



ROBERT DETRANO, MD, PhD

Division of Cardiology, Department of Medicine,
Harbor-UCLA Research and Education Institute,
Los Angeles

The case for clinical trials of noninvasive coronary imaging tests

CORONARY ARTERY DISEASE is not as simple as we once thought: more plaque does not necessarily equal more risk. What we need are better imaging tests that go beyond measuring the amount of plaque in a patient's arteries—we need to know if the patient is truly at risk of having a coronary event and if we can prevent that event.

See related article, page 713

New tests, like new therapies, must undergo clinical trials

Three imaging tests show great promise: intravascular ultrasonography (IVUS), computed tomography (CT), and magnetic resonance imaging (MRI). But before we can apply them on a large scale, they need to undergo clinical trials with “hard” end points. In short, the tests need to be tested.

■ PLAQUE DOES NOT EQUAL RISK

One would think that atherosclerotic plaque—the pathobiologic substrate upon which most cardiovascular events occur—equals heightened risk. Yet atherosclerotic plaque does not lead irrevocably to poor outcomes.¹

Atherosclerosis is characterized by chronic arterial inflammation, which is instigated and exacerbated by disordered lipid metabolism.^{2–5} Atherosclerosis begins surprisingly early and is almost ubiquitous in middle-aged and older adults.^{6,7}

Yet, epidemiologic studies have shown that despite the high prevalence of atherosclerosis, most of us will never suffer any atherosclerotic event and will instead die of other, unrelated causes.^{1,8,9}

■ PLAQUE COMPOSITION, NOT SIZE, DETERMINES RISK

Several investigations have elegantly established that most devastating vascular events are directly precipitated by rupture or erosion of unstable plaque. The composition rather than the amount or size of the plaque appears to determine its instability.^{10–12}

People with fairly extensive atherosclerosis may lead normal, event-free lives if their disease remains structurally quiescent, but those with relatively little atherosclerosis can suffer devastating events if their plaque is vulnerable to rupture.

Accordingly, vascular biologists and clinical scientists have shifted their focus towards understanding plaque composition and why and how plaque becomes vulnerable. Clues to the features of vulnerable plaque and vulnerable arteries have emerged from autopsy data and examination of coronary atherectomy specimens.^{10–12}

■ THE PROMISE OF TOMOGRAPHIC IMAGING

In this issue of the *Cleveland Clinic Journal of Medicine*, Schoenhagen et al¹³ point out the systemic nature of coronary atherosclerosis and the need for imaging tests that show much more than the vessel lumen.

These authors explain the potential value of tomographic imaging tests (CT, MRI, and IVUS) for characterizing subclinical atherosclerosis in vivo. Citing their own work and that of others, they show how these tests have been helpful in establishing the relative instability of positively remodeled arteries and argue for the further development of these tests.



They also argue by analogy that these newer tests may change the course of medical treatment in the same way that coronary angiography led to surgical and percutaneous revascularization.

■ NEW TESTS NEED TO BE VALIDATED

Most physicians share the hope of these authors and also share their belief that the arterial evaluation in the not-very-distant future will be very different from that used today.

However, when Mason Sones first (accidentally) hand-injected contrast media into a right coronary artery on October 30, 1958, not only was the science of imaging poorly developed—so was the science of evidence-driven medicine.

Unlike in the 1950s, we now recognize that new tests, like new therapies, must undergo clinical trials before they are applied to

large populations. The emerging noninvasive imaging studies will require the same kind of rigorous testing that breast mammography has undergone. Economic costs and potential risks from radiation and other factors will have to be weighed against real benefits measured in increased quality-adjusted years of life and similar measures.

Much of the development of coronary angiography was driven by the “oculostenotic reflex,” the often false implication that the patient is better just because we made his picture look better. It would be equally mistaken to allow similar reflexes to drive our application of newer imaging studies. The bottom line must always be reduction in morbidity and mortality, rather than prettier pictures.

In this context, I agree wholeheartedly with the conclusions of Schoenhagen et al: “[The use of these techniques] requires a careful clinical assessment of potential risks and benefits in individual patients.”



■ REFERENCES

1. Lloyd-Jones DM, Larson MG, Beiser A, et al. Lifetime risk of developing coronary heart disease. *Lancet* 1999; 353:89–92.
2. Lusis AJ. Atherosclerosis. *Nature* 2000; 407:233–241.
3. Glass CK, Witztum JL. Atherosclerosis, the road ahead. *Cell* 2001; 104:513–516.
4. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; 340:115–126.
5. Libby P. The vascular biology of atherosclerosis. In: Braunwald E, Zipes DP, Libby P, editors. *A Textbook of Cardiovascular Medicine*. 6th Ed. Philadelphia: W.B. Saunders, 2001:995–1009.
6. Strong JP. Landmark perspective: coronary atherosclerosis in soldiers. A clue to the natural history of atherosclerosis in the young. *JAMA* 1986; 256:2863–2866.
7. Stary HC. *An Atlas of Atherosclerosis Progression and Regression*. New York: Parthenon, 1999.
8. Kannel WB. Epidemiologic contributions to preventive cardiology and challenges for the twenty-first century. In: Wong ND, Black HR, Gardin JM, editors. *Preventive Cardiology*. New York: McGraw-Hill, 2000:3–20.
9. Gordon T, Kannel WB. Premature mortality from coronary heart disease: the Framingham Study. *JAMA* 1971; 215:1617–1625.
10. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; 104:365–372.
11. Davies MJ. Going from immutable to mutable atherosclerotic plaques. *Am J Cardiol* 2001; 88(suppl 4):2F–9F.
12. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; 92:657–671.
13. Schoenhagen P, White RD, Nissen SE, Tuzcu EM. Coronary imaging: angiography shows the stenosis, but IVUS, CT, and MRI show the plaque. *Cleve Clin J Med* 2003; 70:713–718.

ADDRESS: Robert Detrano, MD, PhD, Division of Cardiology, Department of Medicine, Harbor-UCLA Research and Education Institute, 1124 West Carson Street, Torrance, CA 90502.

The goal: fewer deaths, not just prettier pictures