Magnetic resonance and CT imaging

Due to inability of surface ultrasound to imaging coronary artery circulation, attention has focused on other techniques such as CT and MRI (Kim et al., 2001). As far as MRI is concerned , appropriate sequences are needed for plaque imaging and the contrast-enhanced MRI used for clinical purposes is inadequate to this end (Fig. 3).

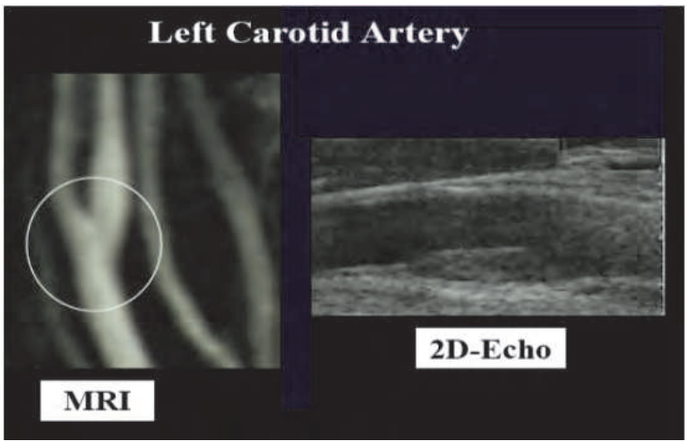


Fig. 3. Contrast-Enhanced MRI (left panel) and B-mode ultrasonography (right panel) of the left crotid artery in a patient with carotid atherosclerosis. In this case the MRI exam has been perfomed for the clinical purpose of a better assessment of vessel stenosis. Plaque imaging would have required a different exam with T1-T2 weighted sequences.

Due to its non-invasiveness carotid MRI has been recently proposed as tool for monitoring individual response to cardiovascular therapy (Yuan, 2008). High-resolution MRI has been recently used for the noninvasive evaluation of carotid plaques showing that is possible to analyze the structure and molecules inside the plaque and to distinguish symptomatic from asymptomatic plaques and patients with low versus high risk through identification of iron deposition (Raman et al., 2008). Moreover, discrimination between lipid core, fibrous cap, intraplaque haemorrhage and calcification as well as distinguishing macrophage-rich from macrophage–poor lesions is possible (Kooi et al., 2003). From these studies emerged the finding that patients with a lipid-rich necrotic core with or without intraplaque haemorrhage represent the desired phenotype for monitoring treatment effects. It has been recently also suggested (Underhill et al., 20011) that throughout advanced tissue specific sequences, acquisition resolution and scan time, in association with techniques allowing monitoring of inflammation and mechanical forces, this technique will enable early assessment of response to therapy.

As far as CT is concerned, significant advances in the last ten years helped this technology to evolve as a real non-invasive alternative to conventional catheter based coronary angiography with the additional great advantage of the possibility of establishing the atherosclerotic burden and plaque characteristics with a radiation exposure less than 1mSv (when a heart rate is kept <60 bpm) which is less than the radiation dose of current CCS imaging. But new evidence that even low-dose ionizing radiation from cardiac imaging and therapeutic procedures is associated with an increased risk of cancer (Eisenberg et al., 2011), suggests that a new word of caution is worthy on the issue and that if the benefits to patients of a single cardiac imaging test probably outweigh any small excess risk of cancer, repeated examinations can induce more harm than good.

4.2 B-mode ultrasound and CCS

During the last 25 years, after the seminal papers by Pignoli and his coworkers (Pignoli, 1984; Poli et al., 1984) in mid eighties, on the feasibility of direct measurement of arterial wall thickness with B-mode imaging in vitro of specimens of human aortic and common carotid arteries, the use of this noninvasive approach through the measurement of the carotid intima-media thickness (CIMT) has become the standard reference method in assessing the presence and the amount of clinical atherosclerosis. Since early studies (Salonen & Salonen, 1991) it has been demonstrated that the presence of different degrees of carotid atherosclerosis (normal, thickening, plaque, stenosis) was associated with a progressive increase of coronary events incidence during a 4-years follow-up period. But at present, after dozens of published studies, the evidence to quantitatively support the use of a CIMT measurement to help in risk stratification on top of a risk function is limited (Platinga et al., 2009). As it will be reported later on, plaque detection by B-Mode ultrasound has become the method of choice for early detection and follow-up treatment in patients deemed to be at higher risk because of preclincal atherosclerosis by carotid and/or femoral plaques, a more reliable manifestation of atherosclerosis as well as stronger prognosticator for future events. Carotid artery plaque are defined as the presence of focal thickening 50% greater than that of the surrounding vessel wall, with a minimal thickness of 1.2 mm (Hurst et al., 2010)Cardiac CT began with electron-beam CT in the early 1980s and continues with multidetector CT. In early studies with electron-beam CT high risk subjects have been identified by a score greater than 80-160 (O'Rourke et al., 2000). The advent of modern CT and high resolution MRI, ranked these techniques at the first approach in the assessment of preclinical atherosclerosis by the American Heart Association guidelines (Greenland et al., 2007). Quantification of coronary artery calcium, the so called coronary calcium score (CCS), as an estimate of atherosclerotic plaque burden has become the current major application of non-contrast CT. Plaque burden is quantified by the Agatston score: according to different tertiles of CCS values (Tertile I = CCS 0-99, Tertile II = CCS 100-309, Tertile III = CCS ≥ 400) the estimated annual risk of CAD death or myocardial infarction rate appears to be 0,4%, 1,3% and 2.4% respectively (Greenland et al., 2007). It has been generally suggested that a zero CCS might exclude the need for coronary angiography among asymptomatic patients. However, it has been also shown in studies that increasing the cut-point for calcification markedly improved the specificity but decreased the sensitivity. For patients with CCS >100 the sensitivity to predict significant coronary artery stenosis on angiography was 87% and the specifity 79% (Haberl et al., 2001). Of note, in a meta-analysis a CCS grater than 400 was associated with an increased risk of CAD (Third Report of NCEP, 2002). But a number of recent studies challenged this statement. The first

study (Lester et al., 2009) in a young to middle-aged population with a low Framingham risk score where CCS was less sensitive than CIMT in the identification of preclinical atherosclerosis. The second from Mohlenkamp et al. (Mohlenkamp et al., 2011) in a group of 1934 healthy participants in whom, despite an improved discrimination was possible by adding CCS to traditional risk factors, the reclassification and the overall event rates appeared to low to justify CCS testing in all subjects. Moreover, and in contrast with the published recommendations on the subject, a third new study from Gottlieb et al. (Gottlieb et al., 2011) showed that even total coronary occlusion frequently occurs in the absence of any detectable calcification, definitely suggesting that a zero CCS value does not exclude obstructive stenosis or even the need for revascularization among patients with high enough clinical suspicion of coronary artery disease to be referred for coronary angiography. The finding of very low or even absent coronary calcium by CT in patients with documented carotid and femoral atherosclerosis has been found in a preliminary study from our group (Fig. 3) suggesting that B-Mode ultrasound imaging of carotid and femoral arteries probably overcomes the CCS approach for preclinical screening of atherosclerosis. As far as the effect on CCS by statin treatment is concerned, initial retrospective studies and observational data suggested that statin treatment resulted in reduction of coronary calcium but a recent exam of five randomized controlled trials proved that statin treatment does not reduce CCS values, with similar progression in either the treated and placebo group (Gill Jr, 2010).

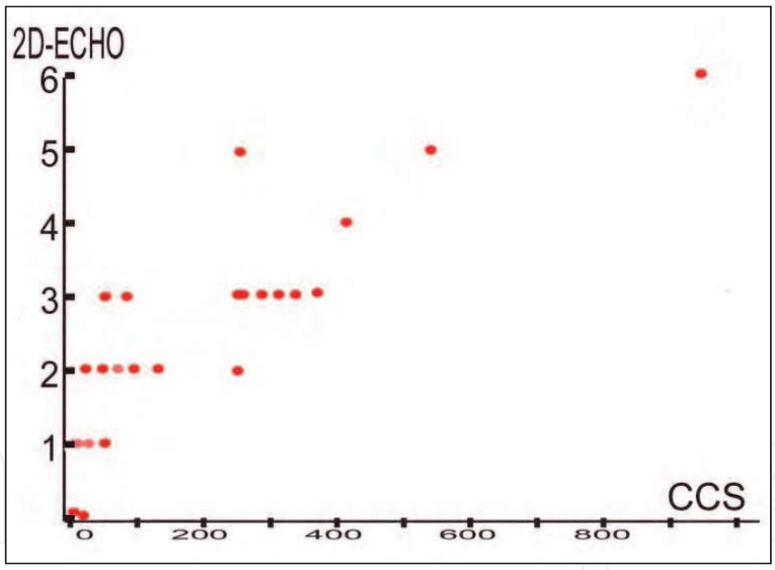


Fig. 4. Relationship between carotid and/or femoral atherosclerosis as assessed by B-Mode ultrasound (2D-ECHO) and CCS by compute tomography in 23 men, 35 to 65 y.o. The amount of carotid atherosclerosis has been arbitrarily graded into 6 grades from low to severe according to the amount of plaques in both arteries (IMT value has not been taken into account). CCS has been graded according to Agatstone score units. Close relationship exists on the presence and the amount of atherosclerosis between the two methods, with ultrasound findings being more sensitive than CCS in identifying subjects with atherosclerosis. These findings have been confirmed in studies and support the view that ultrasounds should be considered the first line approach in the screening for atherosclerosis in apparently healthy people with CV risk factors.

Of note, other clinical circumstances have been suggested to take advantage from use of CCS measurement, these include: 1) distinguishing ischemic from non-ischemic etiology of dilated cardiomyopathy, 2) identifying patients in emergency department with chest pain and nonspecific ECG, 3) predicting very low subsequent event rates in patients with acute MI and negative CCS test. However, and differently from asymptomatic patients setting, prognostic studies in symptomatic patients are lacking probably because a very large number of patients is needed in this setting to obtain the evidence. In any case, according to 2007 guidelines (Greenland et al., 2007) clinical monitoring of CCS progression is not recommended.

Finally, as far as the role of the race is concerned, despite a generally higher prevalence of cardiovascular risk factors also included a broad trait of endothelial dysfunction in this population group (Friedewald et al., 2008) a lower prevalence and extent of coronary calcification has been demonstrated in blacks. Accordingly, the Prospective Army Coronary Calcium (PACC) Project has found a higher prevalence of CCS in white (19.2%) than in black (10.3 %) military personnel with a mean age of 42 years (Mohlenkamp et al., 2011). Higher CCS scores have been also found in whites compared with blacks in the Cardiovascular Health Study (Raman et al., 2008) and lower prevalence of coronary calcium has been observed in Japanese (13%) than in the American men (47%). Overall, as reported in recent guidelines, despite a higher prevalence of cardiovascular risk factors in blacks, the majority of studies demonstrated a lower prevalence and amount of coronary calcification compared to whites. The recently published MESA study (Multi-Ethnic Study of Atherosclerosis) showed that traditional CV-risk-factor-based prediction models, such as the Framingham score, are improved by the addition of CCS especially in patients at intermediate risk for future coronary artery disease, ultimately suggesting the superiority of CCS and CIMT vs the Framingham risk score for risk prediction. In line with these conclusions are the results from the recent Heinz Nixdorf Recall study of 4,129 subjects (age 45 to 75 years, 53% female) without overt coronary artery disease at baseline in whom traditional risk factors and CCS scores were measured. The CCS resulted in a high reclassification rate in the intermediate-risk cohort, demonstrating the benefit of imaging of subclinical coronary atherosclerosis in carefully selected individuals with intermediate risk (Erbel R, et al. 2008)In any case, in the recently published ESNIER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial, it has been shown that compared with no scanning, the simple randomization to CAC scanning appears to improve patients' lifestyle health behaviours (Rozanski et al. 2011).

As far as the CIMT is concerned, a recent reclassification analysis of the ten-year follow-up of the Carotid Atherosclerosis Progression Study (CAPS) has challenged its value as a marker of future CV events rate and did not support its clinical usefulness for risk stratification in primary prevention setting (Lorentz et al, 2010). But evidence has been provided that when associated with risk factor assessment the CIMT may still be a valid tool in risk prediction in dyslipidemic patients (Baldassarre et al, 2007). The bottom line was that we have clear evidence that these two noninvasive methods of risk assessment are superior to Framingham risk score alone, and we think that the time has come to incorporate into new guidelines the cheaper, and completely safe, B-Mode ultrasound technique in primary prevention setting mainly focused on plaque detection.

The new high-resolution imaging technologies have enhanced our understanding of the atherosclerotic disease process and recently a new modified American Heart Association

classification scheme system based on morphological plaque features and the propensity of plaque for thrombosis has been suggested for use (Donnelly et al., 2010). Based on lipid deposition, fibrous cap thickening, lipid pool transition into necrotic core, calcium deposition, plaque disruption, haemorrhage and thrombosis, a number of categories of coronary atherosclerotic lesions have been identified and reported in Table 1 (Stary et al. 1994; Virmani et al. 1999; Virmani et al 2000; Donnelly et al, 2010).

Present status of CT technology clearly indicate that its diagnostic accuracy for the detection of the presence of atherosclerosis is superior over the detection of significant stenosis ultimately suggesting a progressive shift of this technique in the future towards the study of the atherosclerotic process per se rather than to simply assess the stenosis severity (Van Velzen et al., 2011).

AHA Plaque Nomenclature

Type	Finding
Early lesions (Type I-II)	Intimal thickening – Intimal xantoma
Progressive lesions (type III)	Pathological intimal thickening or preatheroma
Progressive lesions (type IV)	Fibrous cap atheroma
Progressive lesions (type Va,Vb,Vc)	Healed cap rupture (with or without Ca++)
Progressive lesions (Type VI)	Thin fibrous cap atheroma
Progressive lesion (Type VI)	Plaque hemorrhage and/or plaque rupture

Table 1.

Although primarily established for coronary lesions, in accordance with the recently emerged clinically relevant idea that carotid and femoral arteries can be considered the "sentinel vessels" of the coronary artery status (Heinecke, 2011., Joy & Hegel, 2008) we think that this classification can be usefully applied to the analysis of these vessels. As atherosclerosis begins early in life and then remains clinically silent for decades, a distinct opportunity for early intervention comes from the identification of subclinical stages of the disease. Accordingly, the concept that atherosclerosis must be viewed as a preventable disease, which should be approached not only in terms of risk-factor control but also in terms of early disease detection, plaque prevention and plaque stabilization, has rapidly gained acceptance (Naghavi et al., 2003). But even plaque regression (the holy grail for therapeutic interventions) appears possible and has become a new target in our clinical practice during the last ten years. Together with a proposal for a strategy for primary CV disease prevention this evidence will be accordingly presented in the following pages.

4.3 Preclinical atherosclerosis and risk prediction

Coronary atherosclerosis starts early in the life and it is progressive in nature and when angiografically identified as minimal vessel stenosis its burden is already diffuse. By the

time a patient has developed minor obstructive disease on angiography, an extensive systemic atheroma is already present. This finding underscores the importance of an aggressive risk factor modification (and statin use) since early stages of atherosclerosis in asymptomatic subjects (Lavoie et al., 2010). In recent years several studies addressed the prognostic implications of detecting asymptomatic atherosclerosis in the general apparently healthy population. Pathological, epidemiological and clinical studies indicate tha atherosclerosis is a systemic disease which develops with a variable extension and severity in all conduit arteries. In particular, an almost constant association exists between carotid, femoral, and coronary artery disease, with first clinical manifestation usually due to a CAD. Ten years ago in the CAFES-CAVE study (Belcaro et al., 2001), subclinical carotid and femoral artery plaques have been found strongly and independently associated with future adverse cardiovascular events rate in low risk subjects by Framingham criteria. Similarly, the presence of peripheral (occlusive or sub-occlusive) artery disease independently predicted myocardial infarction and death in 1,325 individuals with either carotid or femoral plaques by ultrasound (Lamina et al., 2006). And early atherosclerosis (increased IMT) in femoral arteries predicted single-vessel CAD whereas advanced atherosclerotic (plaques) was usually associated with more severe CAD (Sosnowski et al., 2007). Evidence of the systemic nature of the atherosclerotic process comes also fromseveral studies of prevalence of occult CAD in patients with peripheral artery disease or stroke. In a recent study in patients with cerebral infarction without history of CAD (Amarenco et al., 2011) it has been shown that a silent CAD was present in 62% of patients and that 31% and 26% had a 3 vessel disease and vessel stenosis > 50% respectively, and similar findings have been reported in another recent study in which the atherosclerotic process was quite advanced in coronary as well as in peripheral arteries of patients at their first presentation for acute coronary artery disease (Kranjec, 2011). Evidence of high prevalence of subclinical atherosclerosis in the general population comes also from another recent study on a randomly selected sample of 292 subjects (mean age 59.5 years, 50% women) from the offspring cohort of the Framingham Heart Study free of clinically apparent cardiovascular disease, who exhibited high levels of subclinical atherosclerosis on more than 2 imaging tests including MRI of abdominal and thoracic aorta, coronary artery calcification by EBCT, and CIMT by ultrasonography (Kathiresan et al., 2007). Also on this line are the results from the mass screening recently introduced in United Kingdom where an ultrasound scan of the abdomen is offered to all men over 64 years for the screening of abdominal aorta aneurysm by ultrasonography. In a large randomized trial in 67,770 men, age 65 to 74 years, it has been shown that in the group invited for screening the mortality was halved (because of elective surgery): an approach that additionally proved to be highly cost-effective (Kim et al., 2007).

As far as the role of carotid IMT as a predictor of future events is concerned, in a recent meta-anlaysis of 41 randomized trials it has been shown (Costanzo et al., 2010) that regression or slowed progression of carotid IMT by cardiovascular drugs is not accompanied by reduction in cardiovascular events, definitely suggesting that this parameter has a very limited role in cardiovascular risk prediction. Similarly, a recent review including 13.145 patients (Masson et al., 2011) has shown that presence of carotid plaques predicted future risk better than IMT value, supporting the view that when detecting plaque we are not just evaluating a surrogate objective but a process that in itself indicates the presence of the atherosclerotic disease.

The American Society of Echocardiography consensus document (Stein et al., 2008) and the recently published Canadian guidelines (Genest et al., 2009) which formally classify patients with subclinical atherosclerosis as high risk and recommend preventive measures as intensive as those to be used in patients with clinically established atherosclerotic disease, are both in line with this suggestion. Neither those persons with a past history of intensive professional sport activity appear protected by the atherosclerotic assault of modern life as demonstrated by a recent paper in which former professional football players, despite their elite athletic histories, have a similar prevalence of advanced subclinical atherosclerosis as a clinically referred population of overweight and obese men (Hurst et al., 2010). In response to the wall lipid infiltration and plaque formation the arterial wall changes its structure according to two types of anatomical remodelling, positive and negative. Positive remodelling is characterized by outward expansion and negative remodelling by vessel shrinkage. Paradoxically the apparent beneficial and more frequent phenomenon of outward wall expansion is associated with the feature of unstable lesions (fig. 1) i.e. with histological characteristics of plaque vulnerability such as a large lipid core and high plaque macrophage content (Pasternak et al., 1998). These important morphological features have been studied in coronary vessels by intravascular ultrasound (IVUS) and angioscopy, but optical coherence tomography with its unique ability of identifying lipid content, fibrous cap thickness and its macrophage density, is the method of choice (Yabushita et al., 2002; Raffel et al., 2008). Recently, a first report on virtual histology-IVUS assessment of natural history (1 year follow-up with repeated examinations) of coronary artery lesions morphology has been published (Kubo et al., 2010). In this study it has been demonstrated that most thin capped fibroatheroma had plaque progression (most stabilized or healed but new developed) whereas fibrotic and fibrocalcific plaque did not demonstrate any geometric changes during the follow-up and no spontaneous plaque regression has been observed, as usual.

AS highlighted in previous pages an ischemic event is usually associated with an advanced atherosclerotic lesion. And since early regression studies (Blankenhorn et al., 1978; Corti et al., 2001), the evidence clearly emerged that persistent and marked reduction of total and LDL cholesterol plasma levels (with LDL-cholesterol in the range of 50 mg /dl) is the key element for obtaining atherosclerosis regression and significant inverse remodelling with lumen preservation of both aorta and carotid arteries at 12 months, and that the degree of LDL-cholesterol reduction rather than the statin dose was associated with plaque regression. According to this line of conduct we have had evidence in the last 10 years on the possibility to induce plaque regression even up to complete disappearance: moreover we have realized how B-mode ultrasound imaging can help us and motivate patients in many ways in primary prevention setting. As it will be suggested in the next pages, our experience has confirmed the hypothesis that lipid lowering therapy selectively depletes the atherosclerotic plaques lipid content and prevents plaque disruption.

5. Plaque monitoring by ultrasound imaging and plaque regression by statin use

Notwithstanding large-scale clinical trials have proved that both primary and secondary prevention reduce myocardial infarction, stroke and overall mortality, the optimal level of

plasma lipids to achieve these goals remains unresolved. Recent trend suggests "the lower the better" for all risk factors, but recent data suggest that lipid lowering appears to have larger impact than blood pressure lowering on plaque progression (Chhatriwalla et al., 2009) and hence also supporting the view that only intensive plasma lipid reduction can induced plaque regression. As already mentioned in previous pages, in vivo evidence of atherosclerosis regression in thoracic aorta by statin use has been first reported ten years ago (Corti et al., 2001) using MRI. More recently using dedicated carotid MRI protocol (Underhill et al., 2009) it has been demonstrated that intraplaque haemorrhage and statin therapy were key determinants of opposite changes in plaque burden: being intraplaque haemorrhage associated with accelerated plaque growth, whereas statin therapy was associated with plaque stabilization by slowing or halting lesion progression. According to these authors the phase of 16% to 49% of plaque induced vessel stenosis is probably a critical stage of the plaque natural history, whereas plaque regression has been associated with statin use.

In the following pages we describe the process of atherosclerosis regression as it has been documented in a group of selected statin treated subjects in a primary prevention setting during the last ten years in our echo-lab. To be included in this retrospective analysis the subjects should have had at least two B-mode ultrasound plaque imaging examinations of at least 2 years apart during an uninterrupted statin treatment. Twelve subjects have been found to match such criteria. These subjects have been treated with simvastatin or rosuvastatin at a dosage aimed obtaining a total cholesterol plasma level kept round 140 mg/dl. None of them have had any CV events during the study period. The most representative structural findings associated with plaques regression are presented in the following pages and proposed as reference structural changes to be routinely examined in patients for an office-based practice as an alternative to the more demanding and expensive MRI based analyses.

As largely reported in previous page, evidence exists on the possibility to identify subjects with preclinical atherosclerosis who can take advantage from its early detection by improving a safer life style and by statin use in particular. In fact, the possibility to monitor plaque dimension and structure changes along time with a completely noninvasive approach by using ultrasounds allows a safe and personalized treatment approach in the course of years, with an improved patient' and doctor' satisfaction. To recognize the great advancement in the field of primary prevention and of usefulness of early atherosclerotic disease detection by the way we are suggesting, a citation is worthy of David Blankenhorn's intuition and early demonstration of this possibility more than 30 years ago in California and summarized in the following lines from a paper (George Lyman Duff Memorial Lecture) co-authored with Howard Hodis (Blankenhorn DH & Hodis HN, 1994): "Coronary atherosclerosis is ubiquitous, but we know that some individuals develop more severe coronary atherosclerosis at an earlier age than others. A case finding and treatment strategy based on noninvasive imaging would benefit those with premature atherosclerosis who are not recognized with current risk factor screening until they develop symptoms. Screening for peripheral vessel changes indicative of high risk is possible and cost effective with procedures now available". The following cases we are going to describe closely match this position and add new evidence on the real possibility by the simple and totally noninvasive ultrasound exam to characterize carotid and femoral artery plaque structure and the profound changes induced by statin treatment (Fig 4 to 9).

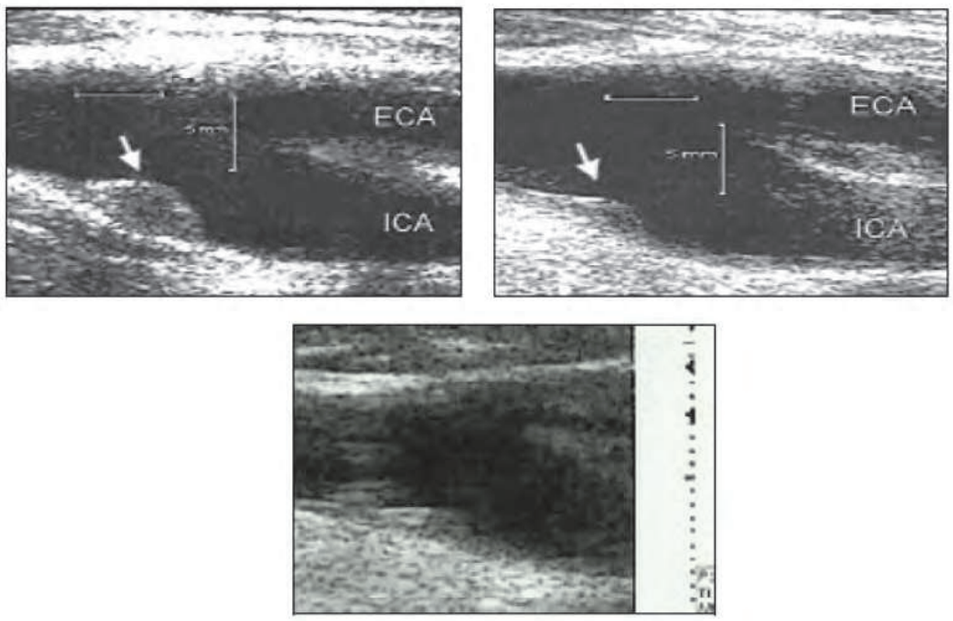


Fig. 4. *Upper left panel* - B-mode ultrasound of the right carotid artery bifurcation in a asymptomatic 50 y.o. man with hypercholesterolemia (280-300 mg/dl). A soft and lipid-rich atherosclerotic plaque (arrow) about 4 mm in thickness and 7 mm in length is present at the posterior wall of the carotid artery bifurcation associated with outward remodeling of the arterial wall. These charcteristics allow classification of the plaque as an advanced atherosclerotic plaque type IV lesion (see pag 12). *Upper right panel* - Imaging of the same artery after three years 20 mg simvastatin treatment and plasma total cholesterol level kept around 150 mg/dl. A marked reduction of plaque dimension is shown (arrow) associated with arterial wall reverse remodeling. *Lower panel:* imaging of the same artery (with same magnification) obtained three years after spontaneous statin treatment interruption. New plaque progression can be appreciated with an associated IMT increase. Legend: ECA = external carotid artery, ICA = internal carotid artery.

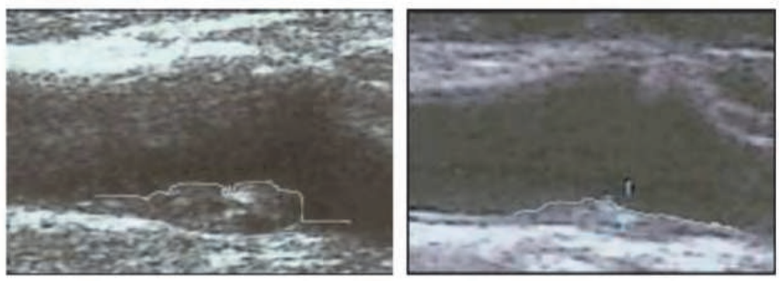


Fig. 5. B-Mode ultrasound (with plaque outlining) of the right carotid artery in a 66 y.o. man with hypercholesterolemia (250 mg/dl) followed-up for 4 years during statin therapy (rosuvastatin 10 mg/day). *Left panel*: Lipid rich plaque with a small (white) calcium deposit. *Right panel*: Same imaging 4 years later demonstrating plaque volume reduction with almost complete regression of the echolucent lipid-rich areas, leaving intact the small nucleus of calcium deposit within the plaque. Almost complete reverse remodelling of the posterior vessel wall also occurred.

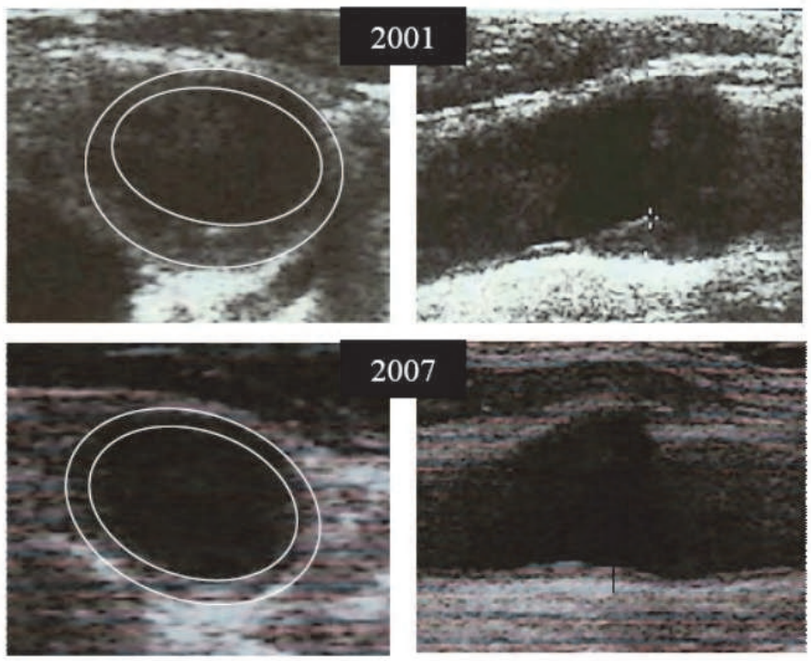


Fig. 6. B-Mode ultrasonography imaging in a short axis (left side) and long axis view (right side) of the right carotid artery in asymptomatic man with hypercholesterolemia (240 mg/dl) followed-up for 6 years during statin therapy.

Upper line: At first examination (age 59 years) a small echolucent plaque was present in the far field of common carotid artery, better appreciated in its extension in the high lightened short axis view. *Bottom line*: Same imaging showing a complete plaque regression after five years of Simvastatin (20 mg/day) treatment. No further examinations were performed during this period. Arterial reverse remodelling, better appreciated in the short axis view, also occurred in association with plaque regression. Cholesterol plasma levels have been kept around 140 mg/dl during the whole treatment period.

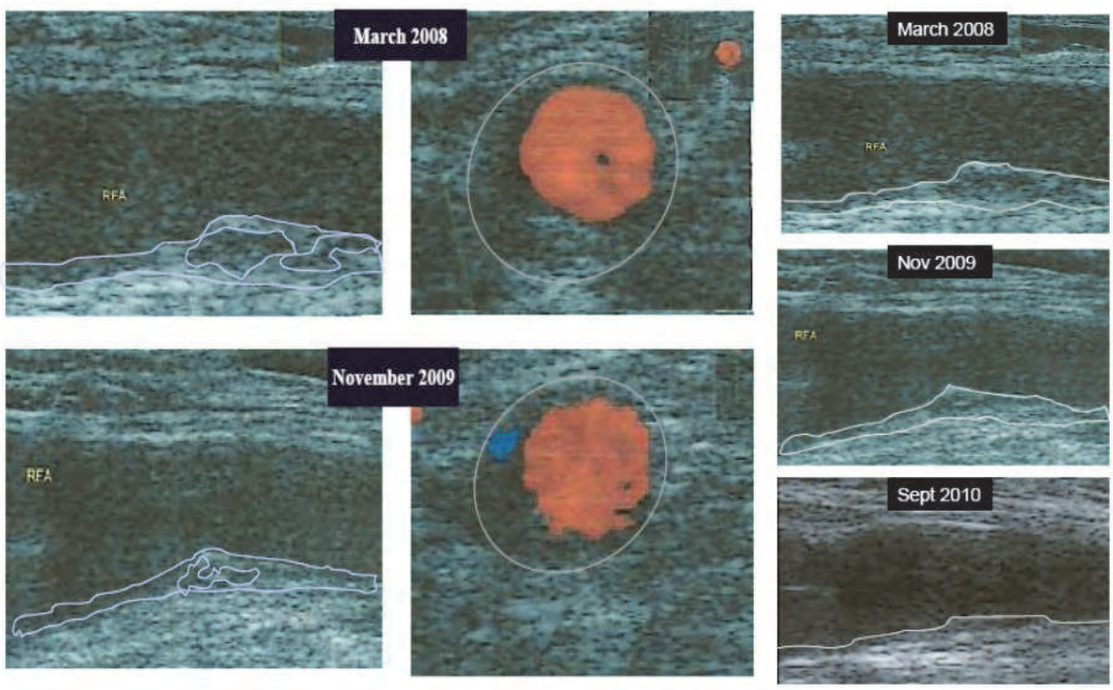


Fig. 7. *Left panel*: B-Mode ultrasonography imaging in a long- and short-axis view (with colour Doppler flow imaging) of femoral arteries in a 69 y.o. healthy man during a 20 months treatment period with rosuvastatin 20 mg/day and cholesterol plasma level kept around 140 mg/dl. Plaque volume reduction and inverse arterial remodelling haves occurred by statin treatment. Far field endothelial surface, total plaque area, and echo-lucent area within the plaques have been manually outlined for better understanding of the plaque structural changes. Plaque volume reduction and arterial reverse remodelling are better appreciated in the short axis view. *Right panel*: Further plaque reduction in the long axis view occurred after additional 10 months of statin treatment.

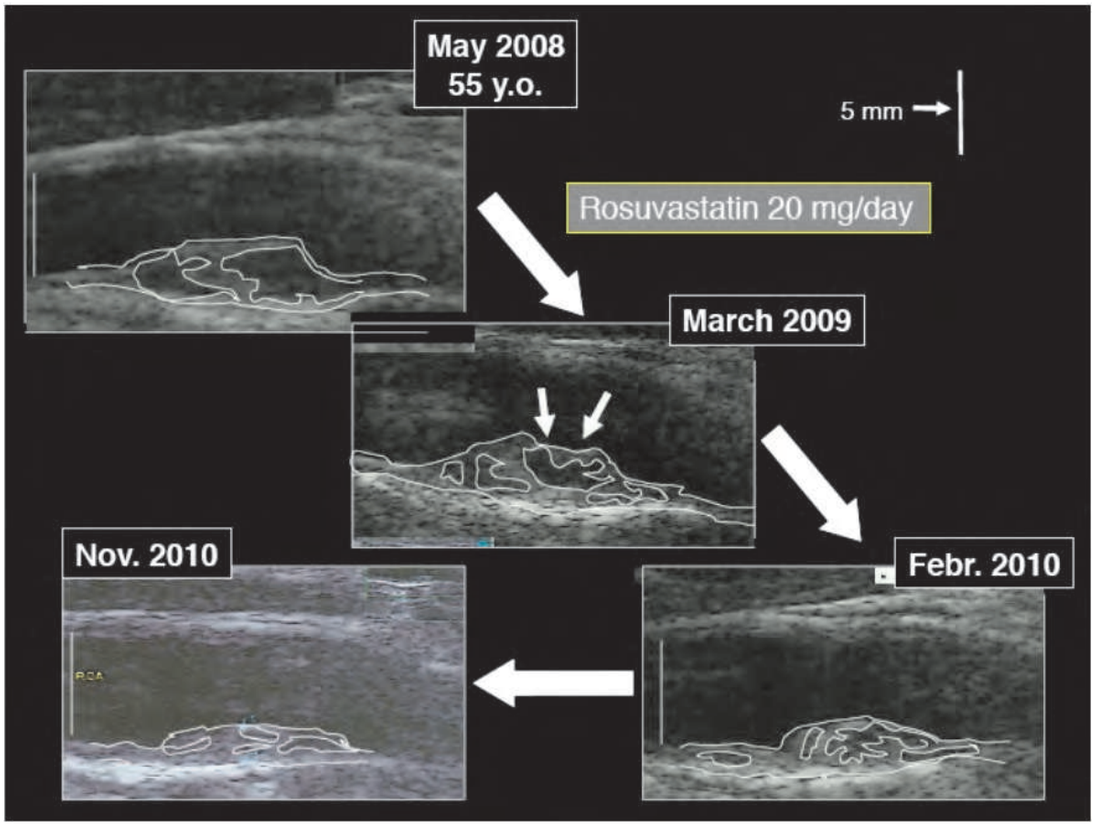


Fig. 8. Left carotid plaque monitoring during a 2.5 years follow-up period in a 55 y.o. subject during statin treatment (rosuvastatin 20 mg/day) with a reduction of cholesterol level from 200 mg/dl to around 140 mg/dl. with HDL Cholesterol increase from 50 to 75 mg/dl. The plaque border and the echolucent areas within the plaque have been outlined for a better understanding of the structural findings associated with plaque regression. At first imaging (May 2008) the plaque exhibits the characteristics of a rupture-prone (vulnerable/instable) plaque represented by the triad of a very thin fibrous cap combined with large echolucent (lipid/necrotic) core and positive (outward) arterial wall remodelling. An impressive volume reduction (~75%) occurred during the treatment period. In this case, the close temporal images' sequence allowed superior understanding of structural modifications associated with plaque regression and stabilization. According to these changes the following observations can be done: 1) The amount of baseline echolucent areas within the plaque predicts the regression potential by statin treatment, even to almost complete plaque regression when the echolucent area is predominant, 2) the reabsorbtion of these areas is progressive and is accompanied by plaque volume reduction and structural findings suggesting plaque stabilization (the arrows in the imaging of march 2009 indicate a partial plaque collapse due to early marked reduction of underlying echolucent area), 3) in association with plaque volume reduction a progressive reverse arterial wall remodelling also occurred, 4) the time interval needed for early regression appreciation appears to be 10 to 12 months. As occurred in this case, plaque regression appears to depend on "robust measures" such as marked reduction in plasma concentrations of LDL cholesterol and large increases in the reverse transport of lipids out of the plaque by an increased HDL-cholesterol.

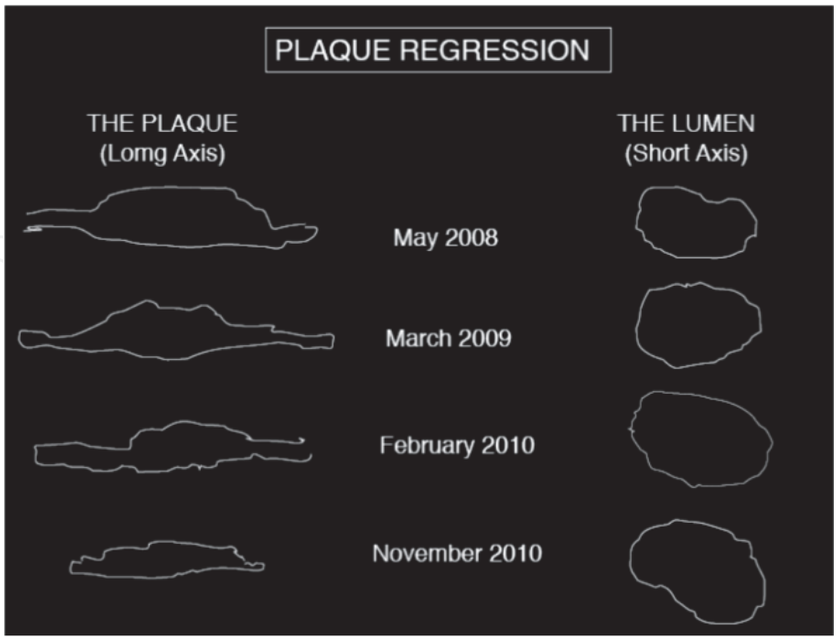


Fig. 9. Same case of the figure 8. Plaque and vessel luminal area (by manual outlining) in a long and a short axis view respectively, by B-mode ultrasound imaging of the carotid artery obtained during the study period. This analysis adds further information on the characteristics of the process of plaque reduction, vessel inverse remodelling and reduced vulnerability in this patient.

6. Conclusions

After arteriographic studies on atherosclerosis regression by lipid lowering drugs pioneered by Blankenorn in late seventhies, conclusive demonstration of the plaque lipid depletion hypothesis in human beings during lipid lowering therapy has been possible only in recent years using ultrasound and MRI. During the last few years the sonographic characteristics of carotid plaques have been thoroughly studied by sophisticated methods enabling semiquantitative analysis of their structure (Reiter et al., 2007). However, as in depth discussed in this chapter we think that the simple, non-invasive, relatively cheap and totally innocuous B-Mode ultrasound examination of carotid and/or femoral arteries represents the first choice and still largely unmet opportunity for atherosclerosis screening of asymptomatic subjects deemed at intermediate risk by traditional risk factors (fig 10).

As already discussed, due to the associated radiation risk, the use of CCS as a screening tool in primary prevention setting (usually requiring subsequent examinations) should be considered in specific circumstances only as alternative to arterial ultrasound scanning when this imaging modality is not available. Definite superiority of the B-mode ultrasound approach is greatly supported by the possibility to monitor the natural course of plaque structural changes and, of outmost importance, to assess the drugs' effect which we have observed to occur during statin use in a very short period of time, ten to twelve months apart.

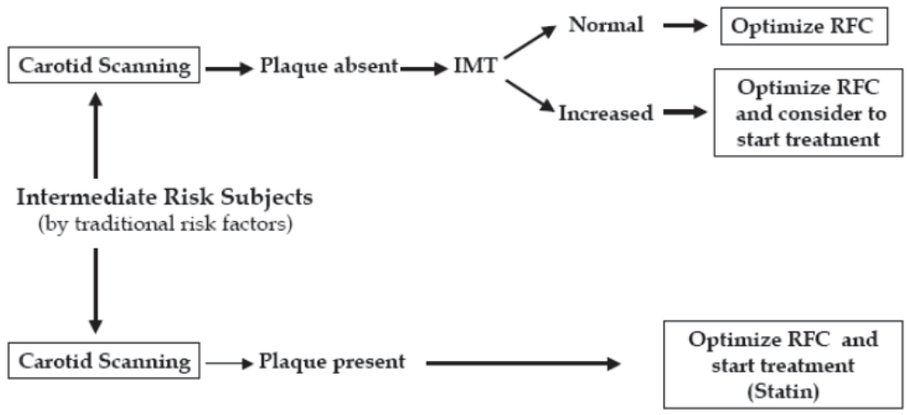


Fig. 10. Algorithm for cardiovascular risk assessment and as decision making approach using B-Mode ultrasound examination of carotid (and femoral) arteries for preclinical atherosclerosis screening in subjects deemed to be at intermediate risk by traditional risk factors. RFC = Risk factor control. (Modified by Gepner et al., 2007)

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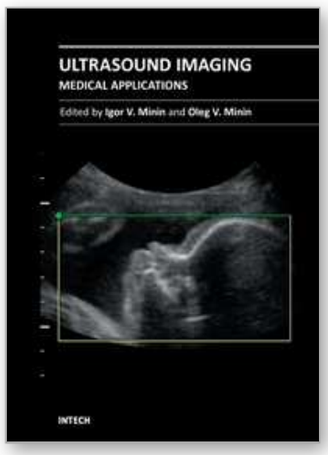
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This book provides an overview of ultrafast ultrasound imaging, 3D high-quality ultrasonic imaging, correction of phase aberrations in medical ultrasound images, etc. Several interesting medical and clinical applications areas are also discussed in the book, like the use of three dimensional ultrasound imaging in evaluation of Ashermanâ€™s syndrome, the role of 3D ultrasound in assessment of endometrial receptivity and follicular vascularity to predict the quality oocyte, ultrasound imaging in vascular diseases and the fetal palate, clinical application of ultrasound molecular imaging, Doppler abdominal ultrasound in small animals and so on.

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