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TRANSLATIONAL PERSPECTIVES

Advances in Cardiovascular Care

How to Stimulate Innovation While Controlling Cost

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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

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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