Table 1. Accuracy Data by Peripheral Region

Peripheral Vessels	n	Sensitivity	Specificity	PPV	NPV
Renal arteries	119	92%	92%	88%	92%
Carotid arteries	88	96%	100%	100%	95%
Total lower extremities	770	88%	96%	91%	90%
Iliac arteries	203	86%	95%	89%	80%
Femoral arteries	182	85%	100%	100%	94%
Superficial femoral arteries	193	90%	90%	90%	84%
Popliteal arteries	192	90%	96%	82%	98%

NPV = negative predictive value; PPV = positive predictive value.

identification of stenotic lesions >50% within the iliac arteries was sensitivity 86%, specificity 95%, PPV 89%, and NPV 80%. Identification of lesions >50% within the femoral arteries was sensitivity 86%, specificity 100%, PPV 100%, and NPV 94%. Identification of lesions >50% within the superficial femoral arteries was sensitivity 90%, specificity 90%, PPV 90%, and NPV 84%. Hemodynamically significant lesions (>50%) within the popliteal arteries were detected at sensitivity 90%, specificity 96%, PPV 82%, and NPV 98% via 64-slice peripheral CT.

With improved spatial resolution, decreased slice thickness, and reduced acquisition times, 64-slice CT angiography has the ability to detect significant atherosclerotic lesions of the peripheral vasculature, while maintaining the ability to reliably identify the absence of significant arterial blockage. Previous citations suggest that CT angiography is a valuable diagnostic tool, capable of accurately ruling out the presence of significant lesions based on sufficient specificity and negative predictive values (4,5). Previous limitations of CT angiography were the marginal ability to sufficiently detect significant lesions and positively predict disease at a high accuracy level (4). Our results suggest that the 64-slice generation of multislice CT has sufficient sensitivity and positive predictive value to allow peripheral CT angiography to be considered for routine diagnostic evaluations. The agreement between 64-slice peripheral CT and catheter angiography supports the strength of the latest generation of CT imaging.

The 64-slice peripheral CT angiography findings compare favorably with traditional catheterization in this study of patients assessed for PAD. The prospect of utilizing peripheral CT angiography in lieu of catheter angiography is appealing based upon the patient-friendly, non-invasive nature of the procedure, as well as the markedly reduced economic impact of CT angiography when compared to catheterization. Among the carotid, renal, and lower extremity arteries both sensitivity and specificity were sufficiently high to rely upon results of peripheral CT angiography when evaluating the presence of PAD.

Our analysis suggests that 64-slice peripheral CT angiography is an accurate and reliable method of non-invasively assessing PAD. The noninvasive nature of this diagnostic test allows for PAD detection that is time efficient for both the patient and medical care providers. Collectively, these advantages of 64-slice peripheral CT angiography may enhance its use as a PAD diagnostic tool.

***Jeffrey J. Fine, PhD, MS**

*Cardiovascular Innovations (CVI), LLC
Vice President of Research and Education
10 Judge Island Drive
Beaufort, South Carolina 29907
E-mail: jfine@csaheart.com

Patrick A. X. Hall, MD, FACC
J. Huger Richardson, MD, FACC
Lee O. Butterfield, MD, FACC

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). National Vital Statistics Reports. New CDC Report on U.S. Mortality Patterns. 1999.
2. Criqui MH, Denenberg JO, Langer RD, et al. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. Vasc Med 1997;2:221–6.
3. Nieman K, Cademartiri F, Lemos PA, Raaijmakers R, Pattynama P, Feyter PJ. Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography. Circulation 2002;2106:2051–4.
4. Schoepf UJ, Becker CR, Ohnesorge BM, Yucel EK. CT of coronary artery disease. Radiology 2004;232:18–37.
5. Fine JJ, Hopkins CB, Hall PA, Delphia RE, Attebery TW, Newton FC. Noninvasive coronary angiography: agreement of multi-slice spiral computed tomography and selective catheter angiography. Int J Cardiovasc Imaging 2004;20:549–52.

Letters to the Editor

Serum Plant Sterols and Atherosclerosis: Is There a Place for Statin-Ezetimibe Combination?

We read with interest the paper by Miettinen et al. (1) demonstrating that the higher the absorption of cholesterol, the higher the plant sterol contents are in serum resulting in their higher contents in atherosclerotic plaque. The prospective Cardiovascular Münster (PROCAM) study found that people in the upper quartile of sitosterol levels had a 1.8-fold increased risk of major coronary events compared with those in the lower three quartiles (2). Statin treatment decreases cholesterol synthesis but increases absorption of plant sterols (3). In the Scandinavian Simvastatin Survival Study (4S), no reduction was observed in recurrence of coronary heart disease with the use of simvastatin in patients with high baseline plant sterol contents and with marked increase of serum plant sterols during the five-year treatment period (4). Additional treatment with inhibition of sterol absorption (e.g., with plant stanol esters) was suggested for this particular group of patients (3,4). To this respect, we were surprised that Miettinen et al. (1) did not consider the potential of combining ezetimibe with statin. Indeed, in addition to inhibiting intestinal cholesterol absorption, a well-known effect, ezetimibe also reduces plasma concentrations of the non-cholesterol sterols sitosterol and campesterol, suggesting an effect on the absorption of these compounds as well (5). It has been demonstrated recently that the Niemann-Pick

C1-like 1 (NPC1L1) transporter is most likely responsible for the transport of cholesterol and plant sterols from the brush border membrane into the intestinal mucosa (6). The intestinal absorption of plant sterols differs markedly from that of cholesterol and their biliary excretion as well. The presence of two specific ABCG5/ABCG8 transporters in the intestinal wall is responsible for rapid resecretion of plant sterols into the intestine lumen and thus rather low intestinal absorption of campesterol and sitosterol, and their presence in the liver explains why plant sterols are excreted much faster in the bile than cholesterol (7,8). Ezetimibe interferes with NPC1L1, reducing the intestinal uptake of cholesterol and plant sterols (6–8). Interestingly, the reduction of plant sterol serum levels with ezetimibe was significantly more pronounced than the reduction of serum cholesterol (7,8). Clinical data on ezetimibe could demonstrate that the concept of inhibiting intestinal absorption of neutral sterols is beneficial in both patients with hypercholesterolemia as well in patients with hypersitosterolemia, an inherited disease with identified mutations in ABCG5/ABCG8 transporters that leads to a high prevalence of cardiovascular disease (9). Recent observations, such as those by Miettinen et al. (1), that elevated serum plant sterols pose an increased cardiovascular risk suggest that increases of serum plant sterol levels should be avoided, especially in atherosclerosis-prone individuals (1). Therefore, subjects with high cholesterol absorption and low synthesis may need a therapy combining statin and ezetimibe to lower more effectively their serum cholesterol levels and prevent an increase in the levels of plant sterols (3). The question remains, however, as to whether lowering serum levels of plant sterols (especially in high-absorber patients on statin therapy) with a drug such as ezetimibe will decrease the incidence of coronary artery disease.

***Régis P. Radermecker, MD**
André J. Scheen, MD, PhD

*Division of Diabetes, Nutrition, and Metabolic Disorders
Department of Medicine
CHU Liège
University of Liège
B-4000 Liège
Belgium
E-mail: regis.radermecker@ulg.ac.be

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REFERENCES

1. Miettinen TA, Railo M, Lepäntalo M, Gylling H. Plant sterols in serum and in atherosclerotic plaques of patients undergoing carotid endarterectomy. J Am Coll Cardiol 2005;45:1794–801.
2. Assmann G, Cullen P, Erbey JR, et al. Elevation in plasma sitosterol concentration is associated with an increased risk for coronary events in the PROCAM study (abstr). Circulation 2003;108:IV730.
3. Miettinen TA, Strandberg TE, Gylling H, for the Finnish Investigators of the Scandinavian Simvastatin Survival Study Group. Noncholesterol sterols and cholesterol lowering by long-term simvastatin treatment in coronary patients. Relation to basal serum cholesterol. Arterioscler Thromb Vasc Biol 2000;20:1340–6.
4. Miettinen TA, Gylling H, Strandberg T, Sarna S, for the Finnish 4S Investigators. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian simvastatin survival study. BMJ 1998;316:1127–30.
5. Sudhop T, Lütjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002;106:1943–8.
6. Davis HR, Zhu LJ, Hoos LM, et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole body cholesterol homeostasis. J Biol Chem 2004;279:33586–92.
7. von Bergmann K, Sudhop T, Lütjohann D. Cholesterol and plant sterol absorption: recent insights. Am J Cardiol 2005;96 Suppl:10D–4D.
8. Sudhop T, Lütjohann D, von Bergmann K. Sterol transporters: targets of natural sterols and new lipid lowering drugs. Pharmacol Ther 2005;105:333–41.
9. Salen G, von Bergmann K, Lütjohann D, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation 2004;109:966–71.

REPLY

In the letter by Drs. Radermecker and Scheen, it was noted that we have not commented the potential of combining ezetimibe to statins (1). The additional low-density lipoprotein (LDL) lowering of combining cholesterol absorption inhibitors to statins is relatively small, usually approximately 15%, for instance, for ezetimibe or plant stanols. No clinical studies have been published defining their additional reduction of coronary events during these treatments, which seems to be true also for their monotherapy, even though they are suitable for treatment of modestly increased LDL cholesterol, and stanol ester management also provides the heart-healthy fatty acids. Relatively low LDL cholesterol lowering either in mono- or in combination with statin treatment certainly requires randomized large-enough study populations treated for relatively long periods of time to record changes in heart events. In addition to LDL cholesterol lowering, cholesterol absorption inhibitors lower also plant sterol levels off or on statin treatment. Thus, they also normalize statin-induced increase of plant sterols. The endarterectomized patients treated with statin in our study had increased serum plant sterol ratios to cholesterol, which appeared also to be reflected in atheromatous plaques of carotid arteries (1). This finding certainly rises a question as to whether the lowering of serum plant sterols with cholesterol absorption inhibitors, e.g., ezetimibe or plant stanols, also could reduce plant sterol contents in the plaques. However, it also raises the question of whether an increase of serum plant sterols, e.g., during the consumption of plant sterol-enriched functional foods, also could enhance their concentrations in atheromatous plaques. Several studies have shown that increased serum plant sterols, even their ratios to cholesterol, are associated with enhanced coronary artery disease in crossover or follow-up investigations (2). However, in the Scandinavian Simvastatin Survival Study, no association was found in the control group between the five-year coronary events and baseline plant sterol concentrations or ratios to cholesterol (2). In the respective simvastatin treatment group, coronary events were reduced significantly in the low absorber but unchanged in the high absorbers, suggesting that additional lowering of LDL cholesterol is needed in the latter type of patients, e.g., by combination with cholesterol malabsorption. Statin treatment seems to improve endothelial function of carotid arteries despite increasing serum plant sterols (3); however, vascular function was unaffected with phytosterol-enriched food when LDL cholesterol was lowered and serum plant sterols were increased (4,5). Drs. Radermecker and Scheen concluded that "elevated serum plant sterols pose an increased cardiovascular risk," but clinical heart event reduction with their pharmacological lowering is still open.

***Tatu A. Miettinen, MD, PhD**
Mikael Railo, MD, PhD
Mauri Lepäntalo, MD, PhD
Helena Gylling, MD, PhD