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TRANSLATIONAL PERSPECTIVES

# Advances in Cardiovascular Care

## How to Stimulate Innovation While Controlling Cost

William S. Weintraub, MD,[a] Kelvin H. Lee, PhD[b]

**SUMMARY**

There is increasing concern over the cost of pharmaceuticals. An approach to assessing the value of new pharmaceuticals compared with previous standards is cost-effectiveness analysis. Although cost-effectiveness analysis may not be able to directly answer societal questions about new drugs, it can make the underlying assumptions clear. As new pharmaceuticals are becoming more expensive, the issues concerning societal willingness-to-pay become more critical. This is especially true of biologics, where the cost of manufacture is much higher than for small molecules. Indeed, new biologics have gone from being unusual to dominating the market for new pharmaceuticals. Efficiency in manufacturing will need to be gradually addressed to make these life-saving therapies more widely available. (J Am Coll Cardiol Basic Trans Science 2018;3:114–8) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Since its peak year in 1968, there has been a remarkable and dramatic decline in cardiovascular mortality, between 60% and 70% (1). This decline is largely attributable to primary and secondary prevention, although there have been dramatic improvements in care for acute myocardial infarction and heart failure as well (2). The cornerstone of cardiovascular care remains a therapeutic lifestyle, including a healthy diet, exercise, and not smoking. However, there remain risk factors for cardiovascular disease, such as diabetes, hyperlipidemia, and hypertension that require pharmacological intervention. Although the treatment of acute myocardial infarction and heart failure require pharmacological intervention, there is also a place for device-based intervention, such as coronary stents to restore blood flow in the setting of acute myocardial infarction and left ventricular assist devices and other mechanical support for heart failure.

In considering how to offer the best cardiovascular care to all people, there is much good news. A therapeutic lifestyle is largely free, and probably offers improved health at reduced cost (3). Major therapies for hypertension (angiotensin-converting enzyme inhibitors, calcium-channel blockers, beta-blockers, and diuretic agents) are available as low-cost generics. Several of the same drugs are also cornerstones of therapy for heart failure. Similarly, the statins used to treat hypercholesterolemia are also available as generics, and the cost of intracoronary stents has fallen.

However, some new pharmaceuticals are expensive (4,5). Treatment for elevated low-density lipoprotein (LDL) cholesterol is a well-known case study. Elevated cholesterol, and more specifically LDL cholesterol, is a well-known risk factor for subsequent cardiovascular events. This is based on several critical epidemiological studies, the most

From the [a]MedStar Washington Hospital Center, Washington, DC; and the [b]University of Delaware, Newark, Delaware. This work was funded in part, by award 70NANB17H002 from U.S. Department of Commerce, National Institute of Standards and Technology. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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important being the Framingham Study (6,7). The discovery of and understanding of the functioning of the LDL receptor was critical to developing pharmaceuticals that could lower LDL cholesterol (8). Statins block the critical step in the synthesis of cholesterol in the liver, resulting in increased expression of the LDL receptor, leading to a fall of 40% to 60% in LDL cholesterol (9). Treatment with statins has been shown to reduce the risk of primary or secondary cardiovascular events by approximately 25% in multiple clinical trials (10). Furthermore, economic studies suggest that for secondary prevention, statins are cost-effective using typical societal willingness-to-pay thresholds (11). Ezetimibe works by a different mechanism, preventing the intestinal reuptake of cholesterol (12). Either alone or in combination with a statin, it will reduce LDL cholesterol by approximately 18%. Evaluating the efficacy of ezetimibe in preventing cardiovascular events proved to be challenging, as it would be difficult to conduct a randomized trial of ezetimibe versus placebo without background statins. Nonetheless, ezetimibe has been shown to decrease cardiovascular events in a randomized trial in a secondary prevention population in which all patients were on statins (13). Among other things, this provides a level of confirmation that LDL cholesterol was causative of events, and that lowering LDL, in the absence of other effects, will reduce subsequent events; this is known as the LDL hypothesis.

Given the results of multiple trials, the LDL story may have seemed to be over (14). The physiology seemed to be well understood. However, not all patients tolerate statins, statins are not efficacious in all patients, and even when efficacious, not all patients achieve a therapeutic target with statins (acknowledging that current guidelines in the United States leave the target uncertain) (15). There is also remaining concern that for primary prevention in many patients, the number needed to treat to prevent 1 event is high, and that lifelong therapy in such low- to moderate-risk individuals is not fully justified.

Into this well studied, but still complicated environment comes PCSK9. In 2003, a group of patients in Europe were found to have high LDL cholesterol due to hyperexpression of PCSK9 (16,17). PCSK9 causes the degradation of the LDL receptor. PCSK9 was also shown to increase in patients treated with statins, limiting their beneficial effect on LDL cholesterol. Horton et al. (16) conjectured that if there was hyperfunctioning of PCSK9, then there should also be individuals with a genetic defect in PCSK9 where it was dysfunctional. They found such individuals using the Dallas Heart Study database. Mendelian randomization reveals that such individuals have low LDL cholesterol and a reduced risk of subsequent events.

Inhibition of PCSK9 proved to be an excellent therapeutic target. However, to date, there are no small molecules that inhibit PCSK9. There are 2 monoclonal antibodies that do inhibit PCSK9, and in clinical trials they have been shown to decrease LDL cholesterol by 60%, even on a background of statin therapy (18). There is also increasing evidence that PCSK9 therapy will decrease cardiovascular events, although a mortality benefit has not been shown (19,20). Furthermore, this therapy is safe. The limiting problem with PCSK9 therapy is that it is expensive, costing $12,000 to $14,000 per year (4,5,21). To date, cost-effectiveness analyses of PCSK9 inhibition have been limited, but suggest that at current prices, the cost per quality-adjusted life year saved would be approximately $300,000, which is well above societal willingness-to-pay thresholds of $50,000 to $150,000 per quality-adjusted life year saved. A threshold analysis has suggested that to be below the $100,000 threshold, the price of PCSK9 therapy would need to be $4,500 (22). Such cost-effectiveness evaluations have also been subject to criticism.

Cost effectiveness analysis cannot resolve all economic questions concerning a new therapy, but it does offer a set of tools to make underlying assumptions clearer and help guide societal choices (23). Cost effectiveness analysis can use patient-level data from clinical trials or can be based on simulations based on clinical trial data. All cost effectiveness analyses are incremental, comparing a new therapy to a current standard. This can create a particular problem where the previous gold standard is already quite expensive ("a BMW [looks] like a bargain when the only other car on the lot is a Ferrari") (24). Benefits are generally converted to life years, which are then converted to quality-adjusted life years by multiplying life years by utility. Utility is an overall measure of health status, from perfect health with a utility of 1 to dead with a utility of 0. Nonfatal events can be converted to fatal events by estimating years of life lost due to nonfatal events. The time horizon for clinical trials is generally just a few years, but in principal, the time horizon for cost-effectiveness analysis is lifetime. This means that clinical trial results have to be extrapolated beyond the clinical trial period. The measure in a cost effectiveness analysis is generally the incremental cost effectiveness ratio (ICER), the ratio of incremental cost to incremental benefit. Where the new therapy offers benefit at a lower cost, the new therapy

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is said to be dominant. Where the new therapy has worse outcome at higher cost, the new therapy is said to be dominated. In most cases of efficacious new therapy, there is benefit at higher cost. When the ICER is below a threshold of $50,000, $100,000, or $150,000 per quality-adjusted life year saved, a therapy may be said to be cost-effective. The sources of data for cost effectiveness analysis are all subject to error, and this may be approached with probabilistic sensitivity analysis, where the inputs are varied using published data (25-27). This offers a distribution to the ICER, and then it is appropriate to consider the percent of the time that the ICER is below the threshold. An important point about cost effectiveness is the rule of rescue, whereby we will spend more for an acute therapy, such as a bone marrow transplant for a child with leukemia, than for preventive therapy. In addition, we discount benefits and cost in the future. Both the rule of rescue and discounting disadvantage prevention compared with acute care.

Economics in health care is fundamentally different than in many other areas, where the market can determine whether a new product will be successful. Also, in areas that involve new technology, prices often fall with further innovation. If we consider flat-screen televisions, they were quite expensive a number of years ago when first introduced. Consumers could readily assess how much of an advantage flat-screen televisions offered. A combination of market forces and continuing innovation drove the prices down by approximately 90%, making them widely affordable. This happened without any formal cost-effectiveness analysis.

In health care, there is no such market for new therapies. Consumers cannot readily assess therapeutic benefit. In addition, critical health care (prevention and care for the acutely ill) is generally considered a right, not a good where access is price rationed in the marketplace. Thus, societal willingness-to-pay becomes a critical concern. Now, there is no theoretical basis for a societal willingness-to-pay threshold. Rather, this emerges from a consensus that develops over time, sometimes involving professional organizations and the use of guidelines. Cost-effectiveness analysis cannot solve the problem of how to properly incentivize innovation, but it can help inform the process, both for the company or entrepreneur and for society. As new products are developed, it is appropriate to consider societal willingness-to-pay, and industry should not assume that efficacy alone will ensure acceptance. In addition, the overall burden to society needs to be considered. It may be acceptable to spend hundreds of thousands of dollars per QALY gained for rare diseases, but this may not be acceptable or even possible for more common conditions (24).

Although societal acceptance is critical, the other side of what companies have to face is what it takes to bring a product to market. New pharmaceuticals are estimated to cost $2.6 billion (28). A company's ability to recoup this is dependent on patent protection. However, the patent begins when the product is developed, not when it is introduced to the market. This may limit productive patent life substantially. Nonetheless, a successful pharmaceutical can offer a large return on investment. To return to the LDL cholesterol story, Lipitor (atorvastatin) was the most profitable pharmaceutical in history, with over $125 billion in sales prior to going off-patent (29). That being said, most pharmaceutical compounds never make it to market. Thus, it is a bit of a roll of the dice. Although companies have taken a number of approaches to finding and developing new compounds to lower costs of drug development, including simulation, most new pharmaceuticals are found serendipitously, as was the case with the statins as a class. In addition to the cost to bring a compound to market, there is the cost of manufacture. These costs are generally not in the public domain, but the manufacturing costs of small compounds is a small fraction of the patent-protected price. This explains the dramatic fall in price with patent expiration.

The increasing importance of biologics is changing the dynamics of pharmaceutical pricing. There has been a 155% increase in the number of biopharmaceuticals in clinical trials over a recent 10-year period, and biologics now represent 40% or more of the medicines in development today (30,31). Indeed, 8 of the top 15 medicines by sales are biologics (32). The success of biologics is due in large part because of the ability of these medicines to exert a more targeted effect within the body reducing side effects. However, biologics such as antibodies are far more complex molecules than small-molecule pharmaceuticals and require far more complex manufacturing processes (33). The complexity derives in part because of the use of cells to produce the recombinant protein or antibody and the need to purify the drug substance from all of the other proteins expressed by those host cells. Although significant progress has been made in establishing robust platforms for biologics manufacturing, existing processes are still very complex and highly manual requiring significant investment in the development of the manufacturing process, the training of a skilled workforce to manufacture the medicines and

specialized facilities in which to manufacture the biologic. Moreover, the important role of health authorities in regulating the industry to ensure a reliable supply of high-quality, safe, efficacious medicines means that companies carefully monitor all aspects of their manufacturing process from the acquisition of raw material supplies through to the cold-chain delivery of finished drug products. These factors all help to explain why biologics, including PCSK9 inhibitors, are so expensive to manufacture. As the biologics market continues to grow and mature, and because of the opportunities created by biosimilars, it is expected that innovations in technologies needed for biologics manufacturing will also advance and result in reduced cost of goods and shorter timelines to bring new medicines to market (34).

A key question is how best to spur such innovations. Traditionally, manufacturing processes were developed by in-house teams of scientists and engineers working to develop robust approaches for the production of safe and efficacious biologics. However, as the pace of drug discovery has accelerated and the diversity of the molecules in the development portfolio has expanded, the pressure of process development teams has significantly increased. At the same time, the manufacturing processes for biologics has been industrialized to an extent within the industry with many organizations running so-called platform processes with many similarities. As a result, one of the greatest opportunities with biologics manufacturing rests with collaborative consortia that bring together relevant stakeholder groups to address these issues. One example of a large-scale consortium is the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL). NIIMBL, sponsored by the National Institute of Standards and Technology, is one of 14 Manufacturing USA innovation institutes launched by the federal government to address collaborative innovation in advanced manufacturing across a variety of business sectors. NIIMBL is the institute focused on biologics and is dedicated to advancing technology associated with traditional biologics (e.g., antibodies, vaccines, and proteins) as well as emerging modalities including gene and cell therapies. When manufacturers work with vendors, academics, other nonprofits, patient advocacy groups, and providers to collaboratively advance the available technologies in a pre-competitive manner, the opportunity to develop much-needed technologies is significantly improved.

New, potentially less-expensive therapeutic approaches are being developed that will address similar pathophysiology. Considering therapies to reduce PCSK9, both vaccination to induce PCSK9 antibodies and interference RNA (RNAi), which can cleave the mRNA coding PCSK9, are being developed (35–37). Advances in efficiency as well as therapeutic advances will certainly enhance patient access to biologics that will save, sustain, and improve lives.

**ADDRESS FOR CORRESPONDENCE:** Dr. William S. Weintraub, MedStar Heart & Vascular Institute, MedStar Washington Hospital Center, Suite 4B1, 110 Irving Street NW, Washington, DC 20010. E-mail: william.s.weintraub@medstar.net.

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