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Improving Cardiovascular Risk Assessment to Optimize Therapy

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Abstract

Background: Quantifying ten-year cardiovascular risk can be challenging. Different online risk calculators provide different risk estimates and online risk calculators use only one point in time. However, risk factors occur over the lifetime of the individual. **Purpose:** This manuscript provides three solutions to improving ten-year cardiovascular risk assessment in individuals at intermediate risk. **Methods:** Measuring Lipoprotein(a)—Lp(a) is recommended for assessing cardiovascular risk in all individuals who are in the intermediate risk category by standard online risk calculators. Lp(a) is primarily determined by genetic inheritance. It has the undesirable properties of being proatherosclerotic, proinflammatory, and prothrombotic. Measuring apolipoprotein B (apo B) provides a good index of the number of atherosclerotic particles present. Studies have demonstrated that small, dense LDL cholesterol particles are more atherogenic than larger, less dense LDL cholesterol particles. Measuring high sensitivity C-reactive protein (hsCRP) provides a good estimation of the degree of inflammation in the vascular system. Inflammation is a critical component of heart attacks and strokes. It is increased in diabetes and obesity. Treatment to reduce inflammation results in a reduction of cardiovascular events, independent of lipid values. **Results:** The above three risk factors should be measured in all patients with an intermediate risk score. Routine assays are readily available at a reasonable cost. They are independent risk factors for cardiovascular disease. Their recommendation is based on the pathophysiology of atherosclerotic cardiovascular disease. Successful therapy will result in the decrease of each of these risk factors. **Conclusion:** The recommended approach will improve the assessment of cardiovascular risk and guide the physician and patient to the correct treatment recommendations.

Keywords

Cardiovascular Disease, Atherosclerosis, Risk Equations, Apolipoprotein B, Lipoprotein(a), High Sensitivity C-Reactive Protein

1. Introduction

Assessing the ten-year cardiovascular risk is an important function of all primary care physicians. Not only does this assessment provide a prognosis for the patient, but it also dictates the aggressiveness of the physician's therapy. The traditional approach is to utilize one of the risk score calculators available on the internet (e.g., the American Heart Association risk calculator) [1]. The most common risk category is that of "intermediate risk", which provides a cardiovascular incidence between 7.5% and 19.9% chance of having a cardiovascular event in the next 10 years [2]. This range of risk is much too broad to specifically define a treatment strategy, such as dietary intervention and lifestyle changes, oral medication, and/or injectable medication. Further refining the risk can be accomplished by measuring three readily available blood tests. These three tests are: 1) Lipoprotein(a): (Lp(a)), 2) Beta apolipoprotein (apo B), and 3) high sensitivity C-reactive protein (hsCRP). Each test characterizes various aspects of the atherosclerotic process and permits improved risk stratification. These tests are not included in the majority of internet risk calculators. Since atherosclerosis is a reversible condition, aggressive therapy may be warranted depending upon the patient's degree of risk. The following case illustrates the important use of further refinements of the degree of risk.

GT is a 57-year-old male patient seen one year ago for his annual examination. He is presenting now for another evaluation since his 53-year-old brother recently had a myocardial infarction. He has no known cardiovascular risks (except for a family history of cardiovascular disease) and takes no medication. His lipid panel at the time of his last visit demonstrates the following: total cholesterol 198 mg/dL, triglycerides 140 mg/dL, HDL cholesterol 40 mg/dL, and a calculated LDL cholesterol of 130 mg/dL. His blood pressure is 128/80 mmHg and the ACC/AHA calculated 10-year cardiovascular risk is in the intermediate category of 7.9%. Because of his brother's recent heart attack, the patient wants "to do something now" but does not want to take statins unless it is absolutely necessary. His physician ordered the three tests below to further evaluate his cardiovascular risk. The results demonstrate the following: Lp(a) = 90 mg/dL (normal < 30 mg/dL), Apo B = 145 mg/dL (normal ≤ 90 mg/dL), and hsCRP = 5.5 mg/L (normal ≤ 1.0 mg/L). An explanation of why these results aided his physician in risk assessment follows.

What is Lipoprotein(a) (Lp(a))? Lp(a) is an apolipoprotein with a series of amino acid kringles covalently linked via a disulfide bond to the apolipoprotein B100 moiety on the LDL particle (**Figure 1**). A kringle is a structural motif or

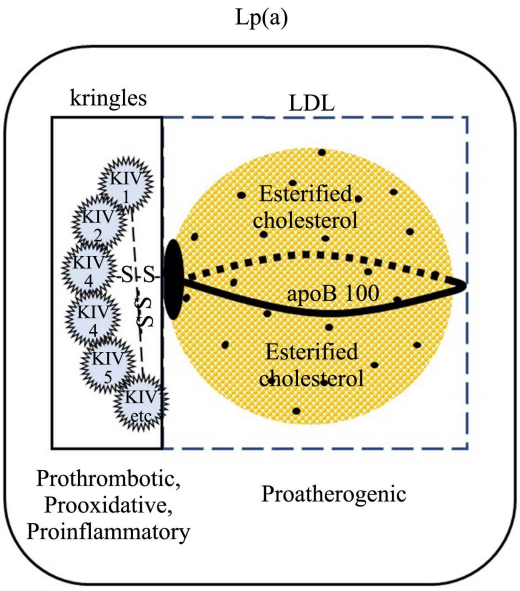

Figure 1. Lipoprotein(a) is an LDL cholesterol ester-containing particle with a covalently attached amino acid side chain composed of kringles. Kringle numbers 4 and 5 are also part of the plasminogen molecule.

domain seen in certain proteins in which a fold of large loops is stabilized by disulfide bonds. The Lp(a) particle has a high content of cholesterol esters that can become easily oxidized, thereby increasing the risk for atherosclerosis. **Figure 1** illustrates the structure of the Lp(a), which includes both the LDL particle and the amino acid kringles that are covalently linked to the LDL apo B 100 lipoprotein.

Mechanisms by which Lp(a) increases the risk of atherosclerosis. Lp(a) (particularly kringle 4) is structurally homologous with plasminogen's kringles causing inhibition of plasminogen activation by inhibiting tissue plasminogen activator. The result is blockage of the conversion of plasminogen to plasmin, the prime protein that causes the breakdown of the fibrin clot into fibrin degradation products (**Figure 2**). This blockage ultimately results in an inhibition of clot lysis [3]. This mechanism is important, as arterial thrombosis is often the final arterial event causing a myocardial infarction.

Lp(a) also increases the risk of atherosclerosis by other mechanisms such as: 1) promoting macrophage foam cell formation, 2) binding to vascular endothelium and increasing adhesion molecule and chemoattractant protein-1, and 3) activation of epidermal growth factor, vascular endothelial growth factor-2, and monocyte chemotactic protein-1. All of these activities increase access of the monocytes (macrophages) into the arterial wall to form foam cells [4]. Foam cells coalesce in the arterial wall to form fatty streaks, the precursor of atherosclerotic plaques [5].

Measurement of Lp(a). There are 34 isoforms of Lp(a) (two or more functionally similar proteins that have a similar but not identical amino acid sequence), and this particle can be measured either as an isoform-dependent or an

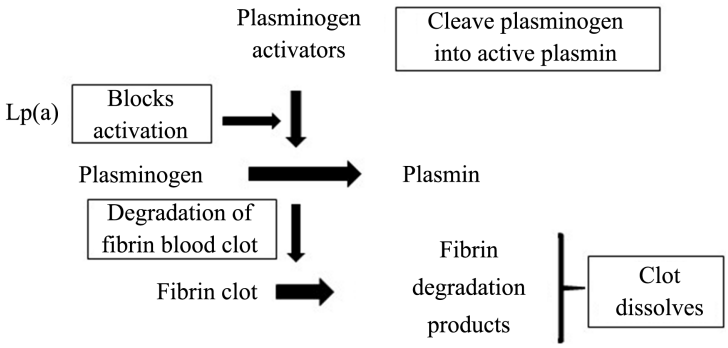

Figure 2. One mechanism by which Lp(a) enhances clot formation and increases the risk of atherosclerosis. Lp(a) blocks the activation of plasminogen and thereby enhances clot formation and stability. This activity, in turn, favors a coronary artery thrombosis.

isoform-independent method. In the isoform-dependent method, the entire mass of Lp(a) is measured in mg/dL [6]. There is much variation in the concentration of Lp(a) measured depending on the number of kringle IV-repeat motifs present. Unfortunately, most of the antibodies used to measure Lp(a) cross-react with several K-IV repeats which may lead to under- or overestimation of the Lp(a) concentration. The currently recommended assay is the isoform-independent method that measures kringle IV (type 9) in nmol/L [7].

Evidence that Lp(a) is associated with increased risk of cardiovascular disease. It is estimated that 20% of the world's population has elevated Lp(a) levels in excess of 50 mg/dL [8]. A positive correlation between elevated Lp(a) levels and increased risk of myocardial infarction has been shown in many types of studies. For example, in a study of 2047 patients experiencing either a myocardial infarction or cardiovascular death, the Lp(a) level was an independent risk factor for cardiovascular events [9]. In a review of 36 prospective studies encompasing126,634 patients, there was a continuous, independent, and positive association of Lp(a) concentration with the risk of cardiovascular disease above an Lp(a) concentration of 30 mg/dL as shown in **Figure 3**.

Finally, in studies of clinical trials examining the association of Lp(a) and risk for cardiovascular disease and stroke, the data show a continuous, independent positive association [10] [11]. Thus, knowing the Lp(a) level will alter the prognosis in many patients, including those with either pre-diabetes or diabetes.

2. What Treatments Lower Elevated Lp(a)?

Diet and exercise has been the mainstay for the initial treatment for individuals with elevated lipids and moderate to high cardiovascular risk. However, these interventions have not been shown to significantly lower Lp(a) levels [12]. In 184 postmenopausal women, estrogen treatment was associated with a 20% reduction in Lp(a) [13]. In the Heart and Estrogen/progestin Replacement study (HERS), estrogens lowered Lp(a) levels (5.8 mg/dL), and Lp(a) was an independent risk for recurrent cardiovascular events [14]. However, the Heart and Estrogen/Progestin Replacement study and the Women's Health Initiative [14]

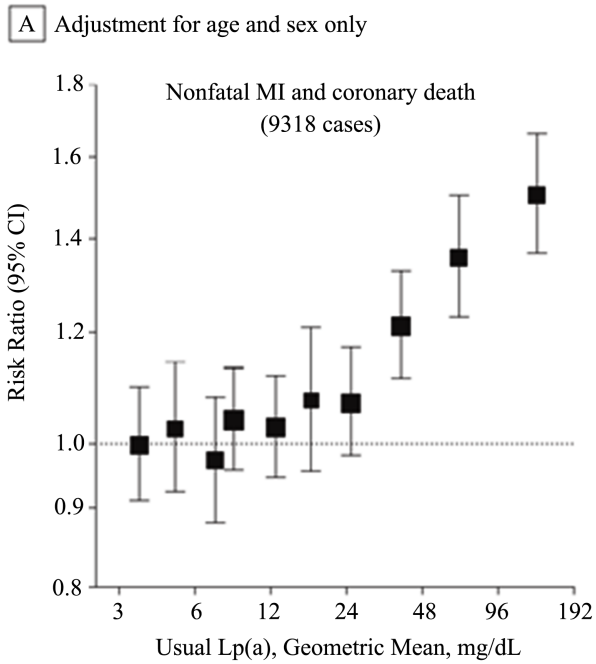

Figure 3. Increasing cardiovascular risk for non-fatal myocardial infarction and coronary artery death as Lp(a) continues to rise above 30 mg/dL. (Adapted from Ref. [10]).

noted that the increased adverse effects of estrogen (including breast cancer) and thromboses (including stroke), "outweighed any benefit on cardiovascular disease". Estrogen replacement therapy is not recommended as a mechanism to lower Lp(a) levels.

Older clinical trials have shown that niacin lowers Lp(a) levels by 23% - 40% [14]. However, in the AIM HIGH and HPS2 THRIVE clinical studies, niacin was associated with a significant risk for new onset diabetes mellitus, myopathy, increased risk of bleeding and increased risk of infections [15] [16]. Most patients at moderate-to-high risk for cardiovascular disease are started on a statin. However, the mechanism for statin reduction in LDL cholesterol is a decrease in hepatic cholesterol synthesis, causing an increase in LDL-receptors on the surface of the liver. Lp(a) is not significantly cleared via this mechanism and statins have actually been shown (in some studies but not all) to modestly increase the Lp(a) level by 10% - 20% [17].

PCSK9 inhibitors have been proven to lower LDL cholesterol significantly in patients with pre-existing cardiovascular disease who were not able to reduce their LDL cholesterol to a prespecified goal. PCSK9 inhibitors increase the LDL receptors on the surface of the liver, thus improving the lowering of the LDL cholesterol level. Clinical trials of evolocumab (a PCSK9 inhibitor) showed that Lp(a) was reduced by 27% in subjects with a baseline Lp(a) level > 37 nmol/L versus only 7% in those with Lp(a) levels less than 37 nmol/L [18]. Similarly, alirocumab (another PCSK9 inhibitor) showed a similar decrease in Lp(a) in subjects with elevated baseline Lp(a) levels [19]. However, PCSK9 inhibitors have not been approved by the FDA for the purpose of lowering Lp(a). Recently,

inclisiran (a PCSK9 protein production blocker) has been FDA approved to lower LDL cholesterol, and it also lowers Lp(a) [20]. New therapies to lower Lp(a) are in clinical trials [21].

3. Who Should Be Screened for Lp(a)?

In the United States, the National Lipid Association has recommended screening for Lp(a) in the following situations [11]:

1) For individuals ≥ 20 years of age with a family history of premature cardiovascular events to redefine cardiovascular risk.

2) In individuals with atherosclerotic cardiovascular disease (ASCVD) in the absence of traditional risk factors.

3) In subjects with familial hypercholesterolemia defined as an LDL cholesterol ≥ 190 mg/dL.

4) In subjects at extreme risk of ASCVD and to identify individuals who may benefit from the newer atherosclerotic therapies (e.g. PCSK9 inhibitors or blockers).

5) In individuals with an ASCVD risk between 7.5% and 19.9% when the decision to start statin therapy is uncertain and to improve risk stratification in primary prevention.

6) In individuals between 5% and 7.5% ASCVD risk when the decision to use a statin is uncertain, and to improve the risk stratification in primary prevention.

7) In individuals with less than anticipated LDL cholesterol lowering despite good adherence to statin medications.

8) In individuals with a family history of elevated Lp(a).

9) In subjects with calcific valvular aortic stenosis.

10) In individuals with recurrent or progressive ASCVD despite optimal lipid-lowering therapy.

4. Apolipoprotein B (apo B)

Apolipoprotein B is a very important protein that is part of the structure of every atherosclerotic lipid particle (**Figure 1**). It is secreted from the liver (as apo B 100) and from the intestine (the latter in a truncated form as apo B 48) in either very low density lipoproteins (VLDL) or in chylomicrons, respectively. It remains in lipoproteins during the conversion of VLDL to intermediate density lipoproteins (IDL) and finally into low density lipoproteins (LDL). Among the most essential functions of apo B is the binding to LDL receptors on the liver that remove atherogenic lipoproteins from the circulation. Since there is only one apo B lipoprotein for each atherogenic lipid particle, it provides an accurate estimate of the number of circulating atherogenic particles.

There is a 1:1 relationship between apo B and all the atherosclerotic particles (low density lipoprotein, intermediate-density lipoprotein, very-low-density lipoprotein, and chylomicron remnant particles). There is a major difference between measuring apo B and non-HDL cholesterol to assess cardiovascular risk.

Measuring apo B is an indication of the number of atherogenic lipoprotein particles independent of the particle's cholesterol content. In contrast, non-HDL cholesterol measures the cholesterol content in all atherogenic lipid particles and therefore does not provide an accurate quantitation of the number of individual particles. The number of small LDL particles determines the degree of ASCVD risk.

Recent data have shown that apolipoprotein B (apo B) is a better marker for atherosclerotic events than LDL cholesterol [22]. For example, 131 coronary artery disease naïve patients on statin therapy were followed for five years for new onset coronary artery disease. There was a 45% increase in residual risk of coronary artery disease per unit increment in natural log of the apo B level. Reducing apo B levels may be required in order to reduce the incidence of cardiovascular events [23].

In a prospective cohort analysis of 389,539 subjects in the UK Biobank and in the FOURIER and IMPROVE-IT clinical trials the risk of myocardial infarction was assessed. Apo B predicted the myocardial infarction risk best (compared to triglycerides and non-HDL cholesterol) by assessing the number of apo B containing lipoproteins, independent from their lipid content or type of lipoprotein (LDL or TG-rich) [24]. In another study of 17,035 subjects who were evaluated to determine whether LDL-lowering therapy reduced the cholesterol indices and apo B levels to the same extent showed that reductions in apo B were superior to either LDL cholesterol or non-HDL cholesterol ($P < 0.001$) [25]. In patients with high triglyceride levels, commonly seen in patients with diabetes or metabolic syndrome, measuring apo B is a better biomarker for cardiovascular risk than LDL cholesterol, since non-LDL lipoproteins (IDL cholesterol, VLDL and remnant particles) may have an increased effect on cardiovascular risk [26] [27] (**Figure 4**).

The measurement of apo B is standardized, automated, and relatively inexpensive. It can be performed on non-fasting samples, and population reference values are now available. Many studies have demonstrated that small LDL particles are much more atherogenic than larger LDL particles [28]. These small LDL particles contain less cholesterol than large LDL particles and yet increase cardiovascular risk to a greater extent. This is the reason that using the cholesterol

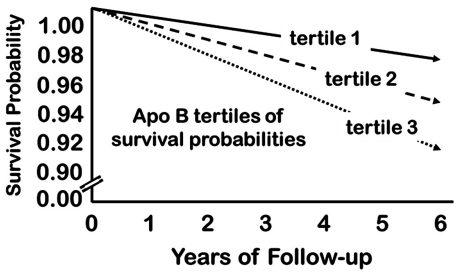

Figure 4. Kaplan-Meier survival analysis across tertiles of apolipoprotein (apo) B and A-I levels from the Quebec Cardiovascular Study. The lower the Apo B, the lower the mortality. Adapted from reference [27].

content of LDL cholesterol as the primary gauge of risk is inaccurate. For example, if the LDL concentration is normal but the number of LDL particles is increased as assessed by an apo B level greater than 120 mg/dL, the risk can be twice the expected amount. The goal for apo B level should be less than 90 mg/dL [27].

Apo B is often a better indicator of CV risk than LDL cholesterol. The focus on LDL cholesterol has been helpful, but may need to be modified to help address the residual risk noted in subjects being treated with statins and the newer medications that will lower LDL cholesterol to significantly lower levels than in the past. Measuring LDL particle concentration either directly with a Nuclear Magnetic Resonance lipid panel or with a surrogate measure of the LDL particle concentration with apo B levels, has been shown to be better predictors of CV risk than non-HDL cholesterol or LDL cholesterol [29].

5. High Sensitivity C-Reactive Protein—Inflammation

Cardiovascular disease is a state of increased arterial inflammation [30]. Inflammation can be beneficial in some medical conditions such as bacterial infections, but when it occurs in the coronary arteries, it has serious consequences. It damages the endothelium lining the arteries, which is essential for preventing blood clotting and transmission of toxic substances (including cholesterol-containing particles) into the arterial wall. Inflammation is mediated through the liberation of various cytokines released by leukocytes in response to noxious stimuli.

The importance of an intact, healthy arterial endothelium cannot be overestimated. Many animal studies have clearly demonstrated that when the arterial endothelium is physically damaged, a cascade of blood clotting events is initiated such that an arterial obstruction often results [31]. An intact, healthy endothelium also secretes vasodilating substances, such as nitric oxide, which dilate the artery and prevent obstruction. Recent data indicate that approximately 25% of myocardial infarctions are not secondary to atherosclerotic plaque rupture but are caused by damaged endothelium [32].

A key mechanism whereby inflammation enhances atherosclerosis is the increased adhesion of monocytes to the blood vessel wall (**Figure 5**). A normal endothelium resists this adhesion and the monocytes in the blood continue their path through the vasculature. However, inflammation results in the endothelial secretion of various adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 binds to leukocytes, particularly the monocyte and T lymphocyte [33]. VCAM-1 is selectively expressed at sites of atheroma formation, particularly branch points of arteries. Nitric oxide, secreted by endothelial cells, inhibits VCAM gene expression and is therefore "atherosclerosis protective".

Once the monocyte is adherent to the endothelium, it gains access to the intima by diapedesis between endothelial cell junctions. Within the arterial intima,

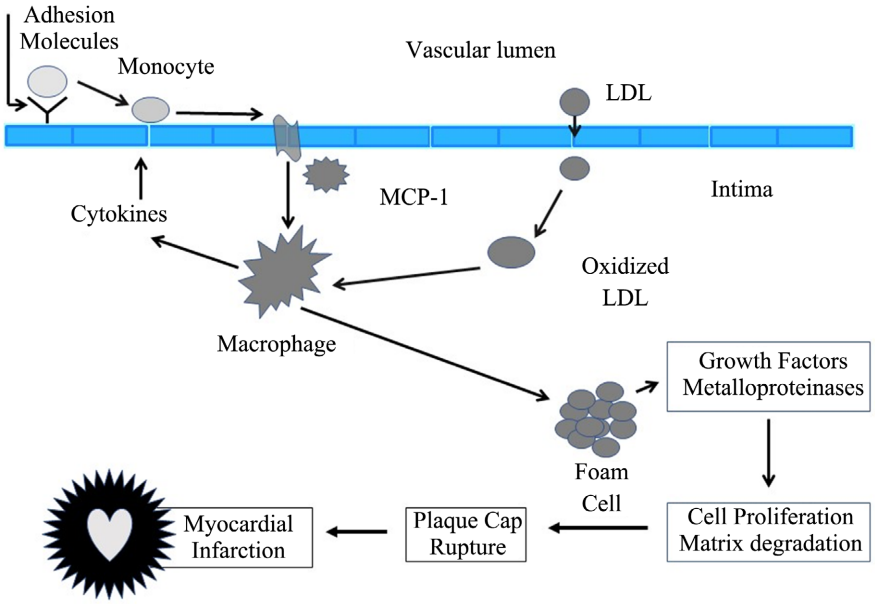

Figure 5. Without inflammation, monocytes do not adhere to the endothelial surface. However, with inflammation, the adhesion molecules bind monocytes, triggering their penetration into the intima. Low density lipoprotein-cholesterol (LDL-C) and Lp(a) also penetrate through the endothelium. LDL-C becomes oxidized and is taken up by the macrophage leading to foam cell formation. Oxidized LDL-C and Lp(a) increase cytokine formation, but Lp(a) also increases MCP-1 (monocyte chemotactic protein-1) and other molecules that increase the cascade toward atherosclerosis.

the monocytes change their morphology and become macrophages. Macrophages subsequently replicate and secrete various growth factors and cytokines. These macrophages coalesce and form foam cells, the earliest form of atherosclerotic plaque. Once a plaque forms, it may continue to grow, containing many different constituents including smooth muscle cells, cytokines, lipoprotein breakdown products, and cholesterol molecules. Of critical importance to stabilizing the plaque is the structure of the plaque's fibrous cap. This cap sequesters the thrombogenic lipid-rich core from the bloodstream and the circulating coagulation proteins. Inflammation can stimulate the production of metaloproteinases which degrade proteins that stabilize the cap. If this cap fractures, a series of events ensue that result in platelet adherence and often an arterial thrombosis. If this thrombosis obstructs a coronary vessel, a myocardial infarction may result. Recent studies suggest that approximately 75% of myocardial infarctions occur in this fashion [33].

However, approximately 25% of myocardial infarctions do not have an identifiable atherosclerotic plaque at the site of thrombosis. For these events, endothelial disruption or cell death is the likely pathogenic mechanisms. This cell death may result from localized inflammatory mediators. Alternatively, degradation of the subendothelial basement membrane by metalloproteinases may result in loss of adhesion of the endothelium to the vascular wall.

Because inflammation is a diffuse, complex process, its estimation in humans

is not a simple process. By necessity, surrogate markers of inflammation are used to provide a semi-quantification of the severity of the inflammation. Although several markers have been suggested, the most common one is C-reactive protein (CRP) [34]. This protein is secreted by the liver in response to many types of noxious stimuli that cause inflammation. The standard assay for CRP that is used to assess the inflammatory response to infection and autoimmune disease is not sufficiently sensitive to quantitate the inflammation accompanying atherosclerosis. Therefore, a high-sensitive assay (hsCRP) was developed which will detect C-reactive protein below 1.0 mg/L [35]. Thus, when assessing the degree of inflammation in a patient for atherosclerotic risk, the high sensitivity CRP should always be specified. This assay is performed in most medical laboratories.

Proof of the importance of inflammation has been reported in human studies. In a randomized controlled study of individuals with elevated inflammation (as assessed by hsCRP), the reduction in inflammation with statin therapy was shown to be the significant factor in preventing cardiovascular events [36]. Colchicine, used for many years for its anti-inflammatory properties to control acute gout, has been administered to individuals with a recent myocardial infarction [37]. When compared to a placebo, individuals who received colchicine had a significant reduction in ischemic cardiovascular events. Furthermore, anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of the degree of lipid-level lowering [38]. The immediate beneficial effects of statins (within weeks) in reducing cardiovascular events may be due to their ability to lower systemic inflammation [31]. The basis for this suggestion is the fact that the reduction in LDL cholesterol by statins is too delayed to account for the rapid reduction in inflammation and cardiovascular events that are observed when acute coronary syndrome patients are treated with statins [39].

How should the physician assess the contribution to risk assessment in patients? Most traditional risk assessment algorithms do not include the degree of inflammation in their risk assessments. Therefore, measuring hsCRP in patients with intermediate risk will further quantify the degree of risk in that individual. The normal hsCRP level that indicates minimal risk is an hsCRP of <1.0 mg/L. Levels between 1.0 and 3.0 are average risk and levels above 3.0 mg/dL are of major concern. There are several inflammatory risk factors for atherosclerosis that increase hsCRP such as obesity and diabetes [40]. In addition, inflammatory conditions, such as rheumatoid arthritis, exhibit an increase in cardiovascular events. Controlling these conditions will reduce inflammation and lower cardiovascular risk. HsCRP should be measured in all patients undergoing cardiovascular risk assessment [41].

6. Conclusion

This manuscript has provided three readily available approaches for improving

the risk assessment for patients at intermediate risk as determined by a computerized calculator risk equation. As depicted in the patient described in the introduction, his risk was significantly more than calculated by a risk equation. Knowing this fact, it changed the physician's advice and treatment of the patient to strongly consider statins as well as ezetimibe in addition to improvement in lifestyle behaviors. The physician decided to obtain a confirmation of the presence of coronary atherosclerosis by ordering a coronary artery calcium scan. This was positive with a total Hounsfield score of 453, placing the patient at significantly high risk of a cardiovascular event within the next fifteen years [42]. As this patient illustrates, measuring Lp(a), Apo B, and hsCRP in addition to using a calculated risk equation will provide the physician with improved patient management and prognostic information.

Conflicts of Interest

The authors above have no conflicts of interest in the preparation of this manuscript and all have participated in its creation.

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