CLINICAL UPDATE

Update on medical management of dyslipidemia and atherosclerosis

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Abstract: Scientific achievements revealing the pathogenesis of atherosclerosis resulted in the second half of the 20th century in major improvement in prevention and therapy of cardiovascular disorders (CVD). Essential became the understanding of a critical pathogenetic role of the low-density lipoproteins (LDL), mainly their oxidized form (oxLDL) and also the protective potential of the high-density lipoproteins (HDL). CVD is now regarded to be an inflammatory disease in which a systemic inflammatory reaction is combined with an accumulation of immune cells in atherosclerotic plaques. Higher intake of antioxidants in fruit and vegetable, lifestyle modifications, cessation of smoking, physical exercise and introduction of medications that lower LDL and promote HDL (statins, niacin and fibrates) resulted in a substantial decline of the killer effect of unmanaged CVD. In the United Kingdom the male CVD mortality declined between 1970 and 2009 from 700 to 200 deaths per 100,000. In France, CVD mortality in the middle age population (25–64 years) is now responsible for death in only 15 % men and in 11 % women. Unfortunately, in many parts of the world CVD mortality remains a prominent population scourge. Recent discoveries, especially on the role of peroxisome proliferator-activated receptors (PPAR) and antisense compounds used in addition to established anti-atherogenic medications, promise further gains in the fight against atherosclerosis (Fig. 4, Ref. 54). Full Text in PDF. www.elis.sk.

Key words: cardiovascular disease, LDL, ox-LDL, HDL, statins, niacin, fibrates, peroxisome proliferator, antisense compounds.

Arterial stiffening is a complex process involving extracellular matrix proteins and smooth muscle cells (1, 2). Increased arterial stiffness generates CVD. Although the exact mechanisms underlying arterial stiffening are not well understood, oxidative stress, inflammation and immunological factors play an important role. CVD is an inflammatory disease in which a systemic inflammatory reaction is combined with an accumulation of immune cells, such as monocytes/macrophages, dendritic cells and numerous lymphocytes, in atherosclerotic plaques. The oxidative transformation of low-density lipoprotein (LDL) is recognized as a key step in the initiation and progression of atherosclerosis. Oxidized-LDL are associated with stimulation of collagen synthesis in arterial smooth muscle cells, they promote intimal thickening and impair nitric oxide bioactivity, all of which may contribute to arterial stiffness. Thus ox-LDL and inflammation are the driving forces in atherosclerosis (3). Strong evidence supports the central role of proinflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) in CVD (4). The role of peroxisome proliferator-activated receptors (PPAR) in CVD is now receiving widespread attention. As ligand-activated nuclear receptors, they play a role in regulation of lipid metabolism. This feature of the PPARs has been successfully exploited to manage the metabolic syndrome, associated with hypertension, hyperlipidemia and CVD (5). Thrombosis, the formation of a blood clot within the blood vessel resulting in occlusion of blood flow, is a major problem that accompanies CVD. The therapeutic targeting of platelets is recognized as effective in the prevention and treatment of CVD (6, 7). New cholesterol absorption inhibitors were found. Ezetimibe initially raised hopes because it blocks the absorption of dietary and biliary cholesterol, resulting in intracellular cholesterol depletion (8). The firmly established benefit of statins in lowering the LDL has been further enhanced by combining statins with niacin and fibrates. Novel discoveries leading to a combination of antisense technology with PPARs, may represent a further important breakthrough in the management of dyslipidemia.

Established medications used in lipid disorders

Statins

Presently, statins represent the main agent in combating atherosclerosis (9). Numerous epidemiologic and angiographic studies indicate that elevated serum LDL is a major cause of CVD. Statins act by inhibiting HMG-CoA reductase, the rate limiting enzyme for cholesterol synthesis. By decreasing elevated serum LDL-cholesterol concentration statins can reduce the incidence and progression of CVD (10–12). Although manufacturer brand names may vary by regions, the main representatives of statins are atorvastatin (Lipitor®), simvastatin (Zocor®), pravastatin...
Nicotinic acid and niacin

Niacin is a derivative of nicotinic acid used for management of dyslipidemia for several past decades. It is a water-soluble part of vitamin B complex (also known as vitamin B3 or vitamin PP). Niacin has anti-hyperlipidemic effects: In pharmacological doses it reverses atherosclerosis by reducing total cholesterol, TG, very-low-density lipoprotein (VLDL), LDL, and it increases HDL. It has been proposed that niacin has the ability to lower lipoprotein levels, but persistent, significant elevation of HDL-C and high triglycerides (TG), despite achieving LDL lowering with statins. Livaflo, approved on the basis of 10 clinical trials comparing efficacy and safety with atorvastatin, simvastatin and pravastatin, offered LDL-C lowering of up to 45% at a 4mg dose, at the same time decreasing TG and elevating HDL-C (13). Fixed combinations of statins with other drugs are also available: Simcor is simvastatin with extended release niacin, advicor is lovastatin with niacin.

Potential residual cardiovascular risk after treatment with statins due to low HDL-C and high TG, despite lowering of LDL may be resolved by combining statins with niacin (15). Flushing is an unpleasant side effect of niacin therapy. A new formulation of niacin shows a slower rate of absorption, substantially reducing flushing, when compared with the traditional niacin (16). Considering beneficial effect of medications on lipid metabolism, new stricter criteria also focus on the effect on sclerotic arterial wall thickness. Efficiency of niacin regarding its effect on arterial wall has been questioned and there have been suggestions to use niacin only as monotherapy, as a last resort. With the recent discovery of a specific receptor for nicotinic acid (GPR109A) (17), the molecular mechanisms underlying the pharmacological effects of nicotinic acid have become clearer. The receptor is expressed in brown and white adipose tissue, in various immune cells, including monocytes, macrophages, dendritic cells and neutrophils.

GPR109A is coupled to Gi type G proteins. Its activation by nicotinic acid results in a Gi-mediated inhibition of adenyl cyclase, resulting in a decrease in intracellular cyclic AMP, the principal mediator of adipocyte lipolysis. Strong evidence exists that at least the initial steps of the nicotinic acid-induced changes in lipid metabolism are mediated by GPR109A (18). New agents acting via the nicotinic acid receptor are currently being developed.

Fibrates

These belong to a class of amphipathic carboxylic acids that exert an impressive therapeutic effect when combined with statins.
and skin; γ (gamma) – expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas, spleen, in macrophages, large intestine and white adipose tissue.

All PPARs heterodimerize with the retinoid X receptor (RXR) and bind to specific regions on the DNA of target genes. Endogenous ligands for the PPARs include free fatty acids, prostaglandins and leukotrienes that originate from free fatty acids under the effect of lipoxygenase and cyclooxygenase. PPARα and PPARγ are the molecular targets of a number of marketed drugs. Fibrates activate PPAR-α receptor in muscle, liver, and other tissues. The mechanism underlying the beneficial effect of PPARs is not confined to whole body metabolism, but also includes modulation of other vital processes, such as inflammation and cell fate (proliferation, differentiation, apoptosis). PPARs are presumed therapeutic targets in CVD (21). A word of caution: at present the clinical trials have not produced convincing evidence that CVD is prevented with the use of PPARalpha and PPARgamma agonists (22).

Antioxidants

Free oxygen radicals represent potential risk for the arterial vasculature by stimulating the rise of ox-LDL. Antioxidants terminate these reactions by removing free radical intermediates and inhibit other oxidation reactions. Essential natural antioxidants in the diet are ascorbic acid (vitamin C), α-tocopherol (vitamin E), carotenoids and polyphenols (PPH) (e.g. resveratrol). Additional antioxidants are represented by the glutathione, lipoic acid and ubiquinol (coenzyme Q).

Polyphenols are a class of chemical compounds consisting of a hydroxyl group (-OH) bonded directly to an aromatic hydrocarbon group. Phenol forms a reduct system with chimone and therefore dietary PPH (for example skin of red grapes) can directly scavenge free oxygen radicals and downregulate expression of proinflammatory mediators, adhesion molecules, and growth factor receptor genes. These polyphenolic compounds have potential therapeutic value as antioxidant and anti-inflammatory agents in the management of CVD. Much attention has been recently focused on resveratrol. This compound was reported in experimental animals and in short term human studies (23, 24) to demonstrate cardioprotective effects. Moore human studies are needed before resveratrol is considered a standard therapeutic agent.

Vitamin E: Several in vitro and animal studies, observational as well as clinical trials suggested a cardioprotective effect of tocopherol (25). It increases oxidative resistance in vitro and prevents atherosclerotic plaque formation in mouse models. However, this remains controversial since clinical studies have not demonstrated a benefit of vitamin E in the primary and secondary prevention of cardiovascular disease. Nearly 200 trials using vitamin E supplements were carried out in the decade after the initial report, then followed by a recent review and meta-analysis. Their conclusion: vitamin E represents neither benefit nor harm (26). The American Heart Association does not support the use of vitamin E supplements to prevent cardiovascular disease, but does recommend the consumption of foods abundant in antioxidant vitamins.

Carotenoids are a class of natural fat-soluble pigments found in plants. The most abundant carotenoids in the diet are beta-carotene, lycopene, lutein, beta-cryptoxanthin, zeaxanthin and astaxanthin. Numerous epidemiologic studies have supported the hypothesis that their antioxidant action could be used as an inexpensive means of prevention and possibly treatment of cardiovascular diseases (27). More recently, sobering conclusions were reported from a multicenter, randomized, double-blind, placebo-controlled primary prevention trial, involving smokers, former smokers and workers exposed to asbestos. When the effects of a combination of beta carotene and vitamin A on the incidence of lung cancer and CVD were compared with those of placebo, the outcome was astounding: mortality related to lung cancer and CVD in the treatment groups was actually higher than on placebo. On the basis of these findings, the randomized trial was stopped 21 months earlier than planned (28). There is a speculation that the high intake of beta carotene competitively inhibited absorption of lycopene, an oxygenated carotenoid with great antioxidant properties. Lycopene has antiatherogenic effect in experimental animals (29).

Vitamin C is a pivotal redox modulator in many biological reactions. Growing epidemiological, clinical and experimental evidence now suggests a more specific role of ascorbate in vasomotion and in the prevention of atherosclerosis (30). For endothelial cells, ascorbate helps to prevent endothelial dysfunction, stimulates type IV collagen synthesis, and enhances cell proliferation. For vascular smooth muscle cells, ascorbate inhibits dedifferentiation, recruitment, and proliferation in areas of vascular damage. For macrophages, ascorbate decreases oxidant stress related to their activation, decreases uptake and degradation of ox-LDL (31). Long term deficiency of ascorbate promotes atherosclerosis-like injury in experimental animals. It is possible that its deficiency promotes human atherosclerosis as well (32). There is a sparsity of randomized, double-blind, placebo-controlled prevention trials to document the role of chronic vitamin C deficiency in human atherogenesis.

In summary, despite the lack of strong evidence for antioxidants to prevent CVD, it is reasonable to assume their beneficial potential. Plant food is the main source of antioxidants. What is the evidence? Meta-analysis of several prospective studies showed no significant difference in the mortality caused by various types of cancer and stroke between vegetarians and “health-conscious” nonvegetarians. The effect of predominantly plant food is complex. In vegetarians a decrease in ischemic heart disease mortality was observed due to lower cholesterol levels, lower prevalence of obesity, non-smoking and higher consumption of antioxidants (33). In the near future we expect a very large cohort study of diet and health on more than half million of persons, the European Prospective Investigation into Cancer and Nutrition (EPIC) study, to bring new data on the relationships between diet, lifestyle, environmental factors and the incidence of cancer, CVD and other chronic diseases. Preliminary results suggest that a higher intake of fruits and vegetables is associated with a reduced risk of CVD mortality (34).

Long-chain n-3 fatty acids

A type of fatty acids, popularly referred to as omega-3 fatty acids are a family of essential polyunsaturated fatty acids that have
in common a final carbon–carbon double bond in the n-3 position; that is, the third bond from the methyl end of the fatty acid (n-3). Nutritionally important long-chain n-3 fatty acids include eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Interest in n-3 was initiated by observing that the Inuits (Eskimos) living in the Arctic, have very low CVD mortality while consuming practically no plant food (35, 36). However, they consume high amounts of n-3 from fatty fish and have increased HDL cholesterol and low TG.

The association between high intake of n-3 and decreased morbidity and mortality from CVD can be explained by several mechanisms: n-3 reduce the synthesis of VLDL particles and increase TG removal from VLDL through the upregulation of the lipoprotein lipase (37). Inhibitory effect on atherothrombosis by n-3 includes the modulation of the expression of pro-atherogenic genes (e.g. endothelial leukocyte adhesion molecules, inflammatory cytokines and cyclooxygenase). Positive effect of n-3 on cardiac arrhythmia includes complex interactions with ion channels (sodium, potassium and calcium channels), typically requiring the presence of free n-3 (38). N-3 increase the production of bioactive lipid mediators (protectins and resolvins) affecting cytokine-induced signal transduction. Mechanisms of beneficial effect of n-3 suggest a synergic action of n-3 with statins. COMBOS study (Combination of Prescription Omega-3 With Simvastatin) achieved significant improvements across a range of lipid indicators beyond the LDL primary target, including TG and lipoprotein particle size (39).

Bile acid sequestrants (BAS)

BAS were among the first drugs approved to lower cholesterol. BAS are positively charged resins that bind to negatively-charged bile acids in the intestine and prevent their absorption. To compensate for the loss of bile acids, the liver increases the conversion of cholesterol to bile acids. The conversion of cholesterol to bile acids reduces cholesterol in the body, resulting in a drop of cholesterol levels in the blood. However, the BAS might also increase the production of TG. BAS cause a small increase of HDL. However, when combined with statins, the BAS can provide an additional reduction in LDL. Some of the side effects of BAS are constipation, flatulence, indigestion, GI distress, decreased absorption of many drugs such as statins, niacin, lovastatin, and digoxin. Presently, BAS are seldom used. Instead, intestinal absorption of cholesterol may be controlled by Ezetimibe, a selective inhibitor of intestinal cholesterol absorption (40). Initial enthusiasm for Ezetimibe was tempered after a trial comparing extended release niacin with Ezetimibe (41). While niacin brought HDL up, Ezetimibe may actually lower HDL and when it is used alone there is a risk of atherogenicity.

Novel antiatherogenic medications

Numerous compounds already in use modulate lipid-lowering effect of statins. The dominant therapeutic role of statins is being threatened for inadequate suppression of TG and weak effect on HDL. For antilipid therapy to be fully effective, in some patients statins have to be combined with supplementary medications. Because various agents, fibrates, niacin, ezetimibe, phytosterols, omega-3 fatty acids and statins each regulate serum lipids by different mechanisms, combination therapy could be more helpful in achieving a comprehensive lipid control when compared with statin monotherapy (42–44).

To promote statin effectiveness there has been a sequence of candidate pharmaceuticals and biochemical agents. These include new and interesting therapeutic options, for example rate-limiting proteins (including Niemann-Pick C1-like 1 (NPC1L1), microsomal TG transfer protein (MTP), acyl-coenzyme A/cholesterol acyltransferase (ACAT), acyl CoA: diacylglycerol acyltransferases 2 (DGAT2), proprotein convertase subtilisin/kexin type 9 (PCSK9)), nuclear receptors (farnesoid X receptor (FXR), thyroid hormone receptor (TR) (45). Novel pharmacological targets for raising HDL-C also include the nuclear liver X and farnesoid X receptors and endothelial lipase (46). Traditional Chinese medicine recommends statin supplementation with Zhitibai derived from extracts of red yeast rice, Chinese hawthorn, oriental water plantain rhizome and large head atractylodes rhizome (47).

The secretory phospholipase A2 enzyme (sPL A2) inhibitor A-002 could be an effective anti-atherosclerotic agent (48). To improve the efficacy of current anti-platelet therapies, a small number of characterized platelet receptors which include proven anti-platelet drug targets, are currently the focus of drug discovery and clinical trials for the prevention and treatment of thrombosis. These include ADP receptor (P2Y1), antagonists and molecules that inhibit activation of PARs for thrombin (49). Novel research on statin pharmacology revealed that the pleiotropic effects of statins are associated with anti-inflammatory activity, enhanced endothelial function and inhibition of oxidative stress (50).

Antisense technology

Antisense technology is a new direction in discovering more effective therapies. When the genetic sequence of a particular gene is known to be causative of a particular disease, it is possible to synthesize a strand of nucleic acid that will bind to the messenger
RNA produced by that gene and inactivate it, effectively turning that gene “off”. This synthesized nucleic acid is termed an “anti-sense” oligonucleotide because its base sequence is complementary to the gene’s messenger RNA, which is called the “sense” sequence. Antisense compounds are designed to have the right nucleotide sequence to bind specifically to and interfere with its associated messenger RNA, the instructions for the production of a particular protein (51) (Fig. 2).

Further research revealed that using antisense technology may be applied to other disorders that affect the exon metabolism, by intervention in the role of exons in controlling the synthesis of proteins. An exon is a nucleic acid sequence that is represented in the mature form of an RNA molecule. Laboratory-designed antisense compounds can make a cell eliminate a specific exon while a functional protein is synthesized from the remaining instructions (Fig. 3). Each antisense drug is designed with the right complementary genetic code to bind to a specific sequence of nucleotides in its mRNA target to form a short area of double strands. Thus ISIS 301012 is an antisense oligonucleotide developed to reduce the hepatic synthesis of apolipoprotein B-100. Apolipoprotein B-100 is made in the liver, and antisense oligonucleotides preferentially distribute to that organ, so antisense apolipoprotein B-100 may have a potential as an efficacious lipid-lowering agent (52).

Another antisense compound, APOCIIIRx, is designed to reduce apolipoprotein C-III (apoC-III), a key regulator of serum TG levels. ApoC-III is a 79-amino acid glycoprotein synthesized in the liver that plays a central role in the regulation of serum TGs. Recent data suggest that loss of function mutations within the apoC-III gene lowers the TG levels (53).

Antisense compounds, compositions and methods are provided for modulating the expression of PPARs (peroxisome proliferator-activated receptors). The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding PPAR-delta. It appears that linking PPARs (Fig. 1) and antisense drugs bears a promise for extensive future use, not only in managing CVD but also for malignancy and other disorders.

Some of these new discoveries may represent a breakthrough in our understanding of disease. Much of this information is very new, being published primarily in patent application prior to undergoing a more lengthy editorial process in scientific journals.

**Conclusion**

Cardiovascular disease (CVD) remains a critical component in population mortality. Figure 4 documents that in Eastern Europe, CVD persists as the main cause of mortality in middle age men, substantially exceeding cancer mortality. In Western Europe, malignancy is becoming the foremost cause of mortality (54). Epidemiological data confirmed that regular dietary intake of plant-derived foods (providing antioxidants) and smoking cessation may reduce the risk of CVD and stroke. Another decisive factor leading to a dramatic decline in CVD mortality in recent decades has been the discovery and introduction of effective medications that normalize blood lipids and inhibit vascular inflammation. Credit has to be assigned to a wide use of statins, alone or in combination with niacin and fibrates. In the parts of the world where these medications are accessible, they contributed to lowering of LDL, oxLDL, TG and to optimizing HDL.

This review provides an insight into established and novel medications, their mechanism of effect and their potential when used in meaningful combinations.

**References**


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