Twilight zone for CVD risk markers?

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February 2013—Times are tough all over. For the middle class, for newspapers, for François Hollande and his fellow French Socialists.

Consider adding cardiac risk markers to that list. Despite decades of research and clinical experience, the marker conversation—what to measure, how, in whom—has become more an endless loop than a solid lineup. Old standbys still turn up in studies of novel markers, and tests that have arguably outlasted their usefulness still adhere, like barnacles, to laboratory menus. Some observers are even questioning the tenets of risk assessment.

While no one is putting cardiac risk markers on the endangered species list, they might no longer be the trophies in cardiology's big game hunt, either. In wide-ranging interviews with CAP TODAY, three cardiac experts offered their off-center views on the field.

If, as some suggest, the search for a magic bullet is languishing, what now? Philip Greenland, MD, predicts a novel approach to risk assessment.

He's co-author of a study (Yeboah J, et al. *JAMA*. 2012;308:788–795) comparing novel markers for enhancing cardiovascular risk assessment in intermediate-risk individuals, a group that some feel is ripe for more-refined risk stratification. The study suggested that coronary artery calcium was the best marker for discriminating between higher- and lower-risk patients in that middle group. High-sensitivity C-reactive protein, like CAC, ankle-brachial index, and family history, also performed as an independent predictor of coronary heart disease/cardiovascular disease, though with less oomph—for incident CHD, it provided the least reclassification improvement when added to the Framingham Risk Score.

The real surprise for laboratories, however, might be the notion that hs-CRP was considered to be a novel marker. By now it should be as familiar in the mouths of physicians as the household names Henry V reels off in his St. Crispin's Day speech.

CRP is not a newcomer, acknowledges Dr. Greenland, the Harry W. Dingman professor of cardiology, Departments of Preventive Medicine and Medicine, Northwestern University Feinberg School of Medicine, Chicago. Its status as an acute-phase reactant has been known for three or four decades, while its association with cardiovascular risk became apparent in the past 15 years or so. Enthusiasm for this marker was understandably high, as it seemed to confirm the hypothesis that the atherosclerotic process was an inflammatory one.

Dr. Stanley Hazen and his colleagues at the Cleveland Clinic are exploring links between phospholipids, gut flora, and cardiovascular risk. “It’s almost as if the gut flora is an endocrine organ,” he says, “making hormones or biologically active species that are acting at a distant site.” [Photo: Dale Dong]

Yet hs-CRP continues to be scrutinized. To what extent is it truly predictive of cardiovascular events, asks Dr. Greenland, especially when other markers—lipid markers, for example—are more available and easily treatable? Even in the JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), the largest to use CRP as a test for sorting risk, the optimal treatment was a lipid-lowering drug, not a classic anti-inflammatory, he says.

“Lots of studies have shown the limited predictive capability of CRP,” says Dr. Greenland, including the aforementioned *JAMA* study.

No one’s picking on CRP. Other studies continue to scratch the same patches of dirt, assessing and re-assessing the likes of fibrinogen, apolipoprotein B, apolipoprotein A-I, lipoprotein(a), homocysteine, and various cytokines, as well as what they mean when added to warhorses such as total cholesterol and high-density lipoprotein cholesterol.

And these are just the laboratory markers. You’d be hard-pressed to find a cardiologist who isn’t equally (if not more) captivated by imaging studies, or a preventive medicine physician who’s willing to shun seemingly quaint lifestyle markers related to exercise, diet, weight, and smoking.

The table is full of markers, in short. If, after decades of looking for the ideal marker, no winner has emerged, maybe it’s because people are playing the wrong game.

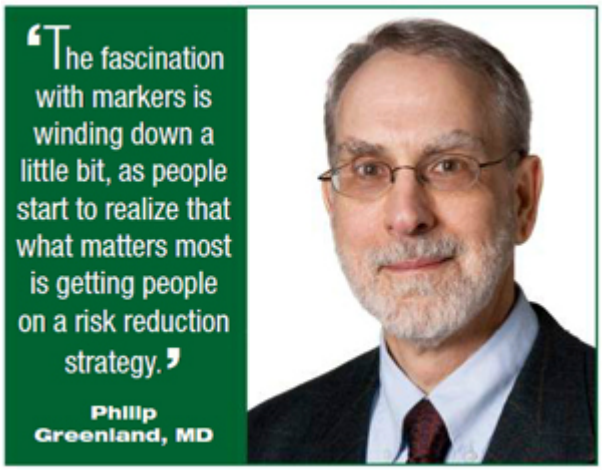
The hunt for cardiac risk markers began in earnest some 15 years ago, motivated by honorable intentions. When researchers started getting excited about finding new predictive markers, says Dr. Greenland, it was in the context of clinical practice guidelines that were suggesting it was important to know where a person fell on the risk spectrum. The chase was on. “Everyone, including me, expected we would find the magic bullet.”

At the time it hadn't been shown that statins could lower risk in intermediate- and lower-risk people, he says. That's no longer the case. But even as recently as five years ago, there was plenty of enthusiasm for knowing as precisely as possible where people fell on the risk spectrum, given the questions about the cost and clinical effectiveness of statins.

That need may be fading, Dr. Greenland suggests, though he adds that his views are not reflected in current guidelines. "I'm talking about tomorrow's medicine, not today's," he says. Statins are powerful, like having the president on speed dial. Clinical trials are now showing that for patients at fairly low levels of risk, statins lower that risk even more. The issue then becomes less about markers/stratification and more about statins' cost (they're cheap) and patient tolerance (it's good).

If the quality of risk prediction is important, Dr. Greenland says, "Then it would matter if we could find the marker that was one size fits all—a test that we want to do in everybody, sort of like a mammogram for breast cancer risk.

"On the other hand, for cardiovascular risk, there are people who say the cardiovascular mammogram is the coronary CT," he continues. Though not every finding is a high-risk lesion, "Pretty much everything you see on a mammogram means there's something you need to be thinking about. Those who are advocates of coronary CT say the same thing." A lesion may not necessarily lead to a heart attack, but an absence of lesions means a person is at low risk.



If coronary calcium is the closest thing providers have to a magic bullet for CAD, however, its cost and the risks of radiation exposure make its broader use a questionable strategy. Nor is Dr. Greenland convinced that the breast cancer–CAD comparison should be stretched much further, given that breast cancer occurs at about one-tenth the rate of coronary disease.

In fact, on the disease spectrum, he places CAD closer to cavities than cancer. Both tooth decay and CAD are widespread in the population. Both can be relatively easy to prevent with lifestyle changes. And both rarely are. Ideally, people would stop eating candy and brush thrice daily, as Dr. Greenland puts it. But since that doesn't happen, the choice has become to treat the population at large by fluoridating the water. "Then everybody is covered."

A similar approach might be worth considering in CAD. So many people are at risk for CAD, Dr. Greenland says, "I would predict that more people with a risk factor will go on statins, sort of like most people today who perceive any sort of risk go on a low-dose aspirin. And if all of what I'm saying is true, then the use of markers becomes much less critical."

"What I see happening is that the fascination with markers is winding down a little bit," he says, "as people start to realize that what matters most is getting people on a risk reduction strategy."

If the magic bullet is a treatment and not a test, however, it's a little strange to Dr. Greenland that third-party payers have not yet calculated the price at which statins could be used among a wider swath of the population. "The effectiveness of statin therapy in low-risk people is published. That's not a secret."

Perhaps health care reform will push matters in that direction; at the very least, he predicts, providers will spend less energy fine-tuning risk.

That sounds like a smaller role for laboratories. Per Dr. Greenland, however, the best labs will continue to offer more than testing. Some already take test results and calculate coronary risk, using, say, the Framingham Risk Score and combining that with clinical recommendations from national guidelines. Laboratories could also work with clinicians to formulate testing strategies for patients. “That could be useful, because a lot of times clinicians get information back and have difficulty integrating it themselves. They may not know what the next step is,” he says.

One other player has gone noticeably silent on the topic of cost savings, says Allan Jaffe, MD. That would be the makers of markers, who, quite reasonably, have to eye market share and profit. “Quite frankly, the companies are ignoring cost containment,” says Dr. Jaffe, a clinical cardiologist and professor of medicine and laboratory medicine and pathology, Mayo Clinic.

That’s cause for concern, especially as health care spending becomes yet again a focus of attention. But Dr. Jaffe, who’s also chair of the Division of Clinical Core Laboratory Services in Mayo’s Department of Laboratory Medicine and Pathology, says any discussion of new markers first needs to address a more primal question: Is the proposed marker any better than what’s currently available? If it isn’t, then the discussion can stop right there.

It’s a hard question to answer. As the hs-CRP discussion has shown, even longstanding markers undergo periodic inquisitions. Dr. Jaffe draws attention to LDL cholesterol testing methods. It’s been clear for years, he says, that the current method of calculating LDL, using the Friedewald equation, has problems because of its reliance on triglycerides. At Mayo, the lab won’t report LDL cholesterol if triglycerides are above 400 mg/dL, though Dr. Jaffe says there’s a reasonable argument to be made that LDL results are confounded when triglyceride levels are lower, perhaps even 200 mg/dL. “So you’re talking about a fairly substantial number of patients.”

In that group, advanced lipid testing might be preferable. Most data show a modest but statistically significant improvement in using LDL particle number or apo B over LDL cholesterol. But, practically speaking, LDL cholesterol is cheap and widely available on multiple platforms. “New testing will be substantially more expensive than prior testing,” Dr. Jaffe says. It’s a complicated tradeoff. What’s the incremental benefit versus the incremental cost of making the switch?

He’s happy to enumerate other questions. How valuable is it to parse out yet another subset of patients—those with high triglycerides—and perform additional tests? Is that subset so large that perhaps a new paradigm, rather than more testing, is in order? And what is the ideal cutoff for triglycerides? The generally accepted level of 70 mg/dL for LDLc is an extrapolation from studies that haven’t asked the question directly, he says. Moreover, most of these studies used calculated LDL—what’s the best way to extrapolate those findings to other methods of determining LDL?

“There are some substantial scientific issues that need to be addressed,” says Dr. Jaffe. “It’s fair to say that there are some patients in whom apo B or LDL-P is apt to be better. But is it enough that we ought to do it on everybody?”

Those who aren’t defeated by the scientific challenges face another foe: behavior. Laboratories have spent years educating physicians about how to measure LDL and how to respond to it. A new method would have to be dramatically better “to want to go through the pain and suffering of re-educating everyone,” Dr. Jaffe says.

Then there’s the patient versus government dialectic. Government is talking about cost because that’s what government wants to reduce. Patients are fine with that. Sort of. “They say, ‘You save money—on someone else,’” says Dr. Jaffe. There’s no shortage of patients who worry about their cardiovascular health, whether they need to or not, and who will demand a new test either because they think it will be of benefit to them personally, or that it’s better, and therefore preferable, in general.

To keep things in balance, laboratories can try removing rusty markers from the menus, although one lab’s castaway could be a clinician’s keepsake, he cautions. “Clinicians have gotten used to certain things over time.” In relationships, familiarity breeds contempt, but in medicine it breeds higher test volumes. Some years ago Mayo

Clinic discontinued use of the bleeding test, a seemingly reasonable move "because there was absolutely no evidence it worked," Dr. Jaffe says. The test did not go gentle into that good night. Recalls Dr. Jaffe: "It was a war."

Rightly or wrongly, clinicians had relied on it. "And now we were taking it away."

Dr. Jaffe is not placing blame. "Life's busy. From the clinicians' point of view, do they want to spend three hours with the lab talking about getting rid of a test they like, or would they rather see more patients?"

Nonetheless, any serious discussion about containing costs should include dropping unnecessary markers, and labs are the ones best able to start those discussions. His lab is now looking at dropping the erythrocyte sedimentation rate, but it won't happen without talking to clinicians first. It's not just to avoid angering clinical colleagues. Those same colleagues are the ones who can decide to send their patients to other hospitals if the laboratory doesn't provide the tests they want. And even if the lab sees no value in a test, it doesn't know how it's used by every clinician. By dropping it, "You may be doing some harm," Dr. Jaffe cautions.

Dr. Jaffe sees the world the way it actually works, which helps explain his view of the marker story. If markers are losing some of their luster, it's for reasons that stretch beyond pure science, he says. The most basic risk markers—weight, exercise, family history, smoking—are the easiest and cheapest to assess, but, echoing Dr. Greenland, he notes that that's no guarantee of success. "We are in a society where sexy wins," says Dr. Jaffe.

That's one reason why biomarkers also receive less attention than imaging studies, he continues. Medical testing may have the equivalent of an old-boy network as well: Imaging historically has been developed by cardiology, not the laboratory, and that's where cardiology's interests naturally turn. It's also to cardiology that reimbursement goes. In short, "Lab testing isn't fun for clinicians. They don't understand it, and they don't get any remuneration from it," says Dr. Jaffe.

Like Dr. Greenland, Dr. Jaffe sees both pros and cons of using cardiac calcium. It's expensive. It exposes patients to radiation. Cardiac calcium scores don't necessarily provide a clear next step either, beyond the obvious—work on lowering a patient's risk. If the "sexy wins" model is viable, though (and it probably is—look how many people follow the gospel of Dr. Oz versus the recommendations of their own boring GP), a cardiac calcium score might spur patients to comply.

As section head of preventive cardiology, Cleveland Clinic, Stanley Hazen, MD, PhD, is all too familiar with patient noncompliance. He says new biomarkers could help give patients an extra push, including those who are at high risk.

"Maybe you need other tests to energize the patient to be compliant with diet, exercise, medication," he says. LDL cholesterol no longer packs a fear factor, but inflammation markers do—and that's important, he says, because the average patient who's prescribed a statin only takes about a third of a year's worth of the medication. "It's as low as a quarter to as high as 40 percent," he says. (Men, he says in an aside, "are actually, believe it or not, a little better at filling their prescriptions than women." More evidence, perhaps, that CVD is an unpredictable science.)

His clinical work goes hand-in-hand with research efforts—he's also department chair of cellular and molecular medicine at the Cleveland Clinic's Lerner Research Institute. His main focus has been on the mechanisms of atherosclerosis and plaque vulnerability. His research group was one of the first to focus on myeloperoxidase, an enzyme linked to both; MPO has become a marker for identifying CVD risk in patients who otherwise might not be identified by other laboratory tests.

More recently, they've begun looking at metabolomic studies. While cholesterol and triglycerides have dominated the CVD discussion, Dr. Hazen and his colleagues have been asking questions about another class of lipids—phospholipids. (Last summer they received a nearly $5 million grant from the National Heart, Lung, and Blood Institute to continue this work.)

A paper published in *Nature* (Wang Z, et al. 2011;472:57–65) looked at the promising relationship between the gut flora-dependent metabolism of dietary lipid phosphatidylcholine and CVD pathogenesis. Three

metabolites—choline, TMAO, and betaine—were shown to predict CVD risk, which could open the door to new tests and therapies. “Trimethylamine *N*-oxide looks like it’s going to be a very strong and complementary diagnostic test that helps identify people at risk” who otherwise would go unrecognized, based on traditional markers and tests, Dr. Hazen says.

The notion is straightforward. What we eat is absorbed through the filter of our intestinal flora. Even the average grade-schooler knows what foods are healthful and which aren’t, in general, but there’s currently only limited testing to tailor diets to an individual. Those who generate significant amounts of TMAO might need to decrease their intake of animal products, Dr. Hazen says, noting that foods that have high phosphatidylcholine also tend to be the same ones that have high fat and high cholesterol.

He’s even more excited by the concept behind this work: that gut flora can generate compounds that are biologically active and contribute to disease processes. “It’s almost as if the gut flora is an endocrine organ, making hormones or biologically active species that are acting at a distant site.” And, perhaps, that are worth monitoring at the individual level to determine the pathway’s contribution to heart disease.

He’s aware that new markers face an uphill battle. Just look at hs-CRP, he says. Which, of course, we have. Dr. Hazen points to the “incredible data” supporting its use. “From a statistical standpoint, it’s as good as a cholesterol level,” even if it’s not mechanistically linked to CVD the way cholesterol is.

It takes time and money to prove something works in medicine, and even then, the cost-benefit discussions are subjective. It’s a gray line, he says, not a black-and-white one. These are hard questions, and there’s no one right or wrong answer. He too refers to the JUPITER trial. “Every pharmaceutical company CEO would give his right arm to have a trial be as positive as that was,” he says. Though the trial showed significant benefit of putting patients on a statin if they had a normal cholesterol and high CRP, plenty of clinicians still argue that the evidence is insufficient to change guidelines. “It’s all in the mindset of the physician.”

Dr. Hazen shares Dr. Greenland’s fondness for statins. He takes as an example a person in his or her early twenties with an LDL on the higher side—135–140 mg/dL. National treatment guidelines say it’s an option to treat that patient with medications, but such a patient, as well as the physician, will often prefer lifestyle changes over a prescription drug. “And then they disappear from physician’s view for the next quarter of a century,” he says. “The next time they show up is with their heart attack, or an angioplasty requirement.” One could argue that pregnant women will see their physicians in the interim, but rarely does that include preventive, cholesterol-related care, he says.

He’s not all that interested in further refining risk categories. Like Berlioz, he thinks big. In preventive cardiology, that means making risk a broad, lifetime category of sorts. So, in the above scenario, Dr. Hazen recommends that the young adult go on a statin. “That’s the very person who’s going to have the single most benefit. It’s your life exposure to cholesterol that counts.”

His concern for low-risk patients is essentially a call for expanded testing. That may be a tough sell in the current cost climate, but he notes that just as he and his preventive cardiology colleagues at Cleveland Clinic add new markers to their algorithms, they’ll also vote old ones off the menu.

Five years ago, that happened to homocysteine. It was part of an initial panel for new patients, and those with high levels were given folic acid and B-complex vitamins. Studies have since shown that while the supplements lowered homocysteine, they didn’t lower cardiovascular risk. “Homocysteine does predict risk,” he says. “But it came off our panel because it raised more questions about what to do next.”

No one marker, but not too many. Trying to get it right, one could sympathize with Henry V at Agincourt. There, too, it was a matter of numbers. Bedford and Exeter, Salisbury, Westmoreland—all calculated the size of the troops and felt the English army lacking. Henry, of course, famously wished for not one man more.

Henry and his band of brothers turned out to be enough. But that was fiction, and it was written by Shakespeare. No wonder it worked. In cardiology, it’s anyone’s guess what the right mix will be.

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