KRONOS LONGEVITY RESEARCH INSTITUTE

Research to promote a longer, healthier life for you, your children and your grandchildren.

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The Safety of Statin Medications

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General Considerations for Medication Safety

By definition, medications are chemical substances taken into the body to treat or prevent illness. Chemicals that are not normally found in the body, as are most medications, always have the potential to cause harmful effects. Even when a medication is identical to a product made by the body, such as hormones (like insulin, estrogen, thyroid hormone, or other), the fact that it comes from outside the body and is given in an artificial way has the potential to cause harmful side effects.

The effectiveness of a medication depends on the strength of its effects on the body's systems. This means that highly effective medications, such as statins (cholesterol lowering medications) often have greater potential to cause harmful effects.

Another factor in medication safety is the question of how broadly it spreads and works in the body. Most medications, including statins, are taken orally and are "systemic", meaning they are distributed throughout the body. Safety concerns are generally greater for systemic than for non-systemic agents, which either are not absorbed from the intestines or are given only in one part of the body such as a small area of the skin.

Finally, side effects of medications are almost always related to the daily dosage, and since statins have a broad dosage range, safety issues with statins can vary greatly in proportion to the dosage given to a patient.

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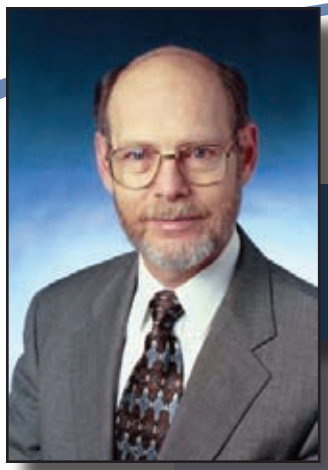

DIRECTOR'S MESSAGE

KLRI's Research Agenda, Today and Where to Next?

KLRI continues to investigate age-related changes in hormone balance, and the risks and benefits of hormone replacement. Some hormones are critical for life, whereas others regulate metabolism, body composition, and various functions such as reproduction. Many of the typical changes in body function and composition that occur with normal aging, such as loss of bone and muscle and increase in fat, are also seen in younger persons with deficiencies in one or more hormones. Thus, the question of whether and how to treat older persons with hormones remains important and controversial. In addition, KLRI studies are aimed at further understanding the loss of muscle that occurs with aging (sarcopenia) and how nutritional factors, exercise/physical fitness, and stress may relate to this loss and to other age-related deficits. Finally, KLRI is pursuing new initiatives to understand how damage from oxygen free radicals (oxidative stress) may contribute to aging and age-related diseases, and the role of stem cells in repairing and restoring damaged organs and tissues.

Testosterone Effects on Atherosclerosis in Aging Men (TEAAM) – We have learned that levels of the main male hormone, testosterone, tends to decrease with age. This hormone helps to maintain bone, muscle, energy, and sex drive. A study recently published in the *Archives of Internal Medicine* suggests that men with high testosterone levels may live longer than those with low levels. The TEAAM is a three-year, three center collaborative study of 340 men over 60 years of age with low to low-normal testosterone levels and will help to determine whether testosterone replacement has effects on the development of heart disease. The TEAAM will also assess the extent of beneficial effects on muscle, bone, mental processes, glucose and insulin metabolism, and sexual interest and performance. We have recruited 120 of the 160 men needed at the Phoenix clinical study center. The study is scheduled to be completed in 2009.

Kronos Early Estrogen Prevention Study (KEEPS) – This study was conceived and planned to address the controversy caused by findings in the Women's Health Initiative (WHI) Hormone Trials, in which estrogen (E alone) or estrogen plus a progestin (E+P) were given to postmenopausal women. Because they studied mainly women over the age of 60, the WHI trials left unanswered the crucial question whether recently menopausal women (ages 42-58) might receive significant protection against heart disease from taking estrogen treatment. The KEEPS, sponsored and coordinated by KLRI, is being performed at nine clinical centers, and four core specialty centers in the U.S. It employs state-of-the-art imaging procedures to test whether hormone treatment prevents progression of hardening of the arteries (atherosclerosis), when administered within three years of menopause. This study has recruited more than 180 women of 720. To accelerate recruiting and complete the study as quickly as possible, KLRI has been added as a ninth study center, which will recruit 50 to 65 women. The KEEPS is scheduled to be completed in 2010 and will cost more than 18 million dollars.

Nutritional Studies – KLRI investigators have completed a small study of dietary supplementation with high doses of omega-3 polyunsaturated fatty acids, the type of "healthy fat" found in fish and

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certain other foods. Results in 12 healthy men and women over 60 years of age were encouraging in that they showed improvement in the blood levels of free fatty acids, and improved action of insulin as well as significant improvement of scores on tests of mental function after only eight weeks of dietary intervention. These results have been presented at a scientific meeting and a paper describing our results in the final stages for submission for publications in a medical journal. Future studies are planned to follow-up on these findings. These trials will examine the interactions of omega-3 fatty acid supplementation with dietary antioxidants and also with exercise (i.e. multiple "healthy lifestyle" interventions) on markers of inflammation, oxidative stress (see below) and other risk factors for age-related diseases.

Sarcopenia and Stress Studies – KLRI is nearing completion of a pilot study examining the effects of a commonly prescribed cholesterol-lowering drug (statins) on muscle strength and fitness in older persons. The major adverse effects of statins are muscle cramping, soreness, and sometimes weakness. KLRI investigators hypothesize that statins may cause this effect by depleting the levels of CoQ10 (a vitamin-like factor important for energy generation) and that the elderly may be more susceptible to these adverse effects due to aging changes in the muscle. Thus, it is possible that statins could contribute to sarcopenia. The 10 research participants have been recruited and one more remains to complete the study procedures. If this preliminary study is consistent with the hypothesis, further studies will be undertaken to learn whether supplementing with oral CoQ10 can prevent or improve this problem, making it safer for the elderly to take statins.

Oxidative Stress Studies – KLRI investigators have initiated a new collaboration with the laboratory of Dr. L. Jackson Roberts at Vanderbilt University College of Medicine. Dr. Roberts is a world-recognized expert in the assessment of oxidative stress. This new pilot study, which began in August, will explore differences in how young and old persons adjust to an acute oxidative stress produced by temporary blockage of arterial blood flow to the forearm. KLRI is studying 10 men and women over 60 years of age and 10 young men and women between 25 and 35 years of age. KLRI hopes to use this "model" of oxidative stress in the future to test interventions (antioxidants, nutritional factors, exercise conditioning, etc.) that may reduce oxidative damage in the elderly.

Lastly, KLRI is supporting studies conducted at the University of Arizona, Tucson and at the Institute for Clinical and Experimental Medicine (IKEM) in Prague on whether stem cells obtained from the cord blood stem cells can be used as a component of a treatment for curing type 1 diabetes, a form of diabetes that strikes children and adults and affects 1.6 million Americans. These preliminary investigations are being conducted in a mouse "model" of type 1 diabetes. If positive results are obtained, they will quickly be extended to human patients.

KLRI is continuing to press forward with studies of hormone and nutritional interventions and at the same time initiating new and exciting research in the "cutting edge" areas of oxidative stress and stem cell therapies.

S. Mitchell Harman, MD, PhD
Director and President
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The Safety of Statin Medications

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General Issues Regarding Statin Safety

Statins are among the many medications widely used in the United States today. Their safety raises particular concerns for several reasons. Since statins are systemic and are present in most cells of the body, they are highly effective in blocking the majority of cholesterol production which can cause harm.

Due to increased use and greater familiarity of statins by doctors, pharmacists and patients, side effects and serious problems are more common. Sometimes familiarity with a medication can lead to greater complacency and additional problems.

Statins are usually given for long periods of time. Side effects of medications may occur soon after they are started. Prolonged medication use increases the chance of harm because of the continued exposure and the changes in health and physiologic state.

Statin Safety in Specific Medical Situations

For some patients, taking a statin poses special risks. An important example is pregnant or nursing women. Since cholesterol is needed for growth and statins work by blocking the production of cholesterol, there are concerns that the use of statins may harm a developing fetus or infant. Statins should not be used during pregnancy, when pregnancy is possible, or during nursing. Due to the possibility of liver irritation from statins, they are not to be used in patients with underlying liver disease, including hepatitis and alcoholism.

Note

Statin use is generally focused on patients at high risk for atherosclerosis (heart disease).

Since age is the strongest single risk factor for atherosclerosis, statins tend to be most widely used in older patients. The age of the patient is an important factor in medication safety. Medications are removed from the body by a process called metabolism. Age strongly affects the metabolism of most medications. Generally, metabolism is decreased as we age and so levels of medications increase, at a given dose, increasing the chance of an adverse effect. This means that even healthy older patients are at increased risk of adverse effects. Also, older tissues tend to be more sensitive to adverse effects of medications. Thus, safety concerns are higher for most medications in general and for statins in particular.

Most patients develop chronic illnesses as they age. Many diseases can interfere with the metabolism, thus increasing the chance of excess levels of medication in the blood and tissues which tend to lead to harmful effects. These conditions can make adverse events more likely even when the patient is taking a safe level

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of medication. Statins are more often used in older, higher risk patients, who tend to have many medical conditions in addition to elevated cholesterol levels.

Statins are more often used in older, more complicated patients, who are already taking many medications, or who may have medications added over time. There are relatively few ways in which the body metabolizes medications, so the pathways of metabolism often overlap. This overlap may interfere with (or increase) the metabolism of another.

Unfortunately, the latter three situations, older age, more medical conditions and more medications, tend to occur together in the same individuals. Furthermore, these same patients tend to have lower lipid goals, and thus may need the greater lipid effects of higher statin doses, which further increase the risk of adverse effects of the statin and of other medications.

Myalgia/Myopathy

Muscle symptoms are the most widely known side effect of statins. There are many types or degrees of muscle symptoms. Although muscle pain is the most common symptom, weakness or excessive stiffness may occur in the absence of pain. Any significant change in the muscles needs to be watched by the patient and reported promptly to health care providers.

There are several types of muscle symptoms, including myopathy (general muscle injury), myositis (inflammation of the muscle), and rhabdomyolysis (severe breakdown of the muscle). Rhabdomyolysis is a severe illness which usually requires hospitalization and may lead to death. While most patients who take statins will have no muscle symptoms, many develop pain or stiffness, especially with exercise. Everyone taking a statin needs to watch for muscle symptoms.

Patients with myopathy or previous medical history of myopathy should communicate this symptom or history to their health care provider prior to statin use, as well as any other medical issues when cholesterol treatment is to be re-started. Health care providers are obligated to explain the possibility of myopathy and its nature to the patient and to encourage them to promptly report any muscle symptoms while taking a statin. Some patients fear myopathy to the point that they will interpret everyday aches and pains as being caused by statins. They may become poorly compliant to long-term statin treatment or they may refuse to take statins. Statin myopathy is reversible and is very rarely serious if statin use is monitored properly. The risk of statin therapy is much smaller than the benefit in the vast majority of patients.

Health care providers have many ways of following and treating statin-induced myopathy, including watchful

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waiting, stopping and restarting the medication, or changing to a lower dose or to another statin. Patients should be cooperative in helping the doctor discover whether a given problem is truly due to a statin or not.

Although physical activity is generally very useful in promoting health, an occasional patient who requires statin therapy might benefit from moderation of exercise to avoid exercise-induced statin myopathy.

The mechanisms by which statins may cause muscle problems have not yet been proven. One possible pathway, however, is reduced levels of coenzyme Q-10 (CoQ-10). CoQ-10 is needed for normal muscle function and its levels are decreased by statin treatment. This statin-induced decrease in CoQ-10 levels can be prevented by taking CoQ-10 supplements. One small research study has suggested that such supplements may reduce muscle pain. Unfortunately, another recent study failed to confirm that finding, so the ability of CoQ-10 to prevent or treat statin myopathy remains in doubt.

Statins vary somewhat in their associated rates of myopathy. There are few good comparison studies to establish and measure these differences. A definite exception to this uncertainty is cerivastatin (Baycol), which clearly has far higher rates of myopathy and rhabdomyolysis than other statins. It was withdrawn from the market in 2001 for this reason. Both pravastatin (Pravachol) and fluvastatin (Lescol) have evidence of very low rates of myopathy, but they are among the statins that have the lowest ability to reduce LDL-C levels. The level of myopathy is generally related to statin dosage, and it may be that the risk of myopathy is comparable with more effective statins used at low doses compared to pravastatin and fluvastatin used at higher doses.

Liver Irritation

Perhaps the complication of statin therapy most feared by patients is liver irritation or damage. As with myopathy, however, patients can be reassured that this complication is relatively rare and essentially always reversible upon discontinuation of the medication, if needed.

The exact mechanisms by which statins may harm the liver are not known, and even those statins which are not metabolized or handled by the liver can cause liver irritation. Inflammation of the liver is usually detected clinically by measuring levels of enzymes released by inflamed liver cells. These enzymes are called transaminases, the most commonly tested ones being ALT and AST. It is generally recommended that transaminase levels be measured before starting statin treatment, and then re-measured at least a time or two while taking the drug. Significantly high levels at baseline suggest the presence of excess fat in the liver, harm from alcohol or other factors known to irritate the liver, or from long-term viral infections. A significant increase of these levels during statin treatment suggests that the liver is being harmed by the statin. In such a case, it is best to reduce the dose or switch to another statin. Only a rare patient will be unable to tolerate statin therapy due to such liver problems. Permanent liver damage caused by statin therapy is virtually unknown. Although an occasional patient might develop flu-like symptoms related to statin use, most cases involve no symptoms and can be detected only by blood tests.

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Kidney Damage

Studies performed with rosuvastatin (Crestor) at the dosage of 80mg/day suggested that it caused an issue with kidney function causing protein to appear in the urine. This was found prior to the medication being approved by the FDA. Fortunately, this issue went away with discontinuation of the drug, which was subsequently removed from consideration for human use. No other dosage of any statin has been shown to cause permanent or temporary harm to the kidney. In fact, three statins (simvastatin/Zocor, atorvastatin/Lipitor, and rosuvastatin/Crestor) appear to improve kidney function slightly with prolonged use. This improvement, which likely occurs with all statins, may be due to reduced cholesterol levels, reduced inflammation and/or reduced oxidation in the blood vessels of the kidney.

Specific Statin Drug Interactions

Some statins (pravastatin/Pravachol and rosuvastatin/Crestor) are dissolved quickly in water and therefore undergo little or no metabolism in the liver, but instead are discharged by the kidney. The lack of liver metabolism may decrease the risk of liver side effects, but does not eliminate the risk altogether. The frequency of higher liver enzyme levels is roughly the same among the various available statins. Due to the statins quickly dissolving in water and a lack of dissolution in the lipid or fat, they generally reduce entry of a drug into the brain. There are little to no side effects of statins that enter the brain, however, there are no proven differences among statins and the potential of brain-related side effects.

Two statins have reputations for extra safety, pravastatin (Pravachol) and fluvastatin (Lescol). In a large study of fluvastatin with cyclosporine use, it is particularly impressive that there is the lack of toxicity, since cyclosporine appears to increase the risk of myopathy with other statins.

Statin Combination Therapy

Note

The latest guidelines (2004) from the National Cholesterol Education program suggests more aggressive statin use for greater LDL-C lowering and an increased emphasis on combination lipid therapy. Adding a second medication to a statin can be useful for:

(1) obtaining lower LDL-C than that achieved with a statin alone,

(2) obtaining equal LDL-C lowering at a lower statin dose, and

(3) obtaining greater effects on triglycerides, HDL-C and other lipid factors.

Any class of lipid medication can be added to a statin, although the combination of a fibrate, and especially gemfibrozil, with a statin may increase the risk of myopathy. For this reason, when combining gemfibrozil with statins other than fluvastatin, the dose of the statin must be kept low. Although the risk of myopathy with the combination of a statin with fenofibrate (TriCor, Antara, Triglide, Lofibra and generics) is far less than with gemfibrozil, the FDA recommends caution with the use of any fibrate with any statin.

The addition of niacin (Niaspan and generics), ezetimibe (Zetia), and bile acid sequestrants (colesevelam/WelChol, cholestyramine/Questran, and colestipol/Colestid) to a statin pose no safety concerns. Bile acid sequestrants, however, should not be taken at the same time as a statin, due to the possibility of interference with absorption of the statin.

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A Graying Nation: Why Funding Age-Related Research Is Critical

In 2004, the 65-plus age group reached 36.3 million. That translates to one in eight Americans, half of which have three or more chronic illnesses and 20 percent of which have five or more. The illnesses are those associated with aging, including diabetes, hypertension, arthritis and clogged arteries (cardiovascular disease). Combine these statistics with increased life expectancy rates and our graying nation is headed for a life of discomfort as they enter their "golden years." Finding preventions for age-related diseases is more crucial now than ever.

While billions of dollars are funneled into this area of research annually, more is needed as this population threatens to reach 71.5 million in the United States by 2030. Many of the potential treatments that arise from basic laboratory research for age-related diseases have to be thoroughly evaluated using translational research methods, a requirement by the Food and Drug Administration. Your financial support helps ensure that this type of research is continued to prolong aged related diseases and promote healthy living.

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Benefit/Risk and Benefit/Cost Ratios

Perhaps the most important consideration in statin safety is the comparison between risk and benefit. The percentage reduction in risk of cardiovascular disease tends to be predicted primarily by the degree of LDL-C lowering and not by the rate of cardiovascular risk. This means that the absolute benefit of statin therapy in patients at high risk for heart attack and stroke (patients with prior cardiovascular disease, diabetes, high blood pressure, smoking, older age, positive family history, etc.) is high. Due to the fact that cardiovascular disease is generally far more devastating and more common in these high risk patients than the risk of a statin complication, the benefit usually far outweighs the risk. This is the reason why statin therapy may now be considered nearly mandatory in most high-risk patients. In contrast, in patients at low risk for cardiovascular disease the benefits are fewer, while the risk remains roughly the same. This means that the risk-benefit ratio tends to be much less favorable. For this reason, as well as the fact that the cost-benefit ratio tends to be much less favorable in such patients, statin therapy is often not appropriate when the risk of atherosclerosis is relatively low, such as in many pre-menopausal women and many young men. In younger patients with moderate to severe risk for atherosclerosis, the risk/benefit ratio can become favorable when lower doses of statins are used.

Conclusion

Statins significantly reduce the likelihood of severe and even fatal medical problems including heart attack and stroke. On the other hand, statins can cause certain health problems including irritation of the muscles and liver. These problems, however, are virtually always reversible, and are quite minor compared to the diseases statins are designed to treat. Statins always need to be used with attention to certain safety rules, but when these rules are followed, the benefit/risk ratio is favorable for almost all patients who are at high risk for atherosclerosis. Patients should be aware of issues regarding statin safety, but should not be overly concerned. Concerns which lead to refusal of statin therapy when it is needed, or to poor long-term compliance in the absence of bothersome symptoms, are inappropriate and can lead to premature disease and even loss of life due to under treatment of lipid problems and atherosclerosis.

Eliot A Brinton, MD, is a scientific advisor for Kronos Longevity Research Institute and is also the Director, Metabolism Section, University of Utah School of Medicine.

Who We Are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

Our Mission

To perform and foster clinical translational research aimed at healthier human longevity and communicate results to the professional and lay communities.

Our Governance

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders govern KLRI. There is also a scientific advisory board of recognized international experts in medical and scientific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer and heart disease.

What Is Translational Research?

Translational research takes promising findings from the basic research laboratory and carries them forward into the clinical arena. It is the link between basic research (experiments done with animals or cultured cells, genes, etc.) and improved clinical care. It requires controlled studies of living human participants.

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