

# A Simple Risk Prediction Tool Remains Elusive

BY SUSAN LONDON

FROM THE WORLD CONGRESS ON HEART DISEASE

VANCOUVER, B.C. – Subclinical markers of cardiovascular disease are helping to better predict the risk of clinical events in asymptomatic adults, according to Dr. Michael H. Criqui. But the search continues for a simple risk-estimation tool that relies on just a few powerful factors.

Standard CVD risk factors, based on the Framingham score, are often the starting point for comparisons, he told attendees at the congress, which was sponsored by the International Academy of Cardiology.

“The question is whether additional information gathered either from biomarkers or from subclinical markers of [CVD] can significantly add to the prediction based on these ... standard risk factors,” said Dr. Criqui, chief of the division of preventive medicine at the University of California, San Diego.

Improvement of CVD risk prediction is complicated by the many different statistical metrics used to assess the added value of these factors and variation in how demanding these measures are for demonstrating a gain in predictive value, he observed.

Dr. Criqui gave an update of results from the 10-year prospective

Multi-Ethnic Study of Atherosclerosis (MESA), exploring CVD risk prediction. The study enrolled 6,814 men and women aged 45-84 years from six U.S. communities who had no clinical evidence of CVD at baseline. Slightly more than half were female. Thirty-nine percent were white, 28% black, 22% Hispanic, and 12% Asian, mainly Chinese. (Percentages are rounded.)

In addition to measuring standard risk factors, the researchers assessed novel biomarkers and subclinical markers of CVD: coronary artery calcium on CT, carotid artery intima-media thickness (IMT) on ultrasound, flow-mediated dilation in the brachial artery, and ankle-brachial index (ABI).

Dr. Criqui, who was on the MESA planning committee 15 years ago, recalled that “the idea was that we should be able to get a parsimonious estimation of risk” without having to “measure everything.” Two or three key factors might provide the necessary information, he said.

## Coronary Artery Calcium

Studies have shown that of the four subclinical markers, coronary artery calcium is the strongest predictor of CVD outcomes overall and of coronary outcomes in the MESA population, according to Dr. Criqui.

For example, participants with a coronary artery calcium score that exceeded 300 (0 = no evidence of disease; 400 = extensive evidence) had an adjusted 9.7-fold increased risk of coronary events and a 6.8-fold increased risk of major coronary events, relative to their counterparts with a score of 0 (N. Engl. J. Med. 2008;358:1336-45). Moreover, it was a consistent predictor in all four racial/ethnic groups.

Coronary artery calcium also improved risk prediction when added to standard risk factors, as assessed from receiver-operating characteristic (ROC) curves, with the

area under the curve increasing for prediction of both coronary events (from 0.77 to 0.82;  $P$  less than .001) and major coronary events (from 0.79 to 0.83;  $P$  = .006).

“In the world of ROC curves, that’s a huge improvement,” Dr. Criqui commented. “So that’s probably the most powerful sort of new risk factor or measure that we found in this study.”

## Carotid IMT

The picture is less clear-cut

for carotid IMT, with analyses that use different statistical measures arriving at different conclusions, according to Dr. Criqui.

Within given ranges of coronary artery calcium scores, carotid IMT stratified MESA participants according to their rate of CVD events, suggesting that it indeed improves risk prediction (Arch. Intern. Med. 2008;168:1333-9).

But when the measure was added to other standard risk factors, carotid IMT only slightly increased the area under the ROC curve for both coronary events (from 0.77 to 0.78) and CVD events (also from 0.77 to 0.78).

“And if you have coronary calcium in the model, clearly adding IMT gives you almost nothing,” Dr. Criqui added. “So this is a little bit paradoxical.”

At the same time, analyses showed that among the various subclinical markers, carotid IMT was the strongest predictor specifically of the risk for stroke.

## Flow-Mediated Dilation

The findings for flow-mediated dilation in the MESA population have similarly been mixed, Dr. Criqui said.

When this factor was added to standard risk factors, the area under the ROC curve for predicting CVD events was unchanged, at 0.74 (Circulation 2009;120:502-9).

But flow-mediated dilation independently predicted CVD events. Also, it yielded a net 29% improvement in the correct classification of participants according to whether they experienced an event ( $P$  less than .001), mainly because of a 52% improvement in correctly classifying which participants would not experience events.

“Here is a marker with no improvement at all in the ROC curve, and yet you are substantially able to better predict who will get an event,” Dr. Criqui observed.

However, this substudy did not adjust for the other subclinical CVD markers. “If it had adjusted for those, I think it would have been less impressive,” he commented.

## Ankle-Brachial Index

A recent analysis, to be published in full later this year, has shown ABI to be an independent predictor of CVD events in MESA participants, according to Dr. Criqui.

“We sort of gave the ankle-brachial index the third degree, if you will,” he elaborated. The investigators adjusted the analyses for standard risk factors, novel risk factors, coronary artery calcium, carotid IMT, and major electrocardiographic abnormalities at baseline.

After these adjustments, participants with a low ABI (lower than 1.0) and those with a high ABI (1.4 or greater) both had a roughly doubled risk of CVD events relative to their counterparts with a normal index.

In addition, after the exclusion of participants with a high ABI, each 0.1-unit increase in this index was associated with a reduced risk of CVD events across the four racial/ethnic groups studied (hazard ratios, 0.74-0.87). This index also increased the area under the ROC curve for predicting such events ( $P$  = .02).

“Better classification of cardiovascular disease risk is indeed an important goal clinically,” concluded Dr. Criqui. And to that end, MESA has helped by identifying a set of subclinical markers that improve risk prediction.

However, “I think the parsimonious assessment of CVD risk is still elusive, since – much like the cardiovascular disease risk factors themselves – different subclinical cardiovascular measures appear to contribute independently to risk,” he commented. “Everything we try seems to add a little bit, to a greater or lesser degree, to risk prediction.” ■

## VITALS

**Major Finding:** Coronary artery calcium, carotid IMT, flow-mediated dilation, and ABI are improving the ability to predict the risk of CVD events in apparently healthy adults, but research has yet to identify a simple risk-estimation tool that uses just a few key factors.

**Data Source:** The 10-year, prospective MESA study was among a multiethnic sample of 6,814 U.S. adults, aged 45-84 years, who were clinically free of CVD at baseline.

**Disclosures:** The National Heart, Lung, and Blood Institute is sponsoring the study. Dr. Criqui reported that he had no relevant conflicts of interest.

# Smoking Raises Peripheral Artery Disease Risks in Women

BY MITCHEL L. ZOLER

FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – A history of either current or former smoking posed a major risk for peripheral artery disease in the Women’s Health Study, a prospective epidemiologic assessment of nearly 40,000 health professional women who were followed for almost 13 years.

The results “underscore the importance of smoking as a risk factor for developing symptomatic PAD,” Dr. David Conen said at the congress.

Although smoking cessation substantially reduced PAD risk, former smokers who were abstinent for longer than 1 year still had about a threefold higher risk

for PAD than did never-smokers in the study, said Dr. Conen, a cardiologist at University Hospital Basel (Switzerland).

The analysis included 39,825 women who were enrolled in the Women’s Health Study and had smoking data available at baseline. All women in the study were at least 45 years old (average age, 55 years) and free of cardiovascular disease at entry. In all, 51% had never smoked at baseline, 36% smoked in the past, 5%

currently smoked fewer than 15 cigarettes daily, and 8% smoked at least 15 cigarettes daily. During an average 12.7 years of follow-up, 178 women developed

symptomatic PAD, either intermittent claudication or need for peripheral artery surgery. The study included no data on

and physical activity, women who currently smoked at least 15 cigarettes daily had a 17-fold higher risk for symptomatic PAD than did never-smokers.

Current smokers of fewer than 15 cigarettes daily had a ninefold higher risk, and past smokers had a threefold higher risk.

When data were analyzed in a slightly different way, all current smokers had a 14-fold higher risk, compared with never-smokers; women who quit within the past year at baseline had an 11-fold in-

creased risk; and women who had been off cigarettes longer than 1 year at baseline had a threefold higher risk for PAD. Dr. Conen said he had no disclosures. ■

## VITALS

**Major Finding:** Cigarette-smoking women had a 14-fold increased risk for symptomatic peripheral artery disease during 13 years of follow-up, compared with never-smokers. Women who stopped smoking at least a year before entering the study had a threefold increased risk.

**Data Source:** Prospective follow-up of 39,825 women enrolled in the Women’s Health Study with smoking data at baseline.

**Disclosures:** Dr. Conen said he had no financial conflicts.

subclinical or asymptomatic PAD.

In a multivariate model that adjusted for age, hypertension, diabetes, hypercholesterolemia, body mass index, alcohol use,