13

An Anti-Inflammatory Approach in the Therapeutic Choices for the Prevention of Atherosclerotic Events

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1. Introduction

Atherosclerosis, with its dramatic events, represents a heavy burden in terms of morbidity and mortality throughout the entire world (Gibbons et al., 2008). Although the risk factors are very well known and addressed by every physician (genetic background, physical inactivity, hypertension, dyslipidemia, diabetes mellitus, obesity and metabolic syndrome, smoking), the precise mechanisms of the plaque formation and rupture are not completely clarified. These limitations are confirmed by the difficulties in obtaining better results in both primary and secondary prevention of cardiovascular events: recent results of completed clinical trials (such as NAVIGATOR, ACCORD, ROADMAP) suggest that we have reached a limit in terms of reducing events by simply addressing common risk factors appropriately (Zanchetti, 2009). As a matter of fact, at the present time we cannot prevent 70% of clinical events, also with administration of all well established anti-atherosclerotic therapeutics. In addition at least 10% of coronary events can occur in apparently healthy subjects in the absence of traditional risk factors (Baigent et al., 2005; Greenland et al., 2003).

The inflammatory paradigm has represented an important achievement in the understanding of the atherosclerotic process: abundant laboratory and clinical evidence accumulated over the last twenty years, also from our research group (Montecucco et al. 2010), confirming the hypothesis that inflammation exerts a major role through the different stages of atherosclerosis (Ross, 1999; Hansson, 2005; Hansson & Libby, 2006; Libby et al., 2009). Therefore it would be interesting to evaluate how the therapeutic choices exerted by physicians can modulate the inflammatory activation (the so called pleiotropic effects): in other terms do the drugs we use in the attempt of counteracting atherosclerosis (such as anti-hypertensive drugs, statins, fibrates, aspirin, anti-diabetic drugs) exert their protective effects through their main site of action (decrease of blood pressure, cholesterol, triglycerides, and glucose, anti-platelets actions) or can an additional anti-inflammatory effect be proposed, at least for some of them? This is the reason why recently Ridker proposed a clinical trial with low-dose methotrexate, a powerful anti-inflammatory drug extensively used in the treatment of auto-immune disease (suc as rheumatoid arthritis), in post-myocardial infarction (MI) patients (Ridker, 2009); another testable drug could be

canakinumab, a human monoclonal antibody targeted against interleukin-1β (Libby et al., 2011).

In theory these approaches have a great appeal because their main target is represented by the basic mechanism of the atherosclerotic process, i.e. the inflammatory activation, but the risk of untoward effects can overcome the expected benefits: particularly in primary prevention the possible depression of the immune system and defense against cancer may be too dangerous in a substantially healthy population. In addition the involvement of the immune system, and consequently the inflammatory activation, is not completely elucidated because the entire network is particularly complex with many pathways, both redundant and with opposite effects, and many cells (Libby et al., 2011). Another reason for our difficulties is represented by the realization of the incomplete concordance between atherosclerosis in human vessels and the possible animal models (Bentzon & Falk, 2010): the hypotheses generated by the experimental research frequently do not find a confirmation in a clinical scenario.

The road of the anti-inflammatory approach in the treatment of atherosclerosis is paved by many defeats: table 1 tries to summarize the possible explanations.

Possible explanations	**Example**
Important side effects	NSAIDs, Corticosteroids, Torcetrapib
Activation of dangerous pathways	COX-2 inhibitors
Secondary target	Fibrates
Unfavourable effects on lipid profile	Rosiglitazone
Marked differences *in vitro* vs. *in vivo* conditions	Anti-oxidant agents
Too late and too shy treatment	All the possible options?

Table 1. Possible reasons of negative or partly successful trials for atherosclerosis

A new and theoretically safer way to modulate the inflammatory activation could involve new lipid anti-inflammatory mediators, such as lipoxins, resolvins, protectins, and maresins: these molecules derive from the transformation of both the ω-6 fatty acid arachidonic acid and the ω-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid via actions of lipoxygenase, cyclooxygenase-2 and aspirin-acetylated COX-2 enzymes (Hersberger, 2010; Maskrey et al., 2011). These mediators exert significant effects favoring the resolution of the inflammatory process through the activation of a specific program, characterized by apoptosis and subsequent clearance of inflammatory cells. Again anti-inflammatory mediators are tightly linked, in terms of chemical structure and synthetic pathways, to pro-inflammatory molecules, such as leukotrienes. At the present time, among available drugs, aspirin and statins seem to be able to activate these pathways significantly (Spite & Serhan, 2010): the theoretical advantage would be represented by targeting inflammation without precipitating sustained immunosuppression.

Another important preliminary consideration is related to the ongoing debate about the appropriate timing of the beginning in anti-atherosclerotic treatments (Steinberg, 2010; Pletcher & Hulley, 2010). Although we need to never forget the fundamental role of healthy lifestyle choices, we know that some people are at potential high risk of vascular damage and consequently in this subset a more aggressive pharmacological approach can be advisable. The two opposite points of view are represented by physicians who support an

aggressive therapy (at least with statins and antihypertensives, when indicated) at young age, i.e. at the beginning of the atherosclerotic process, and physicians who underline the risk of the creation of a "pseudodisease" (Lauer, 2011).

Directly linked to this topic is the role of biomarkers and vascular imaging in supporting treatment decisions: if we identify subclinical markers of atherosclerotic damage, we can use them in the prognostic stratification and consequently in rational therapeutic strategies. This consideration is an implicit criticism to the Framingham Risk Score (and other related risk calculators), a simple, relatively inexpensive, and useful way to predict cardiovascular events in the general population (Shah, 2010; Forrester, 2010). Limitations of the Framingham Risk Score include a substantial underestimation of lifetime risk and misclassification of some subgroups of subjects; in addition it does not incorporate family history and some components of the metabolic syndrome, important risk factors for coronary heart disease, and more importantly does not take into consideration the possible help of the noninvasive detection of subclinical atherosclerosis. Therefore we can reasonably affirm that Framingham Risk Score is very useful at the population level, but it remains suboptimal for individual subjects.

Subclinical atherosclerosis always begins with fatty streak lesions, which are already extensively diffuse by 30 years of age (Shah, 2010; Lauer, 2010): although we know that fatty streaks are reversible, we are also aware that this lesion is certainly the precursor of the stenotic plaque. Do we have validated imaging tools for subclinical atherosclerosis? Essentially, we can rely on coronary calcium score, obtained by computed tomography without contrast, and on carotid intima-media thickness, evaluated by B-mode ultrasonography (US). With some limitations (Shah, 2010; U.S. Preventive Services Task Force, 2009) they represent a useful aid in better classification of risk categories in human subjects: some years ago the SHAPE (Screening for Heart Attack Prevention and Education) Task Force recommended noninvasive atherosclerosis imaging of all asymptomatic men (age 45 – 75 years) and women (age 55 – 75 years), except those at very low risk, to augment conventional cardiovascular risk assessment algorithms (Naghavi et al., 2006): recently these guidelines were positively evaluated in the Dallas Heart Study, with significant bidirectional reclassification of eligibility for lipid-lowering therapy in the participants (See et al., 2008).

About serum biomarkers the role of high-sensitivity C-reactive protein (hsCRP) is well established and will be evaluated in depth for statins. Recently 30 biomarkers for atherosclerosis, or more in general cardiovascular diseases, were studied in two large cohorts totalling more than 9,000 subjects (Blankenberg et al., 2010): a consistent association with incident cardiovascular events was observed for hsCRP, B-type natriuretic peptide and cardiac troponin I. These observations allowed the development of a biomarker score which was positively validated in a cohort of male subjects.

The present article will present updated information about the anti-inflammatory effects of different classes of drugs and the possible therapeutic advantages obtained with this approach. Before starting the evaluation we need to never forget the fundamental protective role exerted by a healthy lifestyle: very recently we extensively reviewed these choices and their great social value (Pende & Dallegri, 2011). However we know that their implementation and long-term compliance is very low: a possible help is the potentiation of population-based strategies, such as smoking bans and food legislation against trans-fats and high amount of salt.

Table 2 gives some information about the clinical trials discussed in the review with full definition of the names.

Clinical trial acronym	Clinical trial name	Drugs tested
ACCORD-Lipid	Action to Control Cardiovascular Risk in Diabetes	Simvastatin, fenofibrate
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study	Statins
ARBITER 6-HALTS	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 - HDL and LDL Treatment Strategies in Atherosclerosis	Ezetimibe, niacin
ARIC	Atherosclerosis Risk in Communities	Multiple drugs
ARISE	Aggressive Reduction of Inflammation Stops Events	Succinobucol
A-to-Z	Aggrastat to Zocor	Simvastatin
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis	Amlodipine, enalapril
CARE	Cholesterol and Recurrent Events	Pravastatin
DEFINE	Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib.	Anacetrapib
HPS2-THRIVE	Treatment of High density lipoprotein to Reduce the Incidence of Vascular Events	Niacin/laropiprant
ILLUMINATE	Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events	Torcetrapib
JUPITER	Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin	Rosuvastatin
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering	Atorvastatin
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research	Nateglinide, valsartan
PLASMA	Phospholipase Levels And Serological Markers of Atherosclerosis	Varepladib
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events	Pioglitazone
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction 22	Pravastatin, atorvastatin
REVERSAL	Reversing Atherosclerosis with Aggressive Lipid Lowering	Pravastatin, atorvastatin
ROADMAP	Randomised Olmesartan and Diabetes Microalbuminuria Prevention	Olmesartan
SOLID-TIMI 52	Stabilization of Plaques Using Darapladib — Thrombolysis in Myocardial Infarction 52	Darapladib
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy	Darapladib
VISTA-16	Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks	Varespladib

Table 2. Acronyms of clinical trials discussed in this review

2. HMG-CoA reductase inhibitors (statins)

Although the main mechanism of action of this class of drugs is the inhibition of the cholesterol synthesis, since the end of the last century a significant anti-inflammatory effect appeared to be present as additional explanation of the results in randomized controlled trials. The specific biomarker for inflammation was CRP and this molecule maintained its role in many different trials until present time.

Although the association between CRP and coronary artery disease was first observed more than two decades ago (Berk et al., 1990), researchers are still debating about the precise position of CRP in clinical and experimental atherosclerosis (Ridker, 2007; Schunkert & Samani, 2008; Casas et al., 2008; Nordestgaard, 2009; Anand & Yusuf, 2010; Boekholdt & Kastelein, 2010; Després, 2011; Keavney, 2011): some authors think that CRP exerts a fundamental role in the beginning of the vascular inflammatory process (for example through the activation of the classical complement pathway and enhancement of the innate immune response), instead a more conservative opinion regards CRP no more than a useful but unspecific biomarker of inflammation (an innocent bystander). In practical terms, its long half-life (about 19 h), its limited cost and possibility of replication of the assay in the follow-up without health issues for the patients represent good features. In addition CRP seems to meet most of the American Heart Association (AHA) statement criteria for use of a novel cardiovascular risk marker (proof of concept, prospective validation, incremental value beyond other risk factors, and clinical utility) (Hlatky et al., 2009). For these reasons Ridker et al. proposed and validated a new clinical risk algorithm, Reynolds risk score for both women (Ridker at al., 2007) and men (Ridker et al., 2008a), which incorporates information on both inflammation (hsCRP) and genetics (parental history of premature MI). The utility of hsCRP for risk reclassification was confirmed also in the Framingham Heart Study (Wilson et al., 2008).

Statins can exert their anti-inflammatory role through different effects: the combined actions are called pleiotropic effects and are abundantly reviewed in the literature (C.Y. Wang et al., 2007; Ludman et al., 2009). The main mechanism seems to be always related to the inhibition of HMG-CoA reductase enzyme, involved in the rate-limiting step in cholesterol biosynthesis, but also in the production of isoprenoid intermediates, such as farnesyl-pyrophosphate and geranyl-geranyl-pyrophosphate: these molecules are important for the post-translational modification of small GTP-binding proteins Ras, Rac, and Rho, which are known to modulate vascular smooth muscle cell proliferation, platelet aggregation, and plaque stability.

Returning to statin trials, CARE study of secondary prevention was able to demonstrate, in a post hoc analysis, that pravastatin decreased CRP levels significantly in comparison to placebo; this decrease did not correlate with the reduction in cholesterol levels (Ridker et al., 1999). Few years later similar results were obtained in a primary prevention study, the AFCAPS/TexCAPS trial (Ridker et al., 2001): an interesting observation was the absence of clinical benefits in subjects with low density lipoprotein (LDL)-cholesterol <150 mg/dl and hsCRP levels <2 mg/l, instead a significant benefit was found in those with LDL-cholesterol levels <150 mg/dl and hsCRP >2 mg/l. Further studies, such as MIRACL (Kinlay et al., 2003), REVERSAL (Nissen et al., 2005), A to Z (Morrow et al., 2006), and PROVE IT-TIMI 22(Ridker et al., 2005), demonstrated effects of statins on CRP. Again in all these studies the statin-induced reductions of CRP and LDL-cholesterol levels were only weakly correlated,

whereas the decrease in CRP was correlated with slowed atherosclerosis progression, in an independent way with respect to LDL-cholesterol decrease. In PROVE IT-TIMI 22 and in A to Z trials the best outcomes were observed in individuals who reached both LDL-cholesterol levels <70 mg/dl and hsCRP <2.0 mg/l. Therefore the concept of a "dual target" for statin therapy (LDL-cholesterol and CRP) was introduced.

A step forward was represented by the JUPITER trial (Ridker et al., 2008b). JUPITER was a large, double-blind, placebo-controlled trial, multinational, primary prevention trial, which recruited 17,802 apparently healthy subjects with entry criteria of less than 130 mg/dl for LDL-cholesterol levels and hs-CRP levels of 2.0 mg/dl or higher. Subjects were randomly assigned to 20 mg/d of rosuvastatin or placebo and continued their usual standard care; the primary end point was a combination of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

The trial was terminated prematurely, after a mean of only 1.9 years of follow-up by an indipendent data and safety monitoring board. The absolute risk reduction was 1.2%, with the primary endpoint occurring in 2.8% of subjects in the placebo arm versus 1.6% of subjects in the rosuvastatin arm. The active treatment reduced the risk for first MI by 55%, the risk for venous thromboembolism by 52%, the need for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) by 47%, and total mortality by 20%. On the basis of the Kaplan-Meier estimates and with a forward projection of the results, about 25 subjects would have to be treated for 5 years to prevent one primary endpoint. This estimate is very favourable, compared to trials evaluating statins in hyperlipidemic patients, where the 5-year number needed to treat patients was between 44 and 65; more strikingly in hypertension treatment the 5-year number needed to treat patients ranged between 86 and 140. The treatment with rosuvastatin was well tolerated even at very low attained levels of LDL-cholesterol (less than 50 mg/dl) with consequent lower risk of cardiovascular events (Hsia et al., 2011). Moreover the study demonstrated a 43% reduction in venous thrombosis. Another limited but important finding was the increase in the rate of diabetes mellitus as well as a small, significant increase in the median value of glycated hemoglobin: this observation was confirmed in a recent meta-analysis of 13 statin trials which showed a 9% increased risk of development of diabetes associated with statin therapy (Sattar et al., 2010).

The publication of the JUPITER trial spurred intense debate, sometimes with harsh criticisms to the authors (de Lorgeril et al., 2010; Kaul et al., 2010): the main points were the too early termination (with possible overestimation of the results), unprecise definitions of the endpoints (in particular about mortality), the undertreatment for the usual care of the involved patients, the increased health costs of this preventive approach, the excessive role of the pharmaceutical company. The trial however survived to the critics and convinced the United States Food and Drug Administration to approve the indication of rosuvastatin for reduction of acute MI, stroke, CABG, and PCI in men >50 years of age and women >60 years of age with hsCRP levels ≥2 mg/l who also have 1 additional cardiovascular risk factor. In addition in 2009 Canadian Cardiovascular Society guidelines included the results of the JUPITER trial recommending that also subjects at intermediate risk, defined as 10 – 20% risk at 10 years by Framingham criteria, should be treated with a statin when hsCRP is >2 mg/l.

JUPITER conclusions were similar to the results subsequently obtained in the ARIC study (Yang et al., 2009), again showing that, starting with individuals at highest risk, the relative

cardiovascular event rates are high LDL-cholesterol + high CRP > high CRP + low LDL-cholesterol > high LDL-cholesterol + low CRP > low LDL-cholesterol + low CRP.

Another cholesterol-lowering drug, frequently administered with a statin, is ezetimibe, an inhibitor of the intestinal cholesterol transporter Niemann-Pick C1-like protein (NPC1L1): this drug can reduce LDL-cholesterol levels by almost 20% in individuals already taking a statin. However no clinical trial results have so far demonstrated that this combination will reduce cardiovascular events in comparison with statins only. In terms of anti-inflammatory effects ezetimibe per se did not reduce CRP levels, but it was able to help statin in decreasing CRP more deeply (Al Badarin et al., 2009).

3. High Density Lipoprotein (HDL)-modulating agents

Main focus of anti-atherosclerotic therapy is correctly the decrease in LDL-cholesterol levels. Although the success in terms of cardiovascular prevention was outstanding, we know that it is limited: as already stated, no more than 25-30% relative risk reduction was observed in statin monotherapy trials with a large amount of individuals in the active arm still suffering a cardiovascular event. This can be related to the different levels attained for LDL-cholesterol in the trials with progressive updates of the international guidelines for atherosclerosis with the motto "lower for LDL-cholesterol is always better" (Grundy, 2008), but undoubtedly a residual risk is still present: "lower LDL-cholesterol is better but it is not enough" (Superko & King III, 2008).

Another related observation, based on arteriographic findings, is the positive significant effect of statins on the decrease in the rate of atherosclerotic progression but the absent effect on any regression, something demonstrated on the contrary with a combined treatment (LDL-cholesterol reduction + HDL-cholesterol increase) (Superko & King III, 2008). This was confirmed recently by the conclusions of the ARBITER 6-Halts study which compared the effects of ezetimibe, an inhibitor of cholesterol absorption, and extended-release niacin in high risk patients already with statin therapy: the primary end point was the change in the intima-media thickness of common carotid artery (Taylor et al., 2009). Niacin was significantly superior to ezetimibe in the primary end point, suggesting again that the addition of a HDL-cholesterol raising drug to a statin is superior to a further LDL-cholesterol decreasing strategy.

Although a recent meta-analysis has suggested that increasing HDL-cholesterol does not reduce the risk of cardiovascular events in human subjects (Briel et al., 2009), animal studies have provided strong evidence that HDL-cholesterol is protective (Haas & Mooradian, 2011). HDL exerts a key role in the reverse cholesterol transport, whereby cholesterol is transported from peripheral cells to the liver and consequently fostering the removal of this molecule from the lipid-laden macrophages at the vascular level. In addition HDL particles have been shown to be involved in direct anti-oxidative, anti-apoptotic, anti-thrombotic, and also anti-inflammatory functions (Tabet & Rye, 2009), suggesting further protection against the atherosclerotic process. However we need to be aware that, during the inflammatory activation, HDL particles can shift to a "dysfunctional" setting, showing on the contrary pro-inflammatory properties (Säemann et al., 2010): therefore the functional properties of HDL reflect its role more appropriately than mere serum concentrations.

At the present time, among HDL-cholesterol-increasing drugs, niacin (nicotinic acid) is the most effective agent, raising HDL-cholesterol by 20-30% (Farmer, 2009) with an important side effect (flushing), which can be attenuated by both an extended-release formulation (Knopp et al., 1998) and a combination with a prostaglandin D2 receptor 1 antagonist, laropiprant (Perry, 2009). The results of the HPS2-THRIVE ongoing study will give us important information about the therapeutic role of this combination in the prevention of cardiovascular events. In the meantime we already know that niacin exerts direct anti-inflammatory effects, in particular an anti-oxidant and a CRP-decreasing activity (Sanyal et al., 2007; Thoenes et al., 2007).

The most effective way to increase HDL-cholesterol was thought to be the inhibition of the cholesteryl ester transfer protein (CETP), the enzyme responsible for the transfer of cholesteryl esters from HDL particles to very low-density lipoproteins and LDLs (Barter & Kastelein, 2006). The first developed CETP-inhibitor was torcetrapib, which was evaluated in the ILLUMINATE trial (Barter et al., 2007): in this study patients at high cardiovascular risk were randomly assigned to receive either torcetrapib + atorvastatin or placebo + atorvastatin. Despite the very favourable lipid changes obtained in the torcetrapib arm (a 72% increase in HDL-cholesterol and a 25% decrease in LDL-cholesterol), the rate of major cardiovascular events was increased by 25% and the deaths from cardiovascular causes by 40%; all-cause mortality was increased by 58% and an increase in blood pressure and aldosterone levels, therefore unrelated to CETP inhibition, was also observed in the active arm. Whereas the pressor and aldosterone-stimulating effects could explain the cardiovascular results, it was harder to understand the increased rate of deaths from noncardiovascular causes induced by torcetrapib: the increase was due to more deaths from cancers and infections. Since CETP inhibition alters the size and the composition of the HDL particles (Barter & Kastelein, 2006), these qualitative changes could predispose to an increased susceptibility to neoplasms and infections.

These negative results did not stop the development of other drugs of the same class: very recently the safety of anacetrapib was positively evaluated in the DEFINE study (Cannon et al., 2010) and the increased HDL particles exhibited a strong ability to suppress macrophage toll-like receptor 4-mediated inflammatory responses (Yvan-Charlet et al., 2010). A more direct way to stimulate the reverse cholesterol transport is the infusion of reconstituted HDL or Apo A-I mimetic peptides: with both therapeutic approaches a potent anti-inflammatory effect was observed (Natarajan et al., 2010).

4. Anti-platelet agents

Atherosclerotic thrombotic events are always characterized by an important inflammatory activation which is a consequence of the release of chemokines and cytokines from the platelets (Gurbel et al., 2009); however platelets are also involved in the initiation and the early progression of atherosclerosis mediating leukocyte recruitment and adhesion to the vascular wall (Antoniades et al., 2010). Many markers of platelet activation are currently investigated: in this context prospective studies and meta-analysis suggest a correlation between an increase in mean platelet volume and the risk of thrombosis (Gasparyan et al., 2011); in addition the soluble form of CD40 ligand has been studied in sera of human subjects and seems to have a prognostic role in atherothrombosis (Antoniades et al., 2010).

The most used anti-platelet drug, aspirin, is able to decrease serum CRP and patients with the highest baseline CRP levels derives the greatest benefit from this drug.

Trials of cardiovascular prevention with aspirin do not always confirm the positive effects of an anti-thrombotic approach, at least in the primary setting: also recently updated guidelines suggest judicious use of anti-platelet drug (Bell et al., 2011). The limited protective effects of aspirin have led to the concept of aspirin resistance (Gasparyan et al., 2008).

5. Phospholipase A_2 and ACAT inhibitors

In atherosclerosis the interactions between lipoprotein metabolism and inflammation are modulated by the complex phospholipase A_2 (PLA_2) superfamily. This family comprises five types of enzymes, of which the secretory PLA_2 ($sPLA_2$) and the lipoprotein-associated PLA_2 (Lp-PLA_2) have been associated with atherogenesis (Garcia-Garcia & Serruys, 2009). These enzymes catalyze the hydrolysis of the centre (sn-2) ester bond of phospholipids to produce non-esterified fatty acids (in particular arachidonic acid) and lysophospholipids (lysophosphatidylcholine): the atherogenic consequences are the formation of smaller and denser HDL and LDL particles, the formation of vascular LDL aggregates, the increased LDL oxidation, the synthesis of potent inflammatory lipid mediators such as prostaglandins and leukotrienes (Rosenson, 2009). Therefore inhibitors of the types of PLA_2 have been developed and have reached the phase III clinical evaluation, one for LpPLA2 (darapladib) and one for sPLA2 (varespladib).

In human studies darapladib induced a small but significant decrease in the inflammatory markers hsCRP and interleukin-6 with no changes in plasma lipid levels. In the IBIS-2 trial after 12 months the drug did not affect the primary end point, coronary plaque volume evaluated by intravascular ultrasound (IVUS); however necrotic core size remained unchanged in the active arm but increased in those treated with placebo (Boekholdt et al., 2008). Darapladib is now being evaluated in two large placebo-controlled cardiovascular outcome studies – STABILITY and SOLID-TIMI 52. As for varespladib, in the PLASMA Phase II the drug was demonstrated to induce a decrease in both oxidized LDL and CRP; an ongoing Phase III cardiovascular outcome study (VISTA-16) have recruited high risk patients.

Another important enzyme involved in the cellular cholesterol metabolism is acyl-coenzyme A:cholesterol acyltransferase (ACAT): this protein is able to catalyse cholesteryl ester formation by transfer of fatty acyl chain from acyl-coenzyme A to cholesterol. Two isozymes are present, one expressed in macrophages in atherosclerotic lesions (ACAT-1) and the other mainly expressed in small intestine (ACAT-2): therefore nonselective pharmacological inhibition of ACAT was expected to exert a double favourable effect, suppressing both foam cell formation in arterial walls and cholesterol intestinal absorption. Unfortunately results of the studies in human subjects were disappointing: avasimibe and pactimibe, the two nonselective ACAT inhibitors developed for clinical use, gave null or negative results (Fazio & Linton, 2006). Very recently a potent and selective ACAT-1 inhibitor, K-604, with significant anti-atherosclerotic effects *in vitro* and in experimental animals, entered a Phase II trial (Yoshinaka et al., 2010).

6. Leukotriene pathway inhibitors

Leukotrienes (LTs) belong to the family of eicosanoids and exert potent pro-inflammatory smooth muscle constrictive actions. It is well known their involvement in many inflammatory and allergic diseases, such as rheumatoid arthritis, inflammatory bowel disease, and bronchial asthma. Initially a leukotriene receptor blocker, i.e. montelukast, was administered to acute coronary syndrome patients to evaluate the endothelial function in brachial artery (clinicaltrials.gov NCT00351364, data unpublished). Subsequently inhibitors of both 5-lipoxygenase (5-LO) (atreleuton) and 5-lipoxygenase activating protein (FLAP) (veliflapon) were studied in human subjects. Atreleuton, a potent 5-LO inhibitor, was administered in acute coronary syndrome patients for 24 weeks and was able to reduce both the appearance of new coronary plaques and the volume of noncalcified plaques in comparison with placebo; these effects were paralleled by a 66% reduction of hsCRP (Tardif et al., 2010). Instead veliflapon, a weak FLAP inhibitor, induced a decrease in LTB4 production and myeloperoxidase activity with a nonsignificant reduction in CRP (Hakonarson et al., 2005).

7. CCR2 blockade

One of the main players in the inflammatory cascade induced by the atherosclerotic changes is chemokine CC motif ligand 2 (CCL2), also known as monocyte chemoattractant protein-1: this chemokine, through the interaction with its receptor chemokine receptor 2 (CCR2), efficiently induces the recruitment of circulating blood monocytes to become plaque macrophages. Very recently MLN1202, a highly specific humanized monoclonal antibody that recognizes CCR2 and inhibits CCL2 binding, was evaluated in a randomized, double-blind, placebo-controlled trial: the main aim was to measure possible decrease in hsCRP with the active treatment in cardiovascular high-risk patients (Gilbert et al., 2011). The results of this preliminary study confirmed a significant 26% reduction in the inflammatory marker, but obviously we need to perform outcome studies in order to establish a role of this new therapeutic approach in the treatment of atherosclerosis.

8. Peroxisome Proliferator-Activated Receptor (PPAR) agonists and Polyunsaturated Fatty Acids (PUFAs)

PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily (Oyekan, 2011). Through cellular mechanisms called transactivation, binding of PPAR/nuclear retinoid receptor (RXR) heterodimers to PPAR response elements (PPREs) in the promoter region of target genes, and transrepression, interference with transcription factors such as nuclear factor-kB (NF-kB) and activator protein-1 (AP-1), these transcription factors exert multiple and complex effects involving the regulation of the vascular tone, inflammation and metabolism. The PPAR family consists of three isoforms, α, γ, and β/δ, which possess distinct functions, with corresponding agonists.

PPAR-α agonists (fibric acid derivatives = fibrates) have demonstrated potentially very favourable effects on serum lipids with a significant decrease in triglyceride levels and more modest effects on LDL-cholesterol (a decrease) and HDL-cholesterol (an increase); in addition LDL size is modified with a decrease of more atherogenic small dense particles. All these positive changes are theoretically complementary to those induced by statins

(Abourbih et al., 2009) and are paralleled by a significant anti-inflammatory modulation, as demonstrated both *in vitro* and *in vivo* (Adameova et al., 2009). Despite these considerations and the long time of clinical evaluation (more than 30 years in Europe), considerable controversy still remains about therapeutic efficacy, also after recent reevaluation (Jun et al., 2010; Goldfine et al., 2011).

The same negative results were observed in the ACCORD-Lipid substudy which compared a statin monotherapy with a combination therapy with a statin + a fibrate in type 2 diabetic patients, who are the population with the theoretical maximal advantage from the combination (Ginsberg et al., 2010). However a prespecified analysis showed a 31% reduction in the primary end point (nonfatal MI, nonfatal stroke, or death from cardiovascular causes) in the subgroup of patients with the most negative metabolic profile (baseline triglyceride levels >204 mg/dl and HDL-cholesterol levels <34 mg/dl).

PPAR-γ agonists (thiazolidinediones = glitazones) was known as anti-inflammatory agents for a long time (Duan et al., 2009): two molecules are available for administration in humans, pioglitazone and rosiglitazone. They have a specific therapeutic indication for type 2 diabetes mellitus due to their improvement in insulin sensitivity, supporting the interpretation of type 2 diabetes mellitus as an auto-inflammatory disease (Dinarello, 2010; N. Wang et al., 2011). *In vitro*, in human blood monocytes, pioglitazone reduces synthesis of IL-1β, tumor necrosis factor (TNF)-α, IL-6, MCP-1, Toll-like receptors (TLRs) (Dasu et al., 2009). Also *in vivo*, in human subjects, pioglitazone exerts potent anti-inflammatory effects with a significant decrease in hsCRP levels in both diabetic and nondiabetic individuals (Pfützner et al., 2010).

Like fibrates, cardiovascular end points evaluated in large randomized studies with glitazones gave disappointing results. The only published outcome trial with this group of drugs is the PROactive trial (Dormandy et al., 2005): in this study pioglitazone induced a nonsignificant reduction in the primary end point (a composite of death, nonfatal MI, stroke, major leg amputation, acute coronary syndrome, and coronary or leg revascularization); however the principal secondary end point (a composite of all-cause death, nonfatal MI, and stroke) was significantly reduced by 16%. On the contrary in different trials rosiglitazone gave some suspicions about detrimental effects on cardiovascular events: a large meta-analysis concluded that this drug may increase the risk of cardiovascular events (MI, death) (Nissen & Wolski, 2007), possibly through a more favourable effect of pioglitazone on the lipid profile (Goldberg et al., 2005). A possible step forward in the development of PPARs is the evaluation of a dual α/γ agonist: after the withdrawal of muraglitazar and tesaglitazar for important toxicities, aleglitazar is currently being investigated in type 2 diabetic patients (Paras et al., 2010).

Other drugs which are able to decrease triglyceride levels are omega-3 fatty acids: the attempt to copy Eskimo diet was successful in the secondary prevention of cardiovascular diseases with important complex anti-inflammatory effects, which probably involve the above mentioned mediators resolvins (De Caterina, 2011).

9. Succinobucol and fasudil

Another possible target for atherosclerosis treatment is represented by the blockade of the oxidative stress, and in particular of the oxidation of lipoproteins (Libby et al., 2011): this was the reason why anti-oxidant vitamins (vitamin C and E) were evaluated in randomized controlled trials, unfortunately with no success (Kris-Etherton et al., 2004). Two drugs exert

similar potent *in vitro* anti-oxidant effects and have been studied in atherosclerotic patients: succinobucol and fasudil. Succinobucol is a derivative of probucol, previously withdrawn at Phase III evaluation for safety concerns, with well-demonstrated anti-inflammatory and anti-oxidant effects in endothelial and blood mononuclear cells (Kunsch et al., 2004). The ARISE trial recently examined the effects of succinobucol on cardiovascular events in patients with a recent acute coronary syndrome: there was no significant difference in the primary end point (cardiovascular death, resuscitated cardiac arrest, MI, stroke, unstable angina, or coronary revascularization); the composite secondary end point of cardiovascular death, MI, cardiac arrest and stroke was 19% lower in the succinobucol arm compared to placebo and reached statistical significance (Tardif et al., 2008). Another interesting observation of the study, tertiary end point, was the 63% relative reduction in the onset of new diabetes, related to a reduction in glycosilated haemoglobin in diabetic patients.

Fasudil is an inhibitor of Rho-kinase, an important downstream effector of the small GTP-binding protein RhoA (Satoh et al., 2011). It has been demonstrated that the RhoA/Rho-kinase pathway exerts a specific role in the pathogenesis of vasospasm, atherosclerosis, ischemia-reperfusion injury, hypertension, stroke, and heart failure. Fasudil is already marketed in Japan for the acute treatment of cerebral vasospasm but the possible additional indications in human subjects are not completely established (Zhou et al., 2011).

10. Anti-hypertensive drugs

Despite intensive research the pathogenesis of hypertension, the leading risk factor of death in the entire world (Ezzati et al., 2002), remains elusive. The hypothesis of a low-grade inflammatory activation could explain many aspects of the hypertensive process and therefore is actively investigated (Harrison et al., 2011; Leibowitz & Schiffrin, 2011; Montecucco et al., 2011). If we can translate these observation to the clinical ground, the therapeutic strategies should keep account of possible anti-inflammatory modulations of the hypotensive drugs adding more fuel to the controversy about the protective role exerted by the blood pressure reduction *per se* or the presence of additional pleiotropic actions of some classes of drugs with respect to others: "outcomes beyond blood pressure control?" (Sever et al., 2006; Staessen et al., 2010). In this context the renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin inhibitors) could be the best choice since the fundamental role of this system in the activation of the vascular inflammation is widely demonstrated (Marchesi et al., 2008): this is confirmed by the *in vivo* demonstration of a significant decrease of various inflammatory markers induced by these drugs (reviewed in Montecucco et al., 2009).

However, the most comprehensive guidelines for the treatment of hypertension do not consider an inflammation-based approach: on the contrary the updated versions of the European Society of Hypertension/European Society of Cardiology guidelines did not confirm the role of CRP as a cardiovascular risk factor for the prognostic stratification, as proposed in the first edition (Mancia et al., 2007). All the hypertension guidelines emphasize the control of blood pressure levels as the main target for the therapeutic choices, without a classification of the different available drugs and suggesting that frequently we need to prefer a drug combination to improve effectiveness and limit side effects. In terms of the atherosclerotic process a partial confirmation of this approach comes from the IVUS substudy of the CAMELOT trial which demonstrated a significant slowing in the

progression of the atheroma volume with a calcium-antagonist (amlodipine, a potent and possibly more effective hypotensive drug) compared to an angiotensin-converting enzyme inhibitor (enalapril) (Nissen et al., 2004).

11. Immunosuppressive agents

In this section we will discuss the anti-atherosclerotic effects of drugs developed for immunosuppression and therefore without a primary metabolic action. In terms of immunosuppression nothing is more powerful and studied than corticosteroids (Rhen & Cidlowski, 2005). 35 years ago corticosteroid administration was shown to exert deleterious effects in patients with MI (Roberts et al., 1976); however very recently oral prednisone was used successfully to prevent restenosis after PCI with bare metal stents in comparison with bare metal stents alone(better event-free survival) and drug-eluting stents (similar outcome) (Ribichini et al., 2011).

As discussed in the introduction, a proof-of-concept for the role of inflammation in the atherosclerotic process would be a clinical trial with well tolerated anti-inflammatory drugs, devoid of metabolic effects: methotrexate and canakinumab could be good choices and have been proposed recently.

For other drugs the tolerability in uncomplicated atherosclerotic subjects could be more problematic with a disadvantageous risk-benefit ratio, but their potentially positive cardiovascular effects in patients with a specific immunosuppressive indication can be carefully monitored in clinical trials for post hoc analysis (Westlake et al., 2010). Another possible application is the administration of these drugs for a limited period of time (e.g. for a few days after PCI).

TNF-α antagonists are extensively used in autoimmune diseases with a significant cardiovascular protection (Tracey et al., 2008), possibly related to the pivotal role of this cytokine in vascular dysfunction: recently, in a population of subjects who underwent carotid endarterectomy for a significant stenosis, we found an increase in TNF-α plasma levels in symptomatic patients for an ischemic cerebrovascular event with respect to asymptomatic patients (Montecucco et al., 2010). TNF-α antagonists have been evaluated in vascular disorders accompanying chronic disordes (Crohn' s disease and rheumatoid arthritis) with the demonstration of improvement in endothelial function (Schinzari et al., 2008; Hürlimann et al., 2002). In addition to the anti-inflammatory effects, these drugs also induce a favourable lipid profile with an increase in HDL-cholesterol and apolipoprotein A-I (van Eijk et al., 2009).

IL-1 seems to exert a central role in the intense inflammatory response which follows a MI. Using a recombinant form of the naturally occurring antagonist (anakinra), a pilot study was recently performed to test the safety and effects of this drug on post-MI left ventricular remodelling and CRP serum levels (Abbate et al., 2010). Anakinra was able to mitigate significantly left ventricular remodelling, evaluated with both cardiac magnetic resonance and echocardiography, and the changes in CRP levels correlated with the changes in cardiac anatomy.

Another new important inflammatory pathway involves p38 mitogen-activated protein kinase (MAPK). This phosphorylation cascade can be activated by a vascular injury, such as

coronary stenting with subsequent neointimal proliferation and in-stent restenosis (Schieven, 2005), and represents an important intracellular switch for the production of key inflammatory cytokines (IL-1β, TNF-α, and IL-6), inflammatory enzyme cyclooxygenase-2 and matrix metalloproteases. Recently a p38 MAPK inhibitor (dilmapimod, SB-681323) has been shown to significantly attenuate the inflammatory activation induced by a PCI procedure with positive consequences in post-procedural outcomes (Sarov-Blat et al., 2010).

Interesting observations came from the administration of the immunosuppressive drug mycophenolate mofetil in atherosclerotic patients for a limited period of time: the drug, devoid of effects on both serum lipids and blood pressure, was able to attenuate cellular and biochemical inflammatory activation in the unstable carotid plaques of patients who subsequently underwent endarterectomy for advanced stenosis (van Leuven et al., 2006; Van Leuven et al., 2010). At the very beginning of the clinical evaluation are the inhibitors of Toll-like receptors, involved in the innate immune response (Hennessy et al., 2010; Cole & Monaco, 2010).

12. Conclusion

Recently the title of an editorial in Circulation was "Could direct inhibition of inflammation be the *next big thing* in treating atherosclerosis?" (Natarajan & Cannon, 2010). This is certainly a fascinating strategy because it tries to exert a fully pathogenetic approach, though we need not to forget the frustrations, caused by so many disappointing results. In this context we know that it is not always wise to found our evaluation on surrogate end points: only randomized controlled trials with cardiovascular hard end points can give the final answer.

Take-home messages

- Lifestyle choices are an essential part of the cardiovascular prevention and physicians must exert every effort to obtain a good compliance from patients
- In terms of therapeutic control of the different risk factors physicians must reach better results
- At the present time physicians have to focus at the single risk factors with the awareness that the inflammatory activation is important for the atherosclerotic process
- hsCRP represents a useful marker of inflammation and an excellent support for the prognostic stratification
- Additional help can derive from carotid US and coronary calcium score
- In the context of blockade of the inflammatory activation statins and RAS-inhibitors offer good choices in terms of safety and effectiveness
- Specific ant-inflammatory drugs need to be carefully evaluated with appropriate trials
- At the present time these drugs may be useful for a limited period of time (e.g.: after a PCI)
- Intense investigation on this topic will certainly suggest new therapeutic targets and strategies

In this review we tried to give an update of the experimental and clinical data with already marketed drugs or with Phase III therapeutic principles but we did not discuss the possible use of an immunomodulating (not immunosuppressive) approach: expansion of regulatory

T cells, a subset of T lymphocytes with a well demonstrated anti-inflammatory role, and atherosclerosis-specific immunization are thought as promising therapeutic opportunities and are actively investigated (Klingerberg & Hansson, 2009; van Puijvelde et al., 2008).

Although at the present time the physicians are confident with the use of drugs developed for particular aspects of the atherosclerotic spectrum (decrease of blood pressure, decrease in LDL-cholesterol, increase in HDL-cholesterol, decrease in glucose, etc.), the "unfinished business" of cardiovascular prevention (Libby, 2005) drives our efforts to find new targets and strategies against the pernicious activation of inflammation in atherosclerosis.

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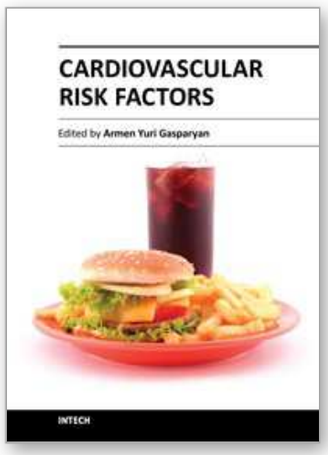

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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