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EXPANDING THE SPECTRUM OF BIOMARKERS FOR HEART DISEASE: HOMOCYSTEINE, us CRP AND LIPOPROTEIN(a)

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Abstract:

Taking into consideration that frequently cardiovascular patients do not present major risk factors, there remains a residual risk that can be, at least in part, measured by biomarkers of thrombosis and inflammation, based on clinical trials and clinical observations. This paper presents the role of three biomarkers - Homocysteyne, ultra sensitive C-Reactive Protein and Lipoprotein(a). The official Cardiac and Atherosclerosis Medical Societies conducts expert meetings that publish Recommendations for each of them. These Recommendations may help and guide clinicians as to their decision making regarding prevention of atherosclerotic cardiovascular diseases. Regarding hyperhomocysteinemia a healthy diet is the first choice, before prescribing folic acid and B vitamins supplements. A physician taking any type of nutritional approach to reducing risk should consider a person's overall risk factor profile and personalized diet. As for the inflammatory marker ultra sensitive C-Reactive Protein there is a strong association with risk of fatal vascular events than non fatal vascular events.

Keywords: Biomarkers, Heart disease, Homocysteine, us CRP and Lipoprotein(a), Inflammation

Abbreviations
CRP: C-Reactive Protein
IL-6: Interleukin-6
LP(a): Lipoprotein(a)
us CRP - ultra sensitive C Reactive Protein

Homocysteine, Folic Acid and Cardiovascular Disease

Homocysteine: The American Heart Association has not yet called hyperhomocysteinemia (high homocysteine level in the blood) a major risk factor for cardiovascular disease. No recommendation of widespread use folic acid and B vitamin supplements to reduce the risk of heart disease and stroke. A healthy balanced diet is recommended, rich in fruits and vegetables, whole grains, and fat-free or low-fat dairy products. For folic acid, the recommended daily value is 400 micrograms (mcg).

Citrus fruits, tomatoes, vegetables and grain products are good sources. Since January 1998, wheat flour has been fortified with folic acid to add an estimated 100 mcg per day to the average diet. Supplements should only be used when the diet doesn't provide enough.

Homocysteine is an amino acid in the blood. Too much of it is related to a higher risk of coronary heart disease, stroke and peripheral vascular disease (fatty deposits in peripheral arteries).

Evidence suggests that homocysteine may promote atherosclerosis (fatty deposits in blood vessels) by damaging the inner lining of arteries and promoting blood clots. However, a causal link hasn't been established.

Folic acid and other B vitamins help break down homocysteine in the body. Homocysteine levels in the blood are strongly influenced by diet and genetic factors. Dietary folic acid and vitamins B-6 and B-12 have the greatest effects. Several studies found that higher blood levels of B vitamins are related, at least in part, to lower concentrations of homocysteine. Other evidence shows that low blood levels of folic

acid are linked with a higher risk of fatal coronary heart disease and stroke.

So far, no controlled treatment study has shown that folic acid supplements reduce the risk of atherosclerosis or that taking these vitamins affects the development or recurrence of cardiovascular disease. Researchers are trying to find out how much folic acid, B-6 and/or B-12 are needed to lower homocysteine levels. Screening for homocysteine levels in the blood may be useful in patients with a personal or family history of cardiovascular disease but who don't have the well-established risk factors (smoking, high blood cholesterol, high blood pressure, physical inactivity, obesity and diabetes).

Although evidence for the benefit of lowering homocysteine levels is lacking, patients at high risk should be strongly advised to be sure to get enough folic acid and vitamins B-6 and B-12 in their diet. They should eat fruits and green, leafy vegetables daily. This is just one possible risk factor. A physician taking any type of nutritional approach to reducing risk should consider a person's overall risk factor profile and personalized diet.[1,2]

us PCR - Inflammatory Markers: Circulating inflammatory markers may more strongly relate to risk of fatal versus nonfatal cardiovascular disease events, but robust prospective evidence is lacking. We tested whether interleukin (IL)-6, C-reactive protein (CRP), and fibrinogen more strongly associate with fatal compared to nonfatal myocardial infarction and stroke.
In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), baseline inflammatory markers in up to 5,680 men and women aged 70-82 y were related to risk for endpoints; nonfatal cardiovascular disease (i.e., nonfatal myocardial infarction and nonfatal stroke [n=672]), fatal cardiovascular disease (n=190), death from other cardiovascular causes (n=38), and non-cardiovascular disease mortality (n=300), over 3.2-y follow-up.[3]

Elevations in baseline IL-6 levels were significantly (p=0.0009; competing risks model analysis) more strongly associated with fatal cardiovascular disease (hazard ratio [HR] for 1 log unit increase in IL-6 1.75, 95% confidence interval 1.44-2.12) than with risk of nonfatal cardiovascular disease (1.17, 95% confidence interval 1.04–1.31), in analyses adjusted for treatment allocation. The findings were consistent in a fully adjusted model. These broad trends were similar for CRP and, to a lesser extent, for fibrinogen. The results were also similar in placebo and statin recipients (i.e., no interaction). The C-statistic for fatal cardiovascular disease using traditional risk factors was significantly (+0.017; p,0.0001) improved by inclusion of IL-6 but not so for nonfatal cardiovascular disease events (p=0.20).

In PROSPER, inflammatory markers, in particular IL-6 and CRP, are more strongly associated with risk of fatal vascular events than nonfatal vascular events. These novel observations may have important implications for better understanding aetiology of cardiovascular disease mortality, and have potential clinical relevance.[3]

In the study Lipoprotein(a) the aim were, first, to critically evaluate lipoprotein(a) [Lp(a)] as a cardiovascular risk factor and, second, to advise on screening for elevated plasma Lp(a), on desirable levels, and on therapeutic strategies.

The robust and specific association between elevated Lp(a) levels and increased cardiovascular disease/coronary heart disease risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated LDL cholesterol, is causally related to premature cardiovascular disease/coronary heart disease.[4]

The association is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels. Mechanistically, elevated Lp(a) levels may either induce a prothrombotic/anti-fibrinolytic effect as apolipoprotein(a) resembles both plasminogen and plasmin but has no fibrinolytic activity, or may accelerate atherosclerosis because, like LDL, the Lp(a) particle is cholesterol-rich, or both.

We advise that Lp(a) be measured once, using an isoform-insensitive assay, in subjects at intermediate or high cardiovascular disease/coronary heart disease risk with premature cardiovascular disease, familial hypercholesterolaemia, a family history of premature cardiovascular disease and/or elevated Lp(a), recurrent cardiovascular disease despite statin treatment, ≥3% 10-year risk of fatal cardiovascular disease according to European guidelines, and/or ≥10% 10-year risk of fatal + non-fatal coronary heart disease according to US guidelines.

As a secondary priority after LDL-cholesterol reduction, we recommend a desirable level for Lp(a) < 80th percentile (less than ~ 50 mg/dL).

Treatment should primarily be niacin 1-3 g/day, as a meta-analysis of randomized, controlled intervention trials demonstrates reduced cardiovascular disease by niacin treatment. In extreme cases, LDL-apheresis is efficacious in removing Lp(a). Screening is recommended for elevated Lp(a) in those at intermediate or high cardiovascular disease/coronary heart disease risk, a desirable level < 50 mg/dL as a function of global cardiovascular risk, and use of niacin for Lp(a) and cardiovascular disease/coronary heart disease risk reduction.

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Conflicts of interest

No conflict of interest.

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