



Re-flection

reinventing reinsurance®

C-REACTIVE PROTEIN

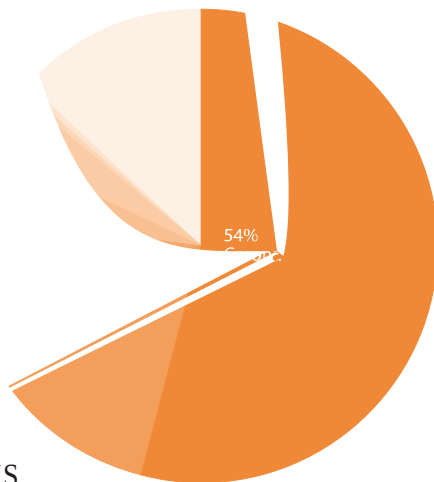
Considerable attention has been given to a study published in the New England Journal of Medicine on Nov. 14, 2002. A large group of healthy women were studied over an eight-year period to determine the prognostic value of measuring C-reactive protein (CRP) in assessing the risk of of M77e Ne protein

>> The idea of measuring CRP in conjunction with acute myocardial infarction dates back to the 1940s, but the test's lack of sensitivity limited its usefulness in detecting the lower degree of inflammation typically found in Coronary Artery Disease (CAD). This test of inflammatory activity is, unfortunately, also not specific to coronary artery inflammation; meaning that elevations of CRP may be due to many other types and locations of inflammation as well. More recently, the availability of highly sensitive assay systems have allowed the development of high sensitivity C-reactive protein (hsCRP) assays that can detect slight elevations in CRP consistent with the amount of inflammation found in coronary arteries or in other parts of the vascular system. CRP testing has a lower limit of sensitivity—about 3 mg/L, whereas hsCRP assays can measure as little as 0.175 mg/L. The problem of specificity has not been satisfactorily addressed, but the level of CRP elevation and correlation with clinical history can be helpful in determining why the CRP is elevated.

What does an elevated CRP mean? CRP is an acute-phase reactant. During severe infection or inflammation, blood concentrations of CRP may increase by a factor of 500 or more. CRP is a protein released into the bloodstream when there is active inflammation in the body. CRP appears to play a role in the process of inflammation by attracting the cells that fight infection. Like other acute-phase reactants, its role in the inflammatory process is probably complex, and it may also promote thrombosis or clotting. The inflammation leading to CRP elevations may be due to various causes, such as infection, injury or conditions like arthritis. Since an inflammatory process is now thought to play a significant role in CAD, it is reasonable to expect that CRP will also be elevated in this condition.

Coronary artery inflammation is thought to produce relatively modest rises in CRP. In general, CRP levels of greater than 15 mg/L should be investigated for non-CAD types of inflammation or infection.² Within the usual test range of hsCRP (<0.7mg/L->3.8mg/L), there is a direct linear relationship between the level of CRP and the risk of cardiovascular events. There may also be a relationship between hsCRP levels and the risk of rupture of soft or vulnerable plaques.³ Post-mortem studies have correlated CRP levels with the appearance of plaque in the coronary arteries, suggesting that hsCRP may be a reasonable biological marker for plaque instability, and by extension, plaque rupture and acute thrombotic events.

Graph 1
Percent Breakdown of Deaths From
Cardiovascular Diseases
United States: 2000



Source: CHC/NCHS.
Heart Disease and Stroke Statistics—2003 Update,
American Heart Association

of coronary atherosclerosis were seen in 78.3 percent of the total study group. A further study of young trauma victims examined in the Pathobiological Determinants of Atherosclerosis in Youth Study (PDAYS)⁷ showed intimal lesions in all of the aortas and more than half of the right coronary arteries of the youngest age group (15–19 yrs). It is clear from these and other studies that CAD and other forms of cardiovascular disease begin even in the teens. In our society, with such a high prevalence of obesity, hypertension, smoking and diabetes, it is perhaps surprising that CAD is not universally present. As more tests are developed to measure this complex disease process, perhaps some day the medical community will realize that all humans are at risk in one way or another.

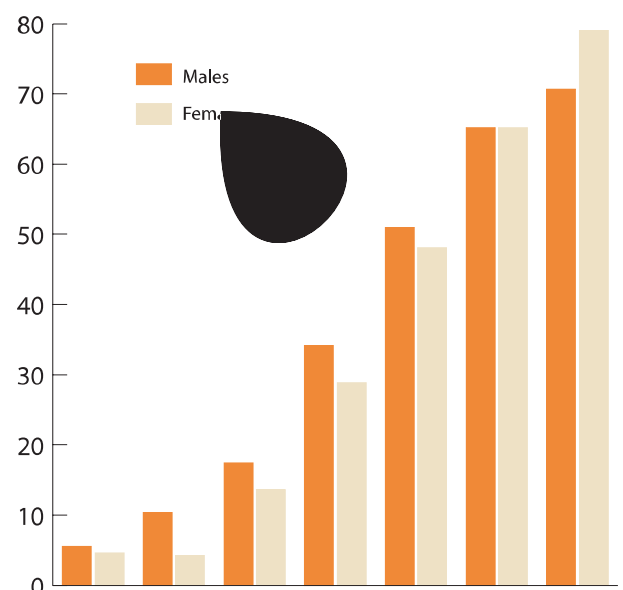
A significant number of underwriting requirements exist primarily to detect this coronary risk. These include blood tests, EKGs, stress tests, paramedical examinations and attending physician statements. These clearly represent a significant cost to the insurance industry, but also provide some level of protection against premature claims experience. We have developed a certain degree of familiarity with these tests and how to use the information they provide to stratify risk.

Historically, as an industry we have applied extra premiums to the policies of people who have already developed clinically recognized CAD, whether this is

established by abnormal EKGs, ECHOcardiograms, stress testing, perfusion studies, angiography, or medical reports of ischemic symptoms. The advent of lipid testing has changed the way CAD is evaluated. While it is accepted that hyperlipidemia plays a role in the pathogenesis of CAD, it appears that not all people with known hyperlipidemia have clinically recognized CAD or will even develop it. Hypercholesterolemia (specifically LDL-cholesterol) is recognized as a risk factor for the development of CAD, but its mere presence does not guarantee that the coronary arteries are already diseased, or indeed that they will ever be diseased enough to lead to angina, infarction or death. The same can be said for all the other known risk factors for the development of CAD such as low HDL-cholesterol, smoking, hypertension, or diabetes. This will likely also apply to CRP.

When evaluating risk factors, the real issue is whether medical underwriters should treat applicants with a propensity or pre-disposition for a disease in the same manner as those who have already demonstrated overt disease. This may very well become the most significant question to face underwriters and the legislators that govern us. We are slowly developing a fuller understanding of the pathogenesis of diseases such as CAD. Scientific publications like the New England

Graph 2
Prevalence of Cardiovascular Diseases in
Americas, Age 20 and Older by Age and Sex
United States: 1988-94



Source: NHANES III (1988-94), CDC/NCHS.
Heart Disease and Stroke Statistics—2003 Update,
American Heart Association

Journal of Medicine have recently published articles suggesting that tests such as hsC-reactive protein have the same prognostic value for CAD as tests like LDL-cholesterol. Assuming we continue to probe into the pathogenesis of CAD, we are likely to find more information pointing to important environmental and/or genetic factors.

In many diseases, the interplay between host and environment determines the outcome. We are all exposed to a plethora of insults to our bodies, yet each of us is a unique individual and we react somewhat differently to these stressors. It is probably safe to say that this also applies to how our coronary arteries respond to the factors that trigger the inflammatory process. Ultimately, we may possess the genetic knowledge that allows us to determine a person's risk of developing serious diseases many years in the future. How we use these early predictors of potential extra mortality will become increasingly important as our knowledge grows.

J. Carl Holowaty, M.D.

1. Ridker P et al. "Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events". N Eng J Med 347:1557-1565, November 14, 2002, Number 20.
2. Braun R. "High Sensitivity C-Reactive Protein: Analysis in an Insurance Population". Insight. Fall, 2002, pp.10-13.
3. Burke A. "Elevated C-Reactive Protein values and Atherosclerosis in Sudden Coronary Death". Circulation. 2002;105:2019-2023.
4. Munford S. "Statins and the Acute-Phase Response". N Eng J Med 344:2016-2018, November 14, 2002, Number 26.
5. Blake GJ. "Projected Life-expectancy Gains with Statin Therapy for Individuals with Elevated C-Reactive Protein Levels". J Am Coll Cardiol. July 3, 2002;40(1):49-55.
6. Joseph A et al. "Manifestations of Coronary Atherosclerosis in Young Trauma Victims—an Autopsy Study". J Am Coll Cardiol. Aug 22, 1993;22(2):459-67.
7. Strong JP et al. "Prevalence and Extent of Atherosclerosis in Adolescents and Young Adults: Implications for Prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study". JAMA. 1999 Feb 24;281(8):727-35.

HERBAL SUPPLEMENTS

The use of herbal supplements in the United States is increasing. Many people feel that herbs are a safer and more natural way to treat ailments than traditional medicine. Although some herbal supplements are safe and effective, others can be dangerous, even life threatening, especially when mixed with other medications. Remember, many powerful traditional medicines such as digoxin and taxol are derived from plant extracts. The difference is that FDA-approved drugs are required to go through rigorous efficacy and safety testing before they are released to the U.S. market; herbal supplements are not. This article includes general information about herbal supplements, followed by information about some specific popular herbs.

Prevalence of Use

In studies completed in 1990 and 1997, surveys of the general population showed herbal supplement use rose from 2.5 percent to 12.1 percent. In a more recent study of adults in the Minneapolis/St. Paul metropolitan area in 2001, 61.2 percent of adults who responded indicated that they had used herbal supplements within the past year. Other studies show varying rates of use from 10 percent to 40 percent. It is obvious to anyone who shops at the mall or the local grocery store that herbal supplement use is becoming very popular. In addition, these surveys indicated that most people using herbs are receiving information about the treatments from family and friends, not from doctors. In fact, many do not even inform their doctor about herbal supplement use, which leads me to conclude that it is unlikely they are informing their insurance agent or paramedical examiner, either.

U.S. Food and Drug Administration Regulation

Before Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994, dietary supplements (which include vitamins, minerals and herbs) were subject to the same FDA regulation as other foods. In 1993, the FDA sought to establish regulations requiring manufacturers of herbal supplements to prove the efficacy of products. However, due to the expense of the studies and the fact that long-used herbal remedies could not be patented, there was a backlash from manufacturers and users of these products. As a result, the DSHEA passed with no proof required from the manufacturer of the safety and efficacy of herbal supplements. In addition, herbal supplements are not subject to the same quality control as traditional medicines, meaning that they can contain contaminants, such as pesticides or heavy metals, and that the amount of active ingredient can vary from product-to-product. Manufacturers of herbal supplements can make claims about a product's action without scientific research to back up claims, which, according to the DSHEA, must be "truthful and not misleading". The FDA has the authority to remove any herbal supplements from the market that are found to be dangerous, but it does not have the authority to test the products.

SOME COMMON HERBAL SUPPLEMENTS

Ginkgo Biloba (gingko, maidenhair-tree)

Commonly used to improve memory, Ginkgo is actually an anticoagulant and, as such, is also used for circulation problems. Studies show that ginkgo provides some benefit

for patients with dementia and intermittent claudication (AmJMed 2000; 108: 276-281). However, it does not prevent the onset of dementia or Alzheimer's disease in healthy adults, nor does it enhance memory (JAMA 1997; 278: 1327-32; JAMA. 2002; 288: 835-840). Ginkgo should not be used in conjunction with other medicines that affect clotting time, including aspirin, plavix or coumadin. Side effects of ginkgo include muscle spasms, cramps, bleeding and digestive problems. Other anticoagulant herbal supplements include feverfew, garlic and ginger.

St. John's Wort (amber, goatweed, hardhay, klamath weed, tipton weed)

St. John's wort is used to relieve depression and is proven effective in the treatment of mild depression with fewer side effects than some prescription antidepressants. However, it is not effective against major depression. St John's wort can effect the metabolism of many other drugs, causing either a buildup or decrease of the medication in the bloodstream. Therefore, it should not be taken concurrently with any other drugs, especially chemotherapy, digoxin, theophylline, cyclosporine, or antidepressants.

Saw Palmetto (sabel)

Saw palmetto is used to treat symptoms of benign prostatic hypertrophy (BPH). Studies indicate that saw palmetto can improve urine flow and emptying of the bladder. Side effects include upset stomach.

Ephedra (ma-huang, herbal ecstasy)

Ephedra is found in a number of diet/appetite suppression preparations (such as Herbalife, Metabolife) and in herbal products that claim to enhance energy. Ephedra is a stimulant, and should not be mixed with caffeine, other stimulants, decongestants, cardiac drugs or antidepressants. Taking ephedra is proven to increase the risk of MIs, CVAs and seizures (NEJM 2000; 343(25): 1833-1839), and the risk is increased when ephedra is mixed with any of the substances listed above. Recently, the FDA proposed new warning labels on ephedra in light of reports of at least 100 deaths linked to its use. Consumer groups are pushing for a ban on the sale of ephedra.

Of note, other diet products that do not contain ephedra, such as dieter's tea, contain potent laxatives and diuretics. The weight loss effect, which is actually the result of large losses of fluid, can also cause dangerously low levels of potassium. This can lead to dehydration and cardiac arrhythmias.

Echinacea

Echinacea is used for preventing or shortening the duration of the common cold by stimulating the immune system. Studies regarding its effectiveness are inconclusive, possibly because there are different species of echinacea plant and different parts of the plant may be used to manufacture the final product. A recent study conducted on college students with early cold symptoms found no detectable difference in the length of illness in students given unrefined echinacea and those given a placebo (Ann Intern Med. 2002; 137: 939-946). Other studies showed that it may have some effectiveness. Echinacea can affect the liver, and should not be taken with any other medication that affects the liver, or in combination with immunosuppressants.

There are a number of other herbals that affect the liver including kava, comfrey, chaparral, black cohosh and celandine. It would stand to reason that some of the elevated liver-function results on insurance-blood testing with no known etiology may be the result of herbal supplement use.

In conclusion, herbal preparations can be potent and effective health supplements if they are taken cautiously and under a doctor's supervision. Although they can be effective in certain cases, using them the wrong way or in combination with the wrong medication can lead to serious side effects, or even death. As underwriters, we should be aware of the different popular herbal supplements available and the possible consequences of use by our applicants.

Jeanne Mariani
Senior Underwriting Consultant

References:

Mayo Clinic Proceedings 2001; 76: 688-694.
JAMA 1998 Nov 11; 280(18): 1569-75.
JAMA 2002; 288: 835-840.

equivalent to less than sedentary work limitations (disabled). See Table 1 for definitions of the limitation levels. In actual use, these classes may be combined according to the symptoms experienced by the individual. For example, a man who is able to work loading trucks but occasionally gets chest pains while doing so would be a Class I to II. A man that can take occasional long walks but cannot tolerate lifting over 10 lbs. on a regular basis, and occasionally has chest pain while sitting watching television would be a Class III to IV. The NYHA Classification is not an objective tool, but it is widely used in disability-claim practice because it allows for quick placement of a claimant within a standard functional scale.

The NYHA Classification framework may appear easily applicable to disability evaluations but actually is not, due to variability in how patients experience symptoms, particularly chest pain and shortness of breath. This type of empirical, subjective evaluation of an individual's functionality based upon record and test reviews depends heavily upon the reviewer's level of expertise. A consistent and replicable application of the NYHA Classification to insurance cases requires a high level of expertise in evaluating cardiovascular symptoms. This is not a methodology that can be applied consistently by personnel with a low level of training or limited experience. However, this does not negate the validity of the NYHA Classification; applicants classified as NYHA Class IV cardiac patients after a valid review by a qualified examiner are disabled from gainful work. These applicants also have a very high cardiovascular mortality and cannot be considered acceptable life insurance risks.

In disability practice, it is desirable to avoid decisions that are based largely upon subjective evaluations. Therefore, sets of objective criteria have been developed around functional limitations resulting from cardiovascular disease. Of these, the most useful are the criteria developed to evaluate standard exercise tolerance tests. SSA has developed very specific, objective criteria for the interpretation of standard exercise stress tests (Bruce protocol) to evaluate cardiac-function capacity. The SSA criteria are used to evaluate inability to function due to an underlying cardiac condition. Under SSA listing rules, a claimant is considered totally disabled if the following general conditions are met:

Table 2
Criteria for Symptomatic Heart Disease

1. A claimant must have active symptomatic heart disease as defined in Table 2.
2. A standard Bruce stress test reveals the following:
 - a) Inability to reach five METS* prior to termination of the test.
 - b) Inability to increase the systolic blood pressure by 10 mm Hg. during exercise, or to decrease the systolic pressure below the usual resting level in the recovery phase.
3. A standard stress perfusion test (thallium test or similar) documenting reversible perfusion defects at a workload equivalent of 5.0 METS or less is indicative of total disability.
4. For applicants with a diagnosis of Congestive Heart Failure (CHF) a standard Bruce stress test reveals the following:
 - a) Evidence of inadequate cerebral perfusion (ataxic gait or mental confusion, for example) during the exercise test.
 - b) Runs of three or more Premature Ventricular Beats (PVB) during the test.
5. For applicants with a diagnosis of Coronary Artery Disease (CAD) a standard Bruce stress test reveals the following:
 - a) A horizontal or downsloping 1.0 mm ST segment depression during the exercise phase at a workload equivalent of 5.0 METS or less, persistent for at least one minute into the recovery phase.
 - b) An upsloping 2.0 mm ST segment or junctional depression during the exercise phase at a workload of 5.0 METS or less, persistent for at least one minute into the recovery phase.
 - c) A 1.0 mm. ST segment elevation during the exercise phase at a workload of 5.0 METS or less, persistent for at least 3.0 minutes into the recovery phase.
6. An applicant's doctor concludes that the performance of a standard Bruce protocol stress test presents a significant risk to the applicant, and the applicant suffers with symptomatic heart disease as listed in Tables 1 and 2.

