Coronary angiography uses a contrast agent and X-ray imaging to search for blockages in the heart's blood vessels.

DIAGNOSTICS

The new risk predictors

New imaging methods and biomarkers may help identify people who are at risk for heart disease but are overlooked by standard risk assessments.

BY PETER GWYNNE

Doctors have long recognized the basic risk factors for cardiovascular disease: age, sex, high blood pressure, high cholesterol, smoking, diabetes and a family history. But these criteria have two significant limitations: many people with all these risk factors do not suffer heart problems, and dying of a heart attack is hardly unknown in people with none of the risk factors. According to cardiologist Jonathan Murrow at Georgia Health Sciences University in Augusta, one-third of the sudden deaths arising from coronary artery disease come without warning[1].

Clinicians have developed new ways of calculating the risk of cardiovascular disease (CVD) for those without any of the traditional risk factors. One new approach involves screening patients for certain biomarkers — through blood tests or imaging technology — that correlate with a higher than usual risk of a major cardiovascular event. So far, the cardiology community remains divided on the value of such non-traditional methods.

Supporters of the traditional approach argue that the new risk predictors aren't much better. Beyond that, new methods can potentially cause harm. In the view of Mark Ebell, an epidemiologist at the University of Georgia in Athens, even relatively innocuous blood tests can lead to over-diagnosis and over-treatment and imaging studies have the added danger of radiation exposure[2].

Advocates of using biomarkers and imaging technology don't expect the new methods to replace the old. Rather, they see them improving the outcomes in some individuals and groups of people. For example, improved risk prediction could personalize disease prevention depending on lipid levels or blood pressure. "There are niche populations for whom biomarkers can be helpful," says John Wilkins, who specializes in cardiology and preventive medicine at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

One of the populations that could benefit most is women. "About a third of women who have had a heart attack don't have significant narrowing of the coronary arteries," explains

Martha Gulati, who heads the Preventive Cardiology and Women's Cardiovascular Health section at Ohio State University in Columbus. "So now we are looking for the small blood vessels in women." That requires new tests, most notably a cardiac form of magnetic resonance imaging (MRI).

RANKING RISKS

Cardiovascular disease comes in several forms, including problems with blood vessels and heart valves, arrhythmias (irregular heart beat), heart attacks and strokes. Predicting the risk varies with the form of CVD. Coronary artery disease, for example, is more predictable. "The most widely used coronary heart disease risk prediction that we use in our current cholesterol-lowering guidelines is the Framingham risk score," Wilkins says. "It is the most strongly validated and robust for 10-year estimates." The score is based on data from the Framingham heart study, a 64-year-old project that aims to identify the common factors or characteristics that contribute to CVD by monitoring the health of various cohorts of people.

The Framingham model involves knowing an individual's age, sex, systolic blood

pressure, total cholesterol level, high-density lipoprotein (HDL) cholesterol level, smoking status and the presence or absence of medication to treat high blood pressure, explains Gregg Fonarow, director of the Ahmanson-UCLA Cardiomyopathy Center in Los Angeles, California. Given those details, the model computes the probability that the individual will suffer a CVD event in the next 10 years, generally segregated into either high risk, intermediate risk or low risk. The predictions provide more than peace of mind for some patients, says physiologist Kerry McDonald at the University of Missouri School of Medicine in Columbia. They also generate the data needed to design a treatment regime appropriate to the level of risk.

The realization that a low risk of CVD in the short term can conceal a much higher risk throughout a lifetime has added to the argument for more sensitive ways to access risk. A study headed by Donald Lloyd-Jones, a cardiologist at Northwestern University Feinberg School of Medicine in Chicago, Illinois, measured the CVD risk factors of more than 250,000 individuals at the ages of 45, 55, 65 and 75 (ref. 3).

"The 10-year risk equations do a reasonable job," Lloyd-Jones explains. "However, they will give low-risk estimates even to young people with elevated risk factors, because they are young." But any elevated risk factor can have long-term consequences. For example, a 45-year-old man whose risk factors are all optimal has only a 1.4% chance of a heart attack, stroke or other form of fatal heart condition in his lifetime; but two or more risk factors at that age increase the risk dramatically, to 49.5%. Thus Lloyd-Jones's team and others have developed algorithms for 30-year and lifetime risks. "These are at the same stage of development as 10-year risk assessments were 10 years ago," Lloyd-Jones says. "People are starting to use them to see if they motivate patients with elevated risk factors to change their lifestyles or adhere to their therapies."

Almost all doctors now realize the importance of emphasizing to young adults the importance of a healthy lifestyle — including diet, regular exercise and not smoking. And cardiologists have realized that some members of the Framingham intermediate group could benefit from drug treatments rather than just lifestyle changes[4]. Those factors suggest that certain patients can benefit from predictive methods more detailed than the Framingham risk score.

PROSPECTS FOR PREDICTION
In mid-2012, one new insight seemed so obvious as to be trivial. Two twenty-year studies headed by nutritionist Lu Qi of the Harvard School of Public Health in Boston, Massachusetts, revealed that individuals with blood types A, B and AB face a higher risk of coronary heart disease than the 44% of Americans with blood type O. People with the rare AB blood type have a heart disease risk 23% higher than O types, and those with types B and A

have 11% and 5% increased risk, respectively[5]. Qi believes that blood typing provides another tool for predicting who is at risk of CVD.

Other predictive techniques involve medical imaging. Among these, scanning for coronary-artery calcium holds the most promise. "In the right patients, it seems to be the best risk predictor to use in conjunction with the Framingham risk score," Wilkins says. "However, several other serum and imaging-based biomarkers may assist in risk prediction in specific patient populations as well."

The calcium scan uses computed tomography (CT) to detect a build-up of calcium in the coronary arteries, a possible indicator of impending atherosclerosis and susceptibility to heart attack. One study looked at the possible value of coronary artery calcium scores (CACS)[6]. About a quarter of the people who would have been designated as intermediate risk according to Framingham risk score methods were determined to be high risk when
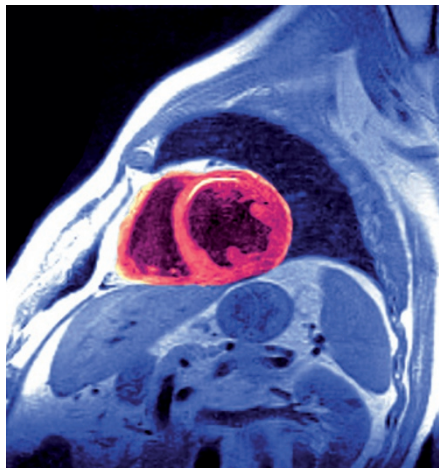
This MRI scan through the chest (blue) reveals dangerous fat (yellow) in the walls of the heart (red).

their CACS were taken into account.

Fonarow points to one disadvantage of the procedure: CT scans expose patients to potentially harmful ionizing radiation. "Some studies suggest screening for coronary calcium in intermediate-risk patients might be useful," he says. "But is the radiation risk worth it?"

That question remains to be answered. However, new techniques such as ultrafast CT minimize the radiation dose, says Gulati. And several scanning techniques applicable to CVD do not involve ionizing radiation. "A lot of echocardiography is pretty non-invasive," says McDonald. "There's a movement toward non-invasive tests that don't exacerbate the problem."

NEW AND NON-INVASIVE
Two non-invasive imaging methods have shown promise in women. The methods have particular value as the differences between women and men's medical history become increasingly evident. "Women aren't small men," Gulati says. "We're physiologically

different." Thus women who smoke have a greater risk of CVD than men who smoke, and diabetic women face three times greater chance of getting heart disease than men with diabetes.

To study small blood vessels in women, Ohio State University's cardiology department is developing a cardiac MRI. "Rather than just running chemicals through a patient's coronary arteries, we can physically stress them on a treadmill under magnetic resonance imaging," Gulati explains. "This appears to be far more useful to detect microvascular disease in women."

Another technique with particular value for women is intravascular ultrasound. "This can show diffuse plaque along the entire artery rather than specific blockages," Gulati says. "Some medical centres will do an intravascular ultrasound if they see evidence of heart attacks in normal arteries."

Studying biomarkers to improve CVD risk prediction has produced fewer encouraging results. A report by the Framingham heart study in 2006 compared the effects of several novel biomarkers with the traditional risk factors. The biomarkers included several types of protein: natriuretic peptides (protein hormones secreted by heart cells); C-reactive proteins (blood proteins linked with inflammation); fibrinogen (a protein involved in coagulation); urinary albumin (a protein from the kidneys) and the amino acid homocysteine. The report also studied the 'multimarker' approach that combines the predictions of several biomarkers[7]. The study concluded that using 10 biomarkers adds only moderately to the ability to assess risk. As Fonarow sees it, that comment applies to the entirety of alternative methods. "Thousands of studies touting genetic risk factors, gene polymorphisms, biomarkers and a variety of invasive and non-invasive imaging tests have generally not improved on the standard risk model, or the improvement has been very modest — not enough to be cost effective or helpful for effective practice," he says. "Some may be considered in intermediate risk patients, but do they improve clinical outcome?"

Instead, Fonarow wants clinicians to wring more value from existing tools. "The real challenge in clinical practice is that the tried and true Framingham risk model is often not applied," Fonarow says. "The issue is applying the model into clinical practice and getting patients to adhere to therapies." ∎

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