Screening Asymptomatic Subjects for Subclinical Atherosclerosis

Not So Obvious

Michael S. Lauer, MD
Bethesda, Maryland

The case for screening asymptomatic adults for coronary artery disease seems to be, on the surface, obvious. Coronary disease is common and serious and involves a prolonged asymptomatic phase. Frequently the first clinical presentation causes serious morbidity or even death. Because of remarkable developments in imaging technology, physicians now have available to them potentially powerful screening tools that are able to identify high-risk patients. Advocates of routine screening argue that, given the public health consequences of coronary disease and given the ability of imaging screening tests to stratify risk more accurately than classical risk factors, we are ready to issue large-scale public health recommendations advocating routine screening for many adults. Critics argue that we are not ready because we have no evidence that screening does what it is supposed to do, namely, prevent premature clinical disease and deaths. In medicine, we have seen a number of screening tests that, when put to the test themselves, failed to improve outcome. One major reason, which is nearly always overlooked in debates about chronic disease screening, is the phenomenon of overdiagnosis. Screening tests are often unable to distinguish real disease from pseudodisease. This inherent failing causes real harm and cannot be dismissed as an academic issue. It is also a major reason why we should not advocate routine screening without first obtaining proper randomized trial evidence of benefit.

Once upon a time, there was a diagnostic screening test that was so powerful it could easily identify people at risk for a serious life-threatening disease. Medical researchers observed that as the value of the test measurement increased from 0 to high normal, to slightly abnormal, and to grossly abnormal, there emerged a strong gradient for the risk of dying of the disease (1). The good news spread. Before too long, over 75% of potentially eligible adults had the test performed as part of their routine clinical care. Professional societies and many prominent physicians strongly advocated for the test (2). Decades later, because of the widespread adoption of this powerful screening test, the disease was stopped in its tracks, so much so that very few people were now diagnosed with advanced disease, and death from the disease was distinctly uncommon.

Unfortunately, that is not how the story ended. The test was a prostate-specific antigen, a marker for prostate cancer, a disease that kills 29,000 men every year in the U.S. (3). The ability of prostate-specific antigen levels to predict the risk of disease-related death is incontrovertible. However, despite decades of use, we have seen no change in the rate of diagnosis of advanced prostate cancer and no change in the rate of prostate cancer deaths (4). There has been a marked increase in the incidence of diagnosed prostate cancer, as would be expected when a screening test is in widespread use. Yet, somehow, the test seems to have failed in its primary mission, which is to stop the disease before it has an opportunity to cause major morbidity or mortality.

The bad news does not end there. Under the leadership of the National Cancer Institute, a large-scale randomized trial was designed and implemented to determine whether prostate cancer screening reduces the risk of cancer-related death (2). The results almost exactly parallel the epidemiological data. Men who were randomized to prostate cancer screening had a higher incidence of prostate cancer, exactly as would be expected with use of a sensitive screening test. However, there was no reduction in the rate of death from prostate cancer.

How could this be? How is it possible that a test that is so good at predicting risk and identifying early disease could fail to prevent morbidity and mortality? Could this be a unique phenomenon of this particular test and this particular disease? Doubtful, as this same pattern has been observed for other screening tests and diseases. Screening tests do not prevent deaths caused by neuroblastoma (5) or melanoma (6), nor do they decrease risk of cardiovascular events in patients with diabetes (7). The problem is overdiagnosis (4,8). Diagnostic tests may be extremely good at detecting early stage disease, yet fail to determine which cases of disease, if left alone, will eventually kill. Many, often most, people with abnormal screening test findings will nonetheless remain free of clinical disease; for example,
among adults with high coronary calcium scores in the MESA (Multi-Ethnic Study of Atherosclerosis), 95% remained asymptomatic over the next 5 years (9). Overdiagnosis is not a trivial, theoretical problem for academic purists; it leads to real harm, because patients with non-threatening disease are nonetheless subjected by their worried doctors to potentially risky tests, treatments, and procedures (10).

Our experiences with failed screening tests remind us why a number of leading prevention authorities, including the U.S. Preventive Services Task Force (11) and some cardiovascular thought leaders (12), insist that cardiovascular screening tests, like all screening tests, be shown to do what they are supposed to do—prevent clinical disease. The ability to predict or reclassify risk is beside the point.

There are 2 valid ways to demonstrate the clinical value of a screening test (13). The most straightforward is to randomize subjects to receive the test or not and then follow them for long-term outcomes. Researchers successfully used this approach to demonstrate the value of mammography (14) and ultrasound imaging of the abdominal aorta (15). This is also the approach that is currently being used by the National Lung Screening Trial investigators (16), who successfully randomized over 50,000 smokers to screening with either chest X-ray or computed tomography scan. Unfortunately, randomized trials that focus specifically on diagnostic screening tests require large sample sizes and long follow-up periods. An alternative approach is to use a screening test to identify subjects believed to be at high risk, and then randomize them to treatment or control (13). This is the approach that was used by the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) investigators to demonstrate a possible screening value for high-sensitivity C-reactive protein as a means of identifying people likely to benefit from statin therapy (17).

In his thoughtful essay, Shah (18) argues that we should screen selected asymptomatic subjects for subclinical atherosclerosis. He bases his argument on the ability of certain screening tests, such as coronary calcium measurement, to provide incremental risk information over the Framingham Risk Score and evidence that screening “may improve adherence to compliance with risk modifying interventions.” He admits that there is no evidence showing that coronary artery disease screening improves clinical outcomes, and he encourages future trials. He laments a “double standard” by which the Framingham Risk Score has been accepted for routine use, despite the absence of randomized trial evidence that use of the risk score improves outcomes.

The ongoing debate about coronary artery disease screening reflects a number of other debates in medical history about the value of interventions that made a lot of sense, yet were untested. There are passionate believers who sincerely feel that the logic is so strong (“the science is so good”) that there should be no need for a large-scale randomized trial (19). There are other elements of this story that we must acknowledge, including conflicts of interest (20) and aggressive direct-to-consumer advertising, advertising that often exploits people’s fears (21). We in the biomedical research community have a moral responsibility to remember our many past failures (19) and to insist upon appropriate levels of skepticism, especially for interventions that are likely to affect large swaths of the population.

Shah (18) is absolutely right. There should be no double standard. Biomedical researchers have performed large-scale randomized trials on a variety of screening tests, and screening tests for coronary artery disease should be subject to the same level of rigor. Shah (18) is correct when he points out the Framingham Risk Score has not been tested in a rigorous way, and indeed prominent authorities have appropriately questioned the value of widespread global risk scoring in the absence of proper evidence (22). It is not at all clear that the risk stratification paradigm is the best way to reduce substantially the burden of clinically active coronary artery disease in our population.

Thanks to the diligent work of many talented cardiovascular researchers, we now have a myriad of potentially valid approaches to assess risk and reduce population coronary artery disease burden. These include global risk scoring, coronary calcium or carotid screening, measurement of biomarkers such as high-sensitivity C-reactive protein, and widespread use of statins or polypills. We should not forget about population-based strategies, such as smoking bans, and legal prohibition of toxic dietary substances such as trans-fats and highly salted foods. Our next step is to have the humility to admit that we do not know which approach or combination of approaches is best, but that, in the public interest, we will join forces to design and implement the definitive large-scale randomized trials that our patients and the public should rightly demand.

Reprint requests and correspondence: Dr. Michael S. Lauer, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, 6701 Rockledge Drive, Room 8128, Bethesda, Maryland 20892. E-mail: lauerm@nhlbi.nih.gov.

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