Assessment of new technologies: Surrogate endpoints versus outcomes, and the cost of health care

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Spending for health care in the United States rose above $2 trillion in 2006, representing a doubling of costs over the last 10 years,[1] an average of $7000 per person. Contributing strongly to the 6.7% rise in health care costs in 2006 was an 8.5% increase in retail spending for prescription drugs, which totaled $216.7 billion. The article cited other factors driving up costs: "the use of existing drugs for new purposes and the increased use of high-cost biotechnology products." Cardiovascular disease accounts for $400 billion of these total costs. Costs of health care continue to rise higher than the rate of inflation, at a time when universal health care coverage is being advocated by candidates for the US presidency.

The controversy surrounding the results of the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients With Heterozygous Familial Hypercholesterolemia) study[2] indirectly ties into this discussion on rising health care costs. The drug initially was approved in 2002 by the Food and Drug Administration (FDA) based on a surrogate endpoint of lowering low-density lipoprotein (LDL) cholesterol levels by more than 15% from baseline levels, in the absence of unfavorable alterations in other lipid parameters.[3] Other trials considered during the approval process also showed that ezetimibe was more effective than placebo in lowering LDL cholesterol levels in patients who were already taking a statin. Thus the drug was launched and later combined with simvastatin (Vytorin, Merck, West Point, Penn), with subsequent sales of $5 billion in 2007.[3] No outcomes trial has been completed showing that the surrogate of effectively lowering LDL cholesterol levels with ezetimibe is associated with a reduction in major cardiovascular events. Such a cardiovascular outcomes trial (IMPROVE-IT [Improved Reduction of Outcomes: VYTORIN Efficacy International Trial]) was started 3 years after the date of approval of the drug. What was finally released, approximately 18 months after its completion, was the ENHANCE trial, which looked at another surrogate endpoint—changes in the carotid-artery intima-media thickness, which is thought to be reflective of the degree of arterial atherosclerosis. The study showed that the addition of 10 mg of ezetimibe to 80 mg of simvastatin did not reduce the intima-medial thickness of the carotid artery wall in patients with a diagnosis of familial hypercholesterolemia, despite a lowering of LDL cholesterol level to 141.3 mg/dL in the combined-therapy group versus 192.7 mg/dL in the simvastatin group. Side effect and safety profiles were similar in the 2 groups. Potential explanations for the findings were presented in the discussion section of the article[2] and in the accompanying editorial by Brown and Taylor.[4]

Citing ENHANCE trial issues highlights the matter of having drugs (as well as diagnostic tests and therapeutic devices) approved for patient use on the basis of surrogate endpoints that may not be associated with clinical benefit and that can only be determined by more expensive outcomes trials using major cardiovascular events as endpoints. If drugs with little or no clinical benefit get approved solely on the basis of their positive effects on surrogate endpoints and are then marketed vigorously to patients, prescription drug costs rise, which in turn raises total health care costs. It still may be that ezetimibe or the combination of ezetimibe and a statin will be shown in the IMPROVE-IT trial to lower event rates compared with a statin alone, but the trial also might show no clinical benefit for the combination. Another drug, torcetrapib, was never approved by the FDA, although—like ezetimibe—it showed benefit in a surrogate endpoint, raising high-density lipoprotein cholesterol levels. This drug was associated with an excess of cardiovascular events[5] despite favorable effects on the high-density lipoprotein levels. The difference was that a major outcomes trial with torcetrapib was well under way before the approval process started.[3]

Now, how do these lessons from the pharmaceutical experience apply to the field of cardiovascular imaging? I would propose that the same principles hold for the embracing of new technology. The bar has been raised in the imaging field as it has in the drug approval and reimbursement areas. Cost-effectiveness may be emerg-

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ing as a criterion for evaluating new imaging tests. Detrano et al[6] recently published an article showing that the coronary calcium score is a strong predictor of incidental coronary heart disease and provides predictive information regarding coronary events beyond that provided by standard coronary artery disease risk factors in all racial and ethnic groups. In their accompanying editorial, Weintraub and Diamond[7] ask whether a relatively small improvement in accuracy of risk prediction is worth it. They suggest that the test provides value only if patient outcomes improve and if the improved outcomes can be translated into improved survival rates or health status, with cost-effectiveness demonstrated. The authors suggest, for example, that value could be provided in calcium scoring if it can be shown to change care in such a manner that there are fewer cardiac events in the future.

Shaw and Narula[8] expand on this theme in their "Editor's Page" in *JACC: Cardiovascular Imaging*. They mention that "expanding on evidence offered over the last few decades on diagnosis and risk assessment, any growth in cardiac imaging must now be justified with supportive data revealing improved patient outcomes." They further state that to improve quality in imaging, we need to link future quality initiatives with the concept that an added test or referral within a patient workup must improve patient outcomes. They state that for this to be accomplished, our "evidence-base must now move beyond the research arena." This approach is consistent with what is being called more "patient-centric" strategies of health care quality.

Thus, because of rising health care costs in the United States, without evidence that we have better health in our population compared with other countries that spend far less on per-capita health care, we are moving into an era in which new drugs, devices, and diagnostic testing technology will be evaluated as to how patient outcomes are benefited in a cost-effective manner. We are already seeing that achieving surrogate endpoints is not enough to determine the worth of a drug or a diagnostic test that is aimed at improving quality of care. Outcomes assessments are being demanded by health care researchers, the FDA, and payers (eg, Centers for Medicare & Medicaid Services) to prove the value of a drug, device, or diagnostic test. Unfortunately, the trials that need to be conducted to show enhanced patient outcomes are difficult to conduct and are very expensive. This is going to be particularly problematic when the value of imaging tests must be demonstrated in an asymptomatic population in which overall cardiac event rates are low in primary-prevention trials.

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