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Carnitine for Cardiovascular Diseases

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Dr. O'Mathúna reports no financial relationships relevant to this field of study.

L-CARNITINE IS BOTH AN AMINO ACID AND A CONDITIONALLY ESSENtial nutrient, defined as an organic compound which is usually produced in sufficient quantities by the body. However, such a compound can become essential under specific circumstances when biosynthesis is less than optimal, and where dietary sources necessarily assume primacy.[1] Carnitine can be synthesized from the essential amino acids lysine and methionine, or is available from the diet.[2] Biosynthesis occurs primarily in the liver, with 10-20 mg produced daily by the average adult.[1] More than 90% of the carnitine in the body is stored in cardiac and skeletal muscle. Dietary intake of carnitine is typically 100-300 mg daily, although it is much lower among strict vegetarians. The primary sources of carnitine are meat, fish, avocados, and some soy products, with lower amounts available in dairy products.[1]

Carnitine is available as a dietary supplement and has become popularly recommended for a number of uses in recent years. These have ranged from use as a weight loss supplement and performance enhancing agent for athletes, to being recommended as part of the management of several cardiovascular disorders. This article will examine the evidence available for the use of carnitine in people with cardiovascular disease.

Pharmacology

In the body, L-carnitine is converted into various esters to constitute an endogenous carnitine pool. The most prevalent forms are acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC), with PLC believed to possess particular therapeutic advantages over the other derivatives.[3] ALC crosses the blood-brain barrier better than L-carnitine and is believed to hold potential in protecting people against neurodegenerative diseases.[3] However, much more research

Summary Points

- Carnitine is an essential cofactor in fatty acid metabolism and energy production.
- Carnitine also possesses antioxidant potential.
- Supplemental carnitine is known to be of benefit in the treatment of carnitine deficiency syndromes, and is likely beneficial in the setting of peripheral arterial disease, but the evidence is as yet inconclusive regarding its use in heart disease.

has been conducted on carnitine and heart disease, particularly using PLC. This derivative has a high affinity for cardiac and skeletal muscle, and its pharmacokinetics are better than the other derivatives.[3]

Mechanism of Action

L-carnitine plays a particularly important role in regulating the supply of energy in cardiac tissues.[2] It is an essential cofactor in fatty acid metabolism. The primary function of L-carnitine is to transport long-chain fatty acids across the inner membrane of mitochondria.[4] Once across this membrane, the fatty acids are broken down to acetyl-CoA via beta-oxidation, thereby allowing the release of their metabolic energy. This process is particularly important in cardiac tissue.[2]

Carnitine supplementation has been promoted as a way to increase fat metabolism for athletes and those seeking to lose weight. The claim is that additional carnitine in skeletal muscle would permit additional metabolism of fatty acids and energy production. However, oral carnitine supplementation has been shown to not increase muscle carnitine concentration, making claims that carnitine promotes weight loss "not only unfounded but theoretically impossible."[4]

Cardiovascular diseases like heart failure and ischemic heart disease often are accompanied by reduced cellular energy production and lower work efficiency.[2] Carnitine is believed to have a beneficial effect in counteracting these changes. Oxidative damage is also involved in some cardiac diseases, and carnitine has been shown to have antioxidant actions, reducing the production of oxidative compounds and stimulating the gene expression of other antioxidants.[3]

In addition to transporting fatty acids into mitochondria for beta-oxidation, carnitine plays a role in transporting intermediate beta-oxidation products out of the mitochondria. Accumulation of these intermediates has been implicated in the development of insulin resistance, heart failure, and ischemia.[2] There is developing interest in the possibility that carnitine and its derivatives may play a role in preventing type 2 diabetes and its associated increased risk for heart disease.

Clinical Studies

The potential therapeutic effects of carnitine and its derivatives have been investigated in clinical trials since the 1980s.[3] During periods of ischemia myocardial carnitine levels decrease, and this reduction may exacerbate ischemia as energy production is compromised.[5] A few small studies in the early 1990s found some benefits from administering L-carnitine to acute myocardial infarction (MI) patients. The largest trial in this area to date, the Italian CEDIM-2 trial, randomly assigned 2330 acute anterior MI patients to either L-carnitine or placebo.[6] The trial was designed to enroll 4000 patients, but this sample size was not achieved due to unexpectedly slow enrollment. Those assigned to treatment with L-carnitine received 9 g/day by continuous IV for 5 days, followed by 4 g/day orally for 6 months. The primary endpoint was a composite incidence of death and heart failure after 6 months, which ultimately did not differ significantly between the groups ($P = 0.27$). The secondary endpoint was mortality after 5 days, which was lower in the L-carnitine group (2.3% vs 3.8%; $P = 0.041$).

The earlier CEDIM trial enrolled 472 patients with a first acute MI diagnosed within 24 hours of the onset of chest pain.[7] The same protocol and doses were used in CEDIM-2, except the trial continued for 12 months. At the end of that time, the composite incidence of death and

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Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

heart failure did not differ significantly between the carnitine and placebo groups (6.0% vs 9.6%, respectively; $P > 0.05$).

While clinical research with L-carnitine did not produce the beneficial effects anticipated, animal research suggested PLC would be more promising. PLC is highly specific for cardiac and skeletal muscle.[8] A number of small studies in people with chronic heart failure (CHF) showed that 1 month of PLC improved maximum exercise duration and peak VO_2 levels.[8] Fifty patients with mild CHF (New York Heart Association class II) were randomized to receive either 1.5 g/day PLC or placebo for 6 months.[9] The PLC group had significantly greater improvements in maximal exercise time ($P < 0.01$), left ventricular shortening fraction ($P < 0.01$), and left ventricular ejection fraction ($P < 0.0001$).

These results led to a multicenter, international study of exercise duration involving 537 CHF patients stabilized on various ACE inhibitors and diuretics.[10] Participants were randomly assigned to receive either 2 g/day PLC or placebo. The primary endpoint was maximal exercise duration evaluated on an exercise bike. No statistically significant differences were found for either primary ($P = 0.092$) or secondary endpoints (evaluations of PLC's safety and tolerability, and quality of life assessments), or for adverse events ($P = 0.289$). Some subgroup analyses showed benefits in the PLC group, but the researchers stated that since the subgroups were not determined before the study was conducted these findings require further evaluation.

Several studies have examined L-carnitine and PLC in patients with peripheral arterial disease (PAD). This condition results from decreased blood flow and resultant lack of oxygen and nutrients to the legs. Walking becomes very difficult and painful, even at slow speeds.[11] Metabolic factors are also involved, leading to interest in carnitine as an adjunctive treatment in PAD. A recent review identified 12 clinical trials of PLC for PAD.[3] Most of these found that PLC significantly improved maximal walking distance and walking distance before onset of claudication. PLC has been found to be more effective than L-carnitine.[2] However, the results were somewhat variable depending on the severity of PAD, route of administration of PLC, and duration of treatment. The latest Inter-Society Consensus for the Management of PAD guidelines concluded that PLC may help improve PAD symptoms when combined with physical exercise.[12]

Adverse Effects

Carnitine and its derivatives are well tolerated and generally safe.[13] One of the larger randomized controlled trials found no significant differences in adverse effects, deaths, or cardiovascular hospitalizations between those taking 2 g/day PLC and placebo.[10] At doses of 3 g/day and higher, carnitine may give people a "fishy" body odor.[13] Some evidence indicates that carnitine may interfere with peripheral thyroid hormone utilization.[14] Theoretically, at least, those with hypothyroidism should be cautious about taking carnitine supplements.

Formulation

L-carnitine is an FDA-approved prescription drug for the treatment of primary and secondary carnitine deficiencies in adults.[13] The usual dose in these cases is 1-2 g/day oral tablets, or intravenous treatments at 50 mg/kg every 3-4 hours for the first 24 hours followed by 50 mg/kg/day. L-carnitine is also available as a dietary supplement. Doses of 2-6 g/day are usually suggested to support cardiac health. A number of clinical trials used IV solutions of L-carnitine. PLC is approved for use in Europe, but not in the United States. It is available in the United States as a dietary supplement.[15]

Conclusion

Carnitine is an important nutrient in the body, particularly in cardiac tissue. It plays an important role in cardiac health, and its metabolism is negatively impacted by various cardiovascular diseases. While early, small clinical trials suggested beneficial effects for patients after MI and with chronic heart failure, these have not been supported consistently by subsequent and larger clinical trials. Clinical trials involving patients with PAD have shown more consistent promise.

Recommendation

A significant body of evidence supports the importance of carnitine in fatty acid metabolism and cellular energy production. Carnitine is known to be beneficial in patients with diagnosed carnitine deficiency syndromes. However, many of the studies of carnitine and its derivatives have been conducted without evaluating patients' tissue carnitine levels. The inconsistent nature of research results to date may arise because patients have sufficient dietary carnitine. Greater attention needs to be paid to pre- and post-treatment tissue carnitine levels in future research to determine if certain patients are more likely to benefit from L-carnitine or PLC supplementation. Meanwhile, L-carnitine (2 g twice daily) may be of benefit along with exercise for those with claudication. However, the evidence does not generally support the use of carnitine supplements in patients with other cardiovascular diseases. ■

References

1. Kendler BS. Supplemental conditionally essential nutrients in cardiovascular disease therapy. *J Cardiovasc Nurs* 2006;21:9-16.

2. Mingorance C, et al. Critical update for the clinical use of L-carnitine analogs in cardiometabolic disorders. *Vasc Health Risk Manag* 2011;7:169-176.

3. Mingorance C, et al. Pharmacological effects and clinical applications of propionyl-L-(carnitine). *Nutr Rev* 2011;69:279-290.

4. Jeukendrup AE, Randell R. Fat burners: Nutrition supplements that increase fat metabolism. *Obes Rev* 2011;12:841-851.

5. Gaby AR. Nutritional treatments for acute myocardial infarction. *Altern Med Rev* 2010;15:113-123.

6. Tarantini G, et al. Metabolic treatment with L-carnitine in acute anterior ST segment elevation myocardial infarction. A randomized controlled trial. *Cardiology* 2006;106:215-223.

7. Iliceto S, et al. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. *J Am Coll Cardiol* 1995;26:380-387.

8. Ferrari R, et al. Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular diseases: A review. *Ann N Y Acad Sci* 2004;1033:79-91.

9. Caponnetto S, et al. Efficacy of L-propionylcarnitine treatment in patients with left ventricular dysfunction. *Eur Heart J* 1994;15:1167-1173.

10. Investigators of the Study on Propionyl-L-Carnitine in Chronic Heart Failure. Study on propionyl-L-carnitine in chronic heart failure. *Eur Heart J* 1999;20:70-76.

11. Hiatt WR. Carnitine and peripheral arterial disease. *Ann N Y Acad Sci* 2004;1033:79-91.

12. Norgren L, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;33(Suppl 1):S1-S75.

13. Editors. Carnitine: Lessons from one hundred years of research. *Ann N Y Acad Sci* 2004 Nov;1033:79-91.

14. Benvenga S, et al. Effects of carnitine on thyroid hormone action. *Ann N Y Acad Sci* 2004;1033:158-167.

15. Office of Dietary Supplements. Carnitine. Available at: http://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional. Accessed March 12, 2012.

Bisphenol A and Canned Soup

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *This brief but important intervention trial was detailed recently in the pages of the* Journal of the American Medical Association. *The conclusion was that eating canned soup on a regular basis could rapidly increase the body load of BPA, high levels of which have been associated with a variety of illnesses.*

Source: Carwile JL, et al. Canned soup consumption and urinary bisphenol A: A randomized crossover trial. *JAMA* 2011;306:2218.

The researchers behind this randomized, single-blind, 2 X 2 crossover trial set out to quantify the degree of exposure to bisphenol A (BPA) that volunteers (n = 84, median age = 27, 68% female) would experience from the regular ingestion of canned soup. Over a 5-day period, one group ate the contents of a 12-ounce can of vegetarian Progresso soup for lunch, a different type at each sitting, while the other group consumed a 12-ounce serving of fresh soup that had been prepared without canned ingredients. A 2-day washout period followed, and then group assignments were switched, with the five different varieties of soup being offered to participants in the same order. The subjects' diet was otherwise unrestricted. Late afternoon urine samples were collected on days 4 and 5 during each phase of the trial, and urinary BPA concentrations determined.

A total of 75 (89%) subjects completed the trial with median treatment adherence of 100%. BPA was detected in 77% (n = 58) of samples after fresh soup consumption, but 100% (n = 75) of samples after canned soup consumption. The specific gravity-adjusted geometric mean concentration of BPA was 1.1 ug/L (95% confidence interval [CI], 0.9-1.4 ug/L) after fresh soup consumption (unadjusted: 0.9 ug/L; 95% CI, 0.7-1.2 ug/L) and 20.8 ug/L (95% CI, 17.9-24.1 ug/L) after canned soup consumption (unadjusted: 17.5 ug/L; 95% CI, 14.1- 21.8 ug/L). For comparison, the authors reference data showing the 95th percentile level for non-occupational urinary BPA concentration to be 13.0 mcg/L.[1] Following canned soup consumption, specific gravity-adjusted urinary BPA concentrations were, on average, 22.5 ug/L higher (95% CI, 19.6-25.5 ug/L) than those measured after a week of fresh soup consumption ($P < 0.001$), representing a 1221% increase.

The researchers concluded that consumption of 1 can

Summary Points

- Bisphenol A (BPA) is a presumed endocrine-disrupting agent that has been tied to increased rates of diabetes and heart disease.
- There are concerns that BPA may promote hormone-sensitive disorders.
- Can linings contain BPA that can leach into foods, especially acidic foods such as tomatoes; results from this study suggest acute exposure to BPA from eating canned soup is significant.

of soup daily over 5 days was associated with significant BPA exposure.

■ **COMMENTARY**

Most people are aware of there being health concerns associated with exposure to BPA, if only because so much effort has been expended to remove BPA from infant bottles; however, researchers express concern that adults, too, may be at risk from high levels of BPA. The current paper brings to light a potential BPA source — canned goods, where BPA may lurk in the inner coatings — that many may not have been aware of previously.

BPA is one of a growing list of chemicals to which the population is exposed that are presumed endocrine disruptors. BPA has been tied to increased rates of diabetes and heart disease, and fears about its potential to promote hormone-sensitive tumors loom large.

With respect to the study at hand, the authors are quick to point out that some may claim "foul" because only a single type of soup product was tested, but the presence of BPA in canned goods already has been well-established, with some of the greatest risks coming from acidic foods present in cans, such as tomatoes. It is unknown how long the elevated levels of BPA may persist after short-term ingestion, but even the short exposure examined in this study caused alarmingly high levels to appear, raising the specter of potential downstream harm.

Until such time that alternative types of can linings are in widespread use, it makes sense to limit exposure to canned food products, especially for acidic foods like tomatoes, and focus primarily on fresh and frozen foods. A great resource for optimizing safety in the age of BPA can be found on the web site of the Environmental Working Group (http://www.ewg.org/bpa/tipstoavoidbpa). ■

References

1. Fourth National Report on Human Exposure to Environmental Chemicals. Centers for Disease Control and Prevention, National Center for Environmental Health. Available at: http://www.cdc.gov/exposurereport. Accessed Feb. 14, 2012.

Vitamin D and Cardiovascular Health

ABSTRACT AND COMMENTARY

By David Kiefer, MD

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Dr. Kiefer reports no financial relationships relevant to this field of study.

Synopsis: *Both vitamin D deficiency and supplementation with vitamin D are significantly associated with several cardiovascular outcomes, including mortality.*

Source: Vacek JL, et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. *Am J Cardiology* 2012;109:359-363.

To evaluate the relationship between cardiovascular morbidity and mortality, and overall survival, and both vitamin D deficiency and supplementation, the researchers of this analysis set up an observational retrospective study on a cohort of 10,899 people. Serum 25-hydroxyvitamin D (25(OH)D) levels were measured and analyzed both as a continuous variable, and as either deficient (< 30 ng/mL) or normal (≥ 30 ng/mL). Patient diagnoses were determined from the problem lists as documented in the electronic medical record, and vitamin D supplementation was established from active prescriptions or patient self-reporting. Serum 25(OH)D and vitamin D supplementation were then compared to a variety of health outcomes, including coronary artery disease, atrial fibrillation, dia-

Summary Points

- Labs often report vitamin D deficiency as a serum 25(OH)D level < 30 ng/mL, but many experts define deficiency as anything below 40 or 50 ng/mL.
- According to the results of this study, vitamin D supplementation lowers overall mortality risk, but only for those who are vitamin D deficient.

betes mellitus, cardiomyopathy, hypertension, and death, over 5 years, 8 months.

The mean age of the cohort was 58 years, 71% were women, and 70.3% were deficient (mean serum 25(OH) D was 24.1 ng/mL). According to the researchers, not all vitamin D doses were reported, but those that were reported ranged from 1000 IU daily to 50,000 IU biweekly, resulting in a mean vitamin D intake of 2254 IU per day ± 316 IU.

When serum 25(OH)D was analyzed as a dichotomous variable, deficiency was significantly associated with an increased risk of all of the above diagnoses except for atrial fibrillation, which actually had a decreased risk (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.693-0.984). Vitamin D supplementation improved overall survival (OR 0.44; CI 0.335-0.589) but only in people who were vitamin D deficient. Interestingly, the statistical significance of the association between vitamin D deficiency and risk of death disappeared in those people receiving vitamin D supplementation.

Alternatively, when serum 25(OH)D was analyzed as a continuous variable, it was negatively associated with body mass index and low-density lipoprotein, and positively associated with high-density lipoprotein.

■ COMMENTARY

The results of this observational study dovetail with many prior research findings documenting effects of vitamin D deficiency and supplementation on cardiovascular conditions and risk factors[1,2] (see the article's introduction for references to some of this important research). The authors expand on existing vitamin D mortality data by showing a benefit from vitamin D supplementation on overall mortality, but only for people who are vitamin D deficient. This, regardless of possible criticisms of this study (see below), is absolutely eye-opening and critical to patient care. Our patients may achieve better survival rates simply by supplementing with vitamin D if they are deficient — a very important finding. As the authors discuss, omnipresent vitamin D receptors make these global findings no surprise. Undoubtedly, research will continue to find connections between vitamin D and many diverse organ systems.

There are many details to criticize in any retrospective, observational study. Clearly, ultimate clinical recommendations need to be based on prospective, randomized controlled trials, rather than simply on proven associations; this fact is mentioned by other recent research reviews on the topic of vitamin D, some of which are more optimistic than others over the gap in current knowledge and clinical applicability.[3,4] Research is beginning in this arena,[5] so it will be exciting to see the results of vitamin D intervention trials.

It is interesting to muse over the use of the definition of vitamin D deficiency here (serum 25(OH)D < 30 ng/mL), considered by many clinicians to be on the low side of what is necessary to avoid various disease states. Perhaps the associations seen would have been stronger with a dichotomous analysis with deficiency defined as 25(OH)D less than 40 or 50 ng/mL. In addition, the method of calculating vitamin D supplementation (from patient reporting or electronic records) seems fraught with important problems. It is well documented that patients underreport their dietary supplement use, likely skewing the data in this study in ways that might be hard to predict. Also, the researchers document that the vitamin D dose for some patients was unlisted, but we don't know how many, so the average intake listed is really just a gross estimate. And the type of vitamin D (D2 or D3) used is not clarified, which, depending on the source or expert consulted, may make a difference. ■

References

1. van Ballegooijen AJ, et al. Vitamin D in relation to myocardial structure and function after eight years of follow-up: The Hoorn Study. *Ann Nutr Metab* 2012;60: 69-77.
2. Muscogiuri G, et al. Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. *Nutr Metab Cardiovasc Dis* 2012;22:81-87.
3. Reid IR, Bolland MJ. Role of vitamin D deficiency in cardiovascular disease. *Heart* 2012; Feb 28 [Epub ahead of print].
4. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: A narrative review. *Ann Intern Med* 2011;155:820-826.
5. Salehpour A, et al. Vitamin D3 and the risk of CVD in overweight and obese women: A randomised controlled trial. *Br J Nutr* 2012;Feb 9:1-8.

MBSR for Type 2 DM: Does Reducing Stress Reduce Complications?

ABSTRACT AND COMMENTARY

By Nancy Selfridge, MD

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Dr. Selfridge reports no financial relationships relevant to this field of study.

Summary Points

- Existing data strongly suggest that mindfulness-based stress reduction (MBSR) training and practice can help reduce stress and mood disorders in patients with chronic disease.
- Preliminary results reported in this study support a role for MBSR in the management of diabetes.
- Prior data suggested that MBSR also may improve control of blood glucose levels.

Synopsis: *The first results of a 5-year study of the effects a mindfulness-based stress reduction program on medical complications and psychosocial outcomes in patients with type 2 diabetes show prolonged reduction in psychological distress and depression compared to usual care.*

Source: Mechthild H, et al. Sustained effects of a mindfulness-based-stress-reduction intervention in type 2 diabetic patients. *Diabetes Care* 2012; DOI 10.2337/dc11-1343.

THE HEIDELBERGER DIABETES AND STRESS STUDY (HEIDIS-Study) is a 5-year prospective, randomized, controlled trial created to evaluate the effects of a mindfulness-based stress reduction (MBSR) program on complications and psychological distress in patients with type 2 diabetes. The report summarizes this study's preliminary data at the end of the first year of follow-up. Prior research on MBSR suggests that it may be helpful in reducing stress and depression in patients with chronic disease, as well as improving diabetic control.[1,2] The authors previously have shown that psychological stress is linked to activation of pro-inflammatory factors involved in late diabetes complications.[3] Thus, a stress-reducing strategy for diabetic patients may have long-term beneficial effects on target end organ disease.

Methods

A total of 110 type 2 diabetic patients fulfilling inclusion criteria were randomized into a control group (n = 57) and an intervention group (n = 53). To be included in the study, all patients were between 30-70 years old, had diabetes for more than 3 years, and had microalbuminuria > 20 mg/L in two separate spot urines. All patients were provided medical treatment-as-usual by a single physician according to diabetes management guidelines in an outpatient clinic. After enrollment, the intervention group completed an 8-week MBSR program[4] in groups of 6-10 participants who met weekly, followed by a "booster" session after 6 months. MBSR was facilitated by a psychologist and a resident in internal medicine. The MBSR intervention was adapted from the original program created by Kabat-Zinn by including practices for difficult thoughts and feelings related to diabetes. Primary outcome was albuminuria progression, and secondary outcomes were psychological distress, subjective health status, mortality, blood pressure, cardiovascular events, and activation of pro-inflammatory transcription factors. Albuminuria was measured in 24-hour urine collections over 3 consecutive days. Blood pressure was determined with a 24-hour measurement. The Patient Health Questionnaire (PHQ), a validated self-report survey for use in primary care, was used to detect and quantify depression, anxiety and eating disorders. Patients reported subjective health status using the SF-12, a peer-reviewed, validated, and reliable instrument for monitoring physical and mental health. Covariate analyses were subjected to intent-to-treat and per-protocol analyses. Nine persons in the intervention group did not attend the full MBSR training as required (at least five sessions). The reasons cited included illness, death of a family member, lack of interest in group and having to provide caregiving in home. In the control group, six individuals were lost to follow-up.

Results

Baseline differences between the two groups showed no statistical differences, nor was there any significant effect on any outcomes immediately after the MBSR intervention. However, at the 1-year follow up, while there was no significant difference between groups on progression of albuminuria, there was a significant improvement in the MBSR group on the PHQ depression score (P = 0.007), subjective mental health status on the SF-12 (P = 0.033), and diastolic blood pressure (P = 0.004) with intent-to-treat analysis. Per protocol analysis resulted in even greater effect sizes for these measures and also significant reduction in the PHQ stress score (P = 0.023).

■ COMMENTARY

Because psychosocial stress activates pro-inflammatory transcription factors, which mediate micro- and macrovascular disease, the authors continue to hope to show that long-term stress reduction will demonstrate a beneficial effect on the progression of diabetic complications. The preliminary data from this study support the conclusions of existing research on MBSR for reducing psychological distress. MBSR programs are normally not offered free of charge, though some insurance products offer rebates to participants who complete the course. Completion of the course requires significant motivation and time commitment from participants and the dropout rate in this study points to this fact. However, MBSR appears effective for reducing perceived stress and is a low-risk intervention,

making it a potentially useful adjunctive therapy for diabetics. Though the number of participants is small in this study, it will be interesting to see over time if microalbuminuria, an established risk factor for cardiovascular and microvascular disease, is reduced. Slowly but surely, the effects of stress and difficult emotional states on cell biology are being elucidated, providing the opportunity to potentially alter the natural history of chronic disease with stress reduction strategies. The authors are applauded for their efforts and excitement awaits future outcomes of this long-term study. ■

References

1. Grossman P, et al. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res* 2004;57:35-43.
2. Rosenzweig S, et al. Mindfulness-based stress reduction is associated with improved glycemic control in type 2 diabetes mellitus: A pilot study. *Altern Ther Health Med* 2007;13:36-38.
3. Bierhaus A, et al. Multiple levels of regulation determine the role of the receptor for AGE (RAGE) as common soil in inflammation, immune responses and diabetes mellitus and its complications. *Diabetologia* 2009;52:2251-2263.
4. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. New York, Delacorte, 1990.

Pycnogenol and Coronary Artery Disease

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *Results from this small, 8-week crossover study suggest that the antioxidant Pycnogenol, which also possesses anti-inflammatory actions, could help improve endothelial function in people with stable coronary artery disease.*

Source: Enseleit F, et al. Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study. *Eur Heart J* 2012; doi:10.1093/eurheart/ehr482.

Summary Points

- A proprietary pine bark extract, Pycnogenol appears to possess anti-inflammatory, antioxidant, and antiplatelet effects
- The agent is widely recognized as an effective aid for the treatment of chronic venous insufficiency
- Results from this small study show that 8 weeks of Pycnogenol, 200 mg/d, improved flow-mediated dilation, a marker of endothelial function, in people with stable CAD

The researchers behind this prospective, single-center, double-blind, randomized, placebo-controlled, crossover trial sought to examine the effects of Pycnogenol on endothelial function and, by extension, coronary artery disease (CAD). Pycnogenol is a proprietary bark extract of the French maritime pine tree (*Pinus pinaster* ssp. atlantica) that reportedly possesses antioxidant and anti-inflammatory actions, as well as antiplatelet effects.

Adult subjects with documented stable CAD whose cardiovascular medications had remained unchanged for at least 1 month were recruited at a university hospital clinic in Zurich, Switzerland. Exclusion criteria included uncontrolled hypertension despite maximal medical therapy, smoking, chronic use of long-acting nitrates, and insulin-dependent diabetes. Subjects were randomized into two groups receiving either Pycnogenol 200 mg/day or matching placebo for 8 weeks, and then were crossed over to the other agent following a washout period of 2 weeks. Participants were evaluated at the clinic at baseline and after 8, 10, and 18 weeks, during which endothelial function (via flow-mediated dilation, or FMD) was assessed and blood for testing was drawn. Subjects were fitted with monitors to evaluate 24-hour ambulatory blood pressure (ABP), with readings taken every 15 minutes during the day and every 30 minutes at night.

The primary endpoint was the change in FMD after 8 weeks' treatment with Pycnogenol compared with placebo. Pre-specified secondary endpoints included change in high-sensitivity C-reactive protein, change in total antioxidative capacity, change in ABP, and change in shear stress-dependent platelet function.

Out of the 28 patients who were enrolled, 23 completed the study (19 men; mean age of 63.1 $\pm$ 7.1 years; BMI of 27.3 $\pm$ 3.3 kg/m^2). Eleven of the subjects had three-vessel disease, while one had two-vessel disease. Mean left ventricular ejection fraction was 62 $\pm$ 10%.

Pycnogenol treatment resulted in an increase in FMD from 5.3 $\pm$ 2.6 to 7.0 $\pm$ 3.1% ($P < 0.0001$), while it remained unchanged in the placebo group (5.4 $\pm$ 2.4 to 4.7 $\pm$ 2.0%, $P < 0.051$). The estimated treatment effect of Pycnogenol on FMD was an increase of 2.75 compared with placebo (mean difference 2.75 with an associated

95% confidence interval [CI] 1.75, 3.74, $P < 0.0001$), which was statistically significant. ABP, both systolic and diastolic, remained unchanged before and after treatment with Pycnogenol. Markers of oxidative stress, including 15-F2t-Isoprostane, decreased significantly after 8 weeks on Pycnogenol compared with baseline and placebo ($P = 0.012$), yet there was no change in total antioxidant capacity. The estimated effect of Pycnogenol on C-reactive protein was an increase of 2.18 mg/L compared with placebo (mean difference 2.18 mg/L with associated 95% CI -3.35, 7.71; $P = 0.42$), but this was deemed a statistically non-significant treatment effect. Additional measures of impact on inflammation showed no change. Shear stress-dependent platelet function did not change after treatment with Pycnogenol.

The study authors concluded that Pycnogenol taken for 8 weeks at a daily dose of 200 mg could improve endothelial function in people with stable CAD.

■ COMMENTARY

Pycnogenol is a supplement well known for its potential health benefits in the setting of chronic venous insufficiency, but less often considered as an aid in the setting of CAD. It is widely reported to possess antioxidant activity, and has been used to help relieve allergy symptoms, as well as to lessen the harmful effects of tobacco smoke on the vascular system. Pycnogenol is known to contain a mixture of flavonoids monomers, phenolic acids, and various procyanidins; has been shown to possess anti-inflammatory effects; and appears to also inhibit oxidation of LDL-C, so its consideration in the area of CAD makes sense.

The current study suggests promise, likely due primarily to Pycnogenol's antioxidant capacity. The investigations performed were both sound and detailed, but the trial was small and of relatively short duration (8 weeks for each intervention arm), so little can be said about long-term effects beyond assumption, and the actual clinical impact on patients has yet to be fleshed out.

It is reasonable to consider the use of Pycnogenol in relatively healthy patients with CAD as long as it is understood that the research in this area is in its infancy. In addition, keep in mind that prior studies have indicated that the supplement can lower blood pressure and inhibit platelet activity, even though such actions were not detected in the current trial. ■

Aspirin for Everyone?

ABSTRACT & COMMENTARY

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This article originally appeared in the March 15, 2012, issue of Internal Medicine Alert. At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Wilke and Dr. Roberts report no financial relationships relevant to this field of study.

Synopsis: *Aspirin can reduce the risk of nonfatal myocardial infarction, but not mortality, in people without coronary vascular disease, at the expense of increased risk of bleeding. It should not be routinely recommended.*

Sources: Seshasai SR, et al. Effect of aspirin on vascular and nonvascular outcomes: Meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209-216. Mora S. Aspirin therapy in primary prevention: Comment on "Effect of aspirin on vascular and nonvascular outcomes." *Arch Intern Med* 2012;172:217-218.

SINCE 2009, THE U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF) has recommended the use of aspirin (ASA) "for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage" and "for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage."[1] These recommendations were based on a systematic review published in the *Annals of Internal Medicine*. Use of ASA for the secondary prevention of cardiovascular disease (CVD) is well established, but its use for primary prevention is less certain. There is an increased risk for gastrointestinal (GI) bleeding that accompanies ASA use that must be factored into the risk-benefit analysis. Since the 2009 publication, three additional articles have been published that were not included in the review.[4-6] Seshasai and colleagues have now performed a meta-analysis of randomized controlled trials (RCTs) that includes the newer data. They also looked at the evidence for ASA's role in the prevention of nonvascular disorders (e.g., cancer).

Seshasai et al searched MEDLINE and the Cochrane Library of Clinical Trials for RCTs that had at least 1000 participants with no history of coronary heart disease (CHD) or stroke. In addition, the studies' designs had to include at least 1 year of follow-up and provide data regarding CHD, stroke, cerebrovascular disease, heart failure, peripheral vascular disease, and bleeding events. Since the initial studies often did not report data on nonvascular outcomes, they searched for subsequent analyses of secondary outcomes that included cancer and other nonvascular endpoints. They also went back to the origi-

Summary Points

- Although there is good evidence for prescribing aspirin for secondary prevention of coronary heart disease, the tradeoff of increased non-trivial bleeding for reduction of nonfatal myocardial infarction (and no mortality benefit) may make primary prevention less appealing.
- It is reasonable to consider using aspirin for primary prevention in higher risk individuals without known cardiovascular disease.

nal investigators for unpublished data on secondary outcomes. Because the original investigators used different definitions of bleeding, Seshasai et al devised a category of "clinically non-trivial bleeding" encompassing fatal bleeding, cerebrovascular or retinal bleeding, GI bleeding, and bleeding requiring hospitalization or transfusion.

Their initial search produced 680 potentially relevant articles, which were narrowed down to nine after appropriate exclusion. These nine studies include 102,621 subjects and were published between 1988 and 2010. Three of the studies enrolled medical and nursing professionals and most of the subjects resided in Western nations. Average age of the subjects was 57 years, and 54% were female. Most of the RCTs enrolled people at increased risk for CHD. Average follow-up was 6 years, during which 2169 CHD events occurred. Nonfatal myocardial infarction (MI) accounted for 1540 CHD events; 592 MIs were fatal. There were 1504 strokes and 1512 cancer deaths. There were 40,712 bleeding events, of which 10,049 were nontrivial. ASA use reduced total CVD events by 10% (odds ratio [OR] 0.90; 95% confidence interval [CI], 0.85-0.96). Nonfatal MI was the largest contributor to this with a 20% reduction in risk (OR 0.80; 95% CI, 0.67-0.96), number-needed-to-treat (NNT) 162. There was no significant reduction in fatal MI, stroke, CVD death, or all-cause mortality. There was no reduction in cancer deaths. ASA increased the risk of total bleeding events by 70% (OR 1.70; 95% CI, 1.17-2.46) and nontrivial bleeding events by 31% (OR 1.31; 95% CI, 1.14-1.50), number-needed-to-harm (NNH) 73.

■ COMMENTARY

One way to view the conclusions of this meta-analysis is to look at the NNT for nonfatal MI events and the NNH for nontrivial bleeding events. Is treating 162 individuals with ASA to prevent one nonfatal MI worth at least two nontrivial bleeding events? The answer to this question depends on how you (and your patients) value MI prevention (hard to prove a negative) vs nontrivial bleeding (usually very apparent when it occurs). While there is good evidence for prescribing ASA for secondary prevention of CHD, the tradeoff of increased nontrivial bleeding for reduction of nonfatal MI (and no mortality benefit) may make primary prevention less appealing. Perhaps our other methods of primary prevention (e.g., smoking cessation, following a healthy diet and exercise program, control of hypertension, statin use, psychosocial stress management, aggressive diabetes treatment) are more effective and have made ASA less valuable.

Limitations of this meta-analysis include the inclusion of studies done among health professionals, who may not represent the average person in your practice. Strengths include the very large sample size and the timeliness of the studies that comprise the meta-analysis.

The USPSTF recommendations include a table that indicates by age when the risks of CHD for men and the risk of stroke for women exceed the risk of GI harms.[7] It also includes links to risk calculators to help you quantify your patient's risk. Some doctors may find this time consuming, and there is no evidence to date that there are subgroups that would benefit from primary prevention. However, as Mora's commentary concludes, "it is reasonable to consider using aspirin for primary prevention in higher-risk individuals without known CVD (above 1% CVD event rate per year) if they are deemed to have a greater benefit to risk ratio and after taking into account patient preferences."[8] I think I'll put away my bottle of baby aspirin. ■

References

1. http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm. Accessed Feb. 20, 2012.
2. Wolff T, et al. Aspirin for the primary prevention of cardiovascular events: An update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;150:405-410.
3. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-1860.
4. Belch J, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
5. Ogawa H, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. *JAMA* 2008;300:2134-2141.
6. Fowkes FG, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: A randomized controlled trial.

JAMA 2010;303:841-848.
7. http://www.uspreventiveservicestaskforce.org/uspstf09/aspirincvd/aspcvdsum.htm. Accessed Feb. 20, 2012.
8. Mora S. Aspirin therapy in primary prevention: Comment on "Effect of aspirin on vascular and nonvascular outcomes." *Arch Intern Med* 2012;172:217-218.

Niacin and Coronary Heart Disease

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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This article originally appeared in the February 15, 2012, issue of Internal Medicine Alert. At that time it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Roberts reports no financial relationships relevant to this field of study. Dr. Karpman serves on the speakers bureau for Forest Laboratories.

Synopsis: *Among patients with coronary heart disease and LDL-cholesterol levels less than 70 mg/dL, there is no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up, despite improvements in HDL-cholesterol and triglyceride levels.*

Source: The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-2267.

Elevated low-density lipoprotein (LDL) cholesterol levels are an established predictor for the risk of developing coronary heart disease (CHD), and, despite the fact that multiple primary and secondary prevention trials have shown a 25%-35% CHD risk reduction in patients receiving statin therapy,[1] a significant residual CHD risk persists even if target LDL cholesterol levels are achieved. Epidemiologic studies have demonstrated that in addition to elevated LDL cholesterol levels, low levels of high-density lipoprotein (HDL) cholesterol are an independent predictor of the risk of CHD with a strong inverse association between HDL cholesterol levels and the rates of incident CHD events.[2,3]

Aggressive lowering of lipid levels with high doses of statins to achieve a target LDL cholesterol level less than 70 mg/dL in very high-risk patients has resulted in major improvements in clinical endpoints. Treatment with simvastatin plus niacin has also resulted in significant regression of angiographic coronary atherosclerosis and reductions in the rate of clinical events.[4,5] The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) investigators prospectively studied 3414 patients who were being treated with simvastatin and randomly assigned them to receive either niacin or placebo. They determined that among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels less than 70 mg/dL, there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up, despite significant improvement in HDL cholesterol and triglyceride levels.[6]

Summary Points

- Niacin therapy appears to be of little value in patients with low LDL cholesterol levels, regardless of niacin's positive effects on HDL cholesterol levels and triglyceride levels.
- The primary goal of clinicians should be to lower LDL cholesterol levels to at least 70 mg/dL in patients at high risk for cardiovascular disease.

■ COMMENTARY

Currently, no one questions the cardiovascular benefits of target LDL-cholesterol reduction to less than 100 mg/dL and even to less than 70 mg/dL in high-risk patients. Also, continuing evolutions in medical therapy over the past several decades with the development of other disease modifying interventions, such as antiplatelet therapy and now beta-blocker and renin-angiotensin system inhibitors, are recommended for all patients who have had a myocardial infarction (MI) to improve outcomes and reduce the incidence of recurrent MI.[6] Raising HDL cholesterol levels has proven to be beneficial,[7,8] but the residual question has been whether there is a true benefit in raising the HDL cholesterol level in persons who have received effective statin therapy. The AIM-HIGH trial was designed to evaluate the possible benefit of adding niacin to statin therapy as compared to statin therapy with or without ezetimide but without niacin. The investigators were attempting to determine if a further decrease in the incidence of major cardiac events occurred among subjects with CHD who had residual dyslipidemia and low levels of HDL cholesterol at baseline but who have met a treatment goal by achieving an LDL cholesterol level of 40-70 mg/dL with statin therapy. It would appear from the results of the study that patients whose LDL cholesterol levels were intensively controlled with simvastatin therapy received no incremental benefit from niacin in reducing the cardiovascular events which occurred over a 36-month follow-up period, despite significant increases in HDL cholesterol and decreases in triglyceride levels.

In summary, the primary goal of clinicians should be to lower the LDL cholesterol to at least 70 mg/dL (although 50-60 mg/dL may be even better). Combined statin therapy and niacin therapy appears to be of little or no value in this group of patients regardless of its positive effects on the HDL cholesterol and triglyceride levels. Further studies will be required to determine whether the raising of HDL cholesterol levels in subjects whose LDL levels are not so intensely controlled will be of added value. ■

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376: 1670-1681.
2. Castelli WP, et al. Cholesterol and lipids in the risk of coronary artery disease — the Framingham Heart Study. *Can J Cardiol* 1988;4 Suppl A:5A-10A.
3. Assmann G, et al. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996;124 Suppl:S11-20.
4. Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-1504 [Erratum in *N Engl J Med* 2006;354:778.]
5. Barter P, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;357:1301-1310.
6. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255-2267.
7. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231: 360-381.
8. Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410-418.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

1. Carnitine is primarily available to healthy adults from:
   a. dietary sources, especially meat.
   b. biosynthesis within the body.
   c. vegetarian diets.
   d. prescription medications.

2. Carnitine plays an important role in:
   a. promoting oxidation of carbohydrates.
   b. neurological regulation of the heart.
   c. releasing metabolic energy from fatty acids.
   d. All of the above

3. Carnitine's use in patients with peripheral artery disease has been:
   a. discouraged due to serious adverse effects.
   b. recommended in combination with exercise.
   c. found to be ineffective.
   d. discouraged.

4. The meta-analysis of aspirin use for the primary prevention of cardiovascular disease (CVD) made what conclusion?
   a. Aspirin reduced the total rate of CVD events.
   b. Aspirin reduced the rate of fatal myocardial infarction.
   c. Aspirin reduced the rate of stroke.
   d. Aspirin reduced the rate of all-cause mortality.
   e. Aspirin reduced the rate of cancer mortality.

5. The addition of niacin therapy to statin therapy in patients with LDL cholesterol levels of less than 70 mg/dL:
   a. did not improve HDL cholesterol and/or triglyceride levels.
   b. demonstrated significant improvement in the rate of cardiovascular events and ischemic stroke frequency.
   c. demonstrated no significant incremental clinical benefit in the rate of deaths from CHD, nonfatal myocardial infarction, ischemic stroke, or hospitalization for an acute coronary syndrome.
   d. did not significantly raise the HDL cholesterol levels.

In Future Issues:

Tai Chi and Cardiac Function
Chocolate and Heart Health
Probiotics for Vulvovaginal Candidiasis