Coronary atherosclerosis, low-density lipoproteins and markers of thrombosis, inflammation and endothelial dysfunction

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Available information regarding the relation among atherosclerosis, low-density lipoproteins, markers of thrombosis, inflammation and endothelial dysfunction has accumulated, but is still very limited, making only minimal contributions to clinical decision-making. Many more clinical trials are needed, but unless there is a relationship between atherosclerosis prevention, specific markers and a pharmaceutical product, financial support for such trials will be difficult to obtain. The anti-inflammatory effect of statins is well established. Angiotensin-converting enzyme inhibitors are generally not thought of as having anti-inflammatory effects, but the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study observed extensive RR reduction with perindopril. It was explained not simply by control of hypertension, but by reduced activity of multiple factors, supported by specific substudies. The 'cardiovascular continuum' is an excellent unifying term to explain atherosclerosis mechanisms, relate mechanisms to clinical understanding, and assist the clinician in selecting the appropriate prevention and control therapies. This so-called continuum actually describes a relationship among different biochemical, enzymatic and hormonal factors that affect the cardiovascular system. It can be seen in the downregulation of the angiotensin II receptor type 1 by statins, which contributes to hypertension control while lowering low-density lipoproteins. Peroxisome proliferator activator receptor-gamma also demonstrates the cardiovascular continuum with activation of the receptor by glitazones. The glitazones increase insulin sensitivity for diabetes control. Activation of the peroxisome proliferator activator receptor-gamma inhibits inflammation, which is possibly related to atherosclerosis, normalization of endothelial function, suppression of metalloproteinases and a decrease in smooth muscle cell migration. All of these effects may decrease atherosclerosis production while improving control of diabetes mellitus, a key disease in the cardiovascular continuum for development of atherosclerosis. Consideration of such interrelationships is just scratching the surface. Nevertheless, it can be seen that the complicated process of atherosclerosis development has a multifaceted explanation that has been minimally defined, but holds the key to prevention and control of this major medical problem faced in modern society.

Key Words: *Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Cardiovascular continuum; Coronary artery disease; Dysmetabolic syndrome; Endothelial dysfunction; Glitazones; Inflammation; Statins*

Coronary artery disease (CAD), low-density lipoproteins (LDLs), inflammation and endothelial dysfunction can all be viewed as parts or results of the cardiovascular (CV) continuum. Their individual relevance and significance to CAD – and their interactions with it – appear to offer keys to a better understanding of the atherosclerotic process, and how to favourably alter its course. For many years, CAD was considered a simple chance mechanical problem with a mechanical treatment solution, although serious consideration of the disease should have led to the realization that there was an underlying biochemical and molecular explanation. Understanding of the process has increased significantly and, besides knowing that LDL levels should be below 70 mg/dL in patients at high risk for CV disease (1-3), we know that understanding of the mechanisms precipitating final thrombotic occlusion of a coronary artery is essential in acute and preventive cardiology. In addition, the significance of inflammation, most commonly measured by high-sensitivity C-reactive protein (hsCRP), must be taken into account by astute clinicians. As shown by the CV risk significance of hsCRP and available information on treatment benefits (4), preventive management plans of high-risk CV patients must include a decrease in this risk factor by treatment such as aggressive use of a statin, even if it is not necessary to achieve an LDL goal (5). As more inflammatory markers are studied, additional knowledge can be expected to accumulate regarding inflammation and its possible direct participation in the atherosclerotic process. This is now considered to be the likely scenario for hsCRP (6). Endothelial cells also play a significant role in atherosclerosis formation. Topics of major interest include prediction the participation of abnormal cells and how to favourably modify their role (7). Therefore, the intention of the present article is to review concepts and the role of LDL, thrombosis, inflammation and endothelial dysfunction in the development of CAD; how the processes can be modified favourably to delay development of significant atherosclerotic disease; and to provide the physician with a useful, focused, practical clinical review applicable to patient care.

LDLs

Understanding of LDLs as a major CV risk factor has been accumulating for many years (8). Data from the Framingham Study showed a progressive increase of CV disease incidence with increasing LDL levels (9). Recommended acceptable LDL levels for the high-risk CV disease patient decreased – it is now considered advantageous for the patient to have levels

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below 70 mg/dL (1-3). Because diabetic patients are at an equivalent high risk for CAD, it appears advisable to recommend a similar goal for their LDL levels. In addition, small dense LDLs are associated with increased CV risk because of increased susceptibility to oxidation, making the LDLs more atherogenic (10). Small dense LDLs can also enter the arterial wall more easily, which contributes to their atherogenicity. Another variant form of LDL is lipoprotein (a), which is actually an LDL with a side group known as a kringle. This kringle promotes thrombogenesis, which is the most clinically significant end point of atherosclerosis (10). The CV risk significance of lipoprotein (a) is unquestionable (11), but there is a lack of comprehensive clinical trials to prove the benefit of aggressive lowering. Nevertheless, clinical trials recommended lowering the general LDL level and adding nicotinic acid, which is the single most effective medication to specifically decrease lipoprotein (a) (12).

SEROLOGICAL MARKERS OF CV RISK

Factors of thrombosis and hemostasis

This classification is a convenient way to start a discussion of serological markers of CV risk. The mechanism by which hyperhomocysteinemia causes significant arterial vascular disease has not been precisely defined. The association with atherosclerosis is definite but clinical evidence for the benefit of lowering homocysteine is lacking. It appears that homocysteine is toxic to the endothelium, is thrombogenic, increases collagen and decreases available nitric oxide (13). Other factors of thrombosis and hemostasis are fibrinogen, acetylsalicylic acid resistance and lipoprotein (a) (7). As in the case of all serological markers, their significance and application in clinical practice is in a state of flux. As discussed above, lipoprotein (a), which is actually a variant of LDL, is associated with atherosclerosis risk and thrombogenicity (14).

Factors of inflammation

There are multiple factors of inflammation that appear to play a role in the development of atherosclerosis (7). Selectins P and E are considered to have a role in atherosclerosis development, due to a contribution to initial vascular inflammation and the occurrence of monocyte adhesion. Unfortunately, clinically relevant assays for selectins P and E are not available. Cellular adhesion molecules (intercellular adhesion molecule-1 [ICAM-1] and vascular cellular adhesion molecule-1) play a role in macrophage adhesion and transmigration. ICAM-1 is expressed by macrophages and endothelial cells after activation by interleukin (IL)-1, tumour necrosis factor-alpha and interferon-gamma. ICAM-1 expression is increased by tobacco and decreased by statins. Also, IL-6 and monocytic chemotactic protein-1 are produced by endothelial cells to foment plaque growth. IL-6 is also a major inductor of hepatic and arterial hsCRP.

For the clinician, hsCRP has the most utility (4). Measurement of the high sensitivity form of C-reactive protein is essential because it reflects inflammatory activity in arteries and is definitely a CV risk factor; it may induce atherosclerosis formation directly. It appears to predict high-risk acute coronary syndrome (ACS), and can predict future CV events in apparently healthy individuals and in CV patients, without regard to plasma lipid levels. It may reflect a variable vascular hyper-response to injury and may have a partial genetic predetermination (15). Also, an elevated hsCRP level indicates which patients are more likely to respond to statins. Statins have been shown to reduce hsCRP; ezetimibe accentuates this effect (16), so any argument for pushing a statin to a maximum dose to achieve this effect should be countermanded. A series of statin and hsCRP dose-response curves is needed because, most probably, all statins lower hsCRP as related to individual statin potency, with approximately a 6% hsCRP reduction every time the statin dose is doubled. With LDL, a 6% reduction appears to occur whenever a specific statin dose is doubled (16).

Also of clinical use is the determination of lipoprotein-associated phospholipase A_2, which was reported to add to CV risk prediction independent of hsCRP (17). Analysis is available to practicing clinicians. Lipoprotein-associated phospholipase A_2 is an enzyme that may directly contribute to atherosclerosis production through the generation of inflammatory products.

PROPOSED PLEIOTROPIC EFFECTS OF STATINS

All statins have several proposed pleiotropic effects that contribute significantly to the overall clinical benefit (18) compared with LDL reduction alone. These effects undoubtedly explain how this potent class of medications can be associated with such rapid clinical benefit even in a few months – a result that has not been associated with LDL reduction alone. Possible pleiotropic effects include a favourable modification of immune function, antithrombotic properties with decreased platelet aggregation, increased fibrinolysis via decreased plasminogen activator inhibitor-1 activity, and decreased metalloproteinase activity with decreased macrophage activity and improved endothelial motor dysfunction (18). Possibly the most important pleiotropic statin effect is the anti-inflammatory effect already discussed in relation to decreased hsCRP activity (16).

GLITAZONES

Glitazones appear to offer multiple CV benefits that are just now being understood, and go far beyond plasma glucose reduction via their well-established augmentation of insulin sensitivity (19,20). One of these benefits is a significant contribution to triglyceride reduction and high-density lipoprotein elevation with pioglitazone, established as much more effective than rosiglitazone for these nonglucose-related effects. Also, pioglitazone does not raise apolipoprotein B nearly as much as rosiglitazone. In addition, the glitazones, especially pioglitazone, through the peroxisome proliferator-activated receptor (PPAR)-gamma (20) are receiving much attention by contributing significant pleiotropic benefits similar to the statins. These pleiotropic benefits include enhanced nitric oxide synthetase, inhibition of inflammation, normalization of endothelial function, inhibition of metalloproteinases and inhibition of smooth muscle cell migration. When these pleiotropic effects are reviewed, it can be seen that they are very similar to the pleiotropic effects of statins, which appear important in the reduction of CV events associated with statins.

There are now medications with combined PPAR-alpha and -gamma activity undergoing phase II clinical studies (21), and it is possible that additional significant blood lipid, diabetic and CV contributions from these medications may be discovered. However, Nissen et al (22) reported that muraglitazar, which is one of the new PPAR-alpha/gamma agonists,

caused an increase in the composite end point of death, myocardial infarction (MI), stroke, transient ischemic attack and congestive heart failure (CHF) compared with placebo or pioglitazone. Their analysis was based on phase II and phase III clinical trials released under public disclosure laws for the United States Food and Drug Administration advisory committee (22). Nevertheless, only extensive clinical testing and trials will establish whether there is a problem or whether valuable new combined clinical benefits could be provided.

THE CV CONTINUUM

The CV continuum has a pleiotropic meaning, but in general can be defined as the continuous relationship among many mechanisms affecting the CV system. It can be seen in the relationship between CV-related problems, such as hyperlipidemia and hypertension, and the medications that help to control these problems. For example, the antihypertensive class of medications known as angiotensin receptor blockers block the angiotensin I receptor for angiotensin II. This receptor mediates many harmful effects of angiotensin II, such as vasoconstriction, hypertension, salt or water retention, and remodelling. At the same time, statins have been shown to downregulate this angiotensin I receptor (23). This provides a ready explanation of how one mechanism and one medication for one problem connect to another problem. Therefore, statins can contribute to blood pressure control by reducing the systolic and diastolic pressure through downregulation of this receptor while reducing the LDL level. At the same time, an angiotensin receptor blocker can help stabilize the endovascular endothelium as the statins do. The concept of the CV continuum adds further emphasis to its importance in the prevention and control of all diseases affecting the CV system.

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) Study (24) showed the importance of the CV continuum, as demonstrated by the benefit of one specific angiotensin-converting enzyme inhibitor (ACEI), perindopril. In this study of 12,218 patients, perindopril was compared with placebo. One-half of the patients received the study drug and the other half received placebo. Both male and female patients were included, all of whom were over 18 years of age, had documented CAD and no evidence of CHF at the onset of the study. Perindopril in a dose of 8 mg per day versus a placebo was administered over 4.2 years. The primary end point was a composite of CV mortality, nonfatal MI and cardiac arrest with successful cardiopulmonary resuscitation. Secondary end points consisted of the composite of total mortality, nonfatal MI, hospital admission for unstable angina (ACS) and cardiac arrest with successful cardiopulmonary resuscitation; CV mortality and nonfatal MI; individual components of these secondary outcomes; and coronary artery revascularization, stroke and admission for CHF. In regard to the primary end point, perindopril was associated with a favourable RR reduction (RRR) of 20% (P=0.0003). In addition, all total and individual primary end points showed a favourable RRR. There also was a favourable RRR for the combined first end points of the secondary end points studied. A total of 50 patients were treated to benefit one and results were consistent in all predefined subgroups. Also, benefits occurred in patients already receiving recommended preventive medication, including platelet inhibitors in 92% of patients, hypolipidemics in 70% and beta-blockers in 62%.

The PERindopril-Thrombosis, InflammatioN, Endothelial Dysfunction and Neurohormonal Activation Trial (PERTINENT) was an important substudy of EUROPA (25). It showed the beneficial pleiotropic effects of the specific ACEI, perindopril, and their overlap into different processes relevant to the CV system. Another example of the incredible breadth of the CV continuum is demonstrated by how harmful mechanisms can be altered favourably by a specific medication, such as perindopril, to yield clinical benefit (25). PERTINENT compared the effects of perindopril versus placebo for one year, in serum incubated with human umbilical vein endothelial cells. In patients taking perindopril there was a statistically significant increase in endothelial cell nitric oxide synthetase activity, a statistically significant decrease in apoptosis, a statistically significant decrease in the activity of tumour necrosis factor-alpha and a statistically significant decrease in von Willebrand factor activity. These are all potential mechanisms for the improvement of endothelial cell function. The conclusions of PERTINENT were that the specific ACEI, perindopril, improves thrombosis, inflammation and endothelial dysfunction. In addition, these important vascular and antiatherosclerotic effects may help explain the positive results of the EUROPA study.

The Heart Protection Study (HPS) (26) supported the CV continuum using simvastatin, a statin. In over 20,000 patients, one-half of whom received simvastatin versus placebo, it was shown that in patients at high CV risk with a starting LDL level of less than 100 mg/dL, simvastatin was as beneficial in high-risk patients with LDL levels between 100 mg/dL and 130 mg/dL as in patients with LDL levels greater than 130 mg/dL. There is, therefore, support for the implication that statin pleiotropic effects occur regardless of starting LDL level and the extent of LDL reduction.

With ACS patients, sudden statin withdrawal, such as that which occurs after hospital admission, was shown to increase ACS event rates (27). This is consistent with the pleiotropic effects of statins and their importance in the CV continuum.

Whether aortic stenosis (AS) fits as part of the CV continuum is problematic. The association was made that later in life the disease is exacerbated by an elevated LDL or elevated lipoprotein (a) level, and that statin use may slow the development of AS (28). On the other hand, a recent limited study (29) failed to show an association or a benefit from statin use in limiting the development of AS. Therefore, the issue remains open. From the perspective of the practicing clinician, seniors at the highest risk of developing atherosclerotic CV disease are also at risk for developing AS. Until the issue can be resolved, it appears appropriate to treat such patients' blood lipids aggressively.

BASIS OF LOWER LDL GOAL IN HIGH-RISK PATIENTS

Three key studies advance the desirability of an even lower LDL level (70 mg/dL) for high-risk CV patients. The Reversal of Atherosclerosis With Lipitor (REVERSAL) study showed greater coronary plaque stabilization in ACS patients using 80 mg of atovastatin per day, as studied by intravascular ultrasound. This was associated with achievement of a mean lowest LDL of 79 mg/dL (1). In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, ACS problems decreased in patients taking 80 mg of atorvastatin per day, associated with a mean lowest LDL level of 62 mg/dL (2).

The Treating to New Targets (TNT) study evaluated stable CAD patients taking 80 mg of atorvastatin per day and found significant clinical benefit associated with a mean lowest LDL level of 77 mg/dL (3). In this particular study, however, there was no overall mortality advantage for using 80 mg of atorvastatin per day versus 10 mg per day. Liver aminotransferase levels were higher in the 80 mg per day group.

THE METABOLIC SYNDROME

Much emphasis has been placed on the metabolic syndrome, more specifically known as the CV dysmetabolic syndrome (30). If any three of the following five conditions are present, the metabolic syndrome is considered present:

1. Triglycerides 150 mg/dL or greater
2. High-density lipoprotein less than 40 mg/dL
3. Blood pressure 130/85 mmHg or greater
4. Waist girth greater than 102 cm
5. Fasting glucose 110 mg/dL or greater

The syndrome has been proclaimed the most prevalent medical problem in the United States and the developed world. Furthermore, the syndrome has been discussed as if it were a specific disease entity. This is now being called into question because the so-called syndrome may simply be an association of conditions present in a sedentary population with specific genetic tendencies, eating a poor diet.

ALTERNATIVE MEDICATIONS

Policosanol is a sugarcane wax extract used as the most prevalent lipid-lowering medication in Cuba. It was reported to decrease LDL up to 29% with a standard dose of 10 mg twice a day (31). However, Wright et al (32), in a clinical follow-up of patients either not tolerating statins or not reaching their LDL target despite maximum treatment with a statin, found that in both groups, the use of policosanol resulted in an average 17% reduction of LDL, less than reported in Cuba. Nevertheless, it offered additional beneficial LDL lowering and has been shown to be safe and well-tolerated. In addition, as part of the CV continuum, policosanol appears to have beneficial pleiotropic effects as in the case of statins, ACEIs and glitazones. Pleiotropic effects associated with policosanol include (31) decreased platelet aggregation, decreased LDL oxidation, decreased thromboxane production, stabilization of the arterial endothelium, decreased foam cell production and reduced hypertension. This alternative medication has significant value and is now readily available in the United States as One-A-Day Cholesterol Plus (Bayer Consumer Care, USA) from a dependable source. Each vitamin tablet contains policosanol 10 mg and can be administered safely twice daily to achieve the recommended LDL-lowering dose.

Coenzyme Q10 is still considered to have an uncertain benefit to risk ratio but there is suggestive information that its use can decrease the myositis-causing toxicity of statins (33). When considering the function of this coenzyme, this possible benefit seems reasonable because coenzyme Q10 plays a role in mitochondrial energy transduction, is a functional element in all cell membranes, plays an apparent role in regeneration of redox capacity and has antioxidant abilities (34). It also plays a part in the control of membrane channels and their biosynthesis; this was shown to be inhibited by statins. Statins also inhibit the functional role of coenzyme Q10 in mitochondria and the endoplasmic reticulum. An appropriate dose for decreasing myositis risk from statins is coenzyme Q10 administered as 100 mg twice daily after meals.

RED WINE

What nicer CV risk reduction treatment could there be than red wine? Its benefit is not rigidly proven through statistical significance but very suggestive evidence is available. The alcohol component itself has reported CV benefits, including decreased insulin resistance (35) and antiplatelet effects (36). Also, polyphenols from red wine (35) appear to offer benefits such as a resultant increase in nitric oxide, with the associated CV benefits of vasodilation, inhibition of cell growth and migration, decreased platelet aggregation and decreased cell adhesion. Also, red wine, dark chocolate and green tea are the richest known sources of flavonoids (37), which offer significant CV benefit by inhibiting the oxidation of LDL.

CONCLUSION

There is now major evidence that aggressive reduction of total and LDL cholesterol can decrease the morbidity and mortality of CAD. In addition, decreasing inflammatory risk factors may be important. Imparting such knowledge supported by evidence remains a significant problem, as in all aspects of medicine where continuous quality improvement regarding management remains a significant issue. Pharmacological and device therapies for CV disease remain important for the foreseeable future, but genetic therapy is likely to be in the forefront in the more distant future.

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