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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

PCSK9 Inhibitors

Economics and Policy

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors substantially reduce low-density lipoprotein cholesterol, but it is presently unclear whether they also reduce mortality. The list prices of PCSK9 inhibitors in the United States (>$14,500 per year) are >100× higher than generic statins, and only a small fraction of their higher cost is likely to be recovered by prevention of cardiovascular events. The projected cost effectiveness of PCSK9 inhibitors does not meet generally accepted benchmarks for good value in the United States, but their value would be improved by substantial price reductions. For individual patients, the high out-of-pocket costs of PCSK9 inhibitors may impede access and reduce long-term adherence. The budgetary impact of PCSK9 inhibitors would be very large if all potentially eligible patients were treated, which poses dilemmas for policymakers, payers, and society. (J Am Coll Cardiol 2017;70:2677–87)

Proroprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors exemplify a central dilemma of modern medicine: a new therapy that is very promising but very expensive. Many new medical technologies have substantially improved patient outcomes; yet, new technologies are the principal driver of increasing health care costs worldwide. Although regulatory authorities evaluate new drugs and devices for effectiveness and safety, their clinical and economic effects are incompletely understood when they are approved, which is the time when policies about their use and reimbursement must be developed. In this paper, we review the framework for assessing the value provided by new medical technologies, summarize the current evidence about the cost effectiveness of PCSK9 inhibitors, and discuss some general policy issues regarding new, costly medical technologies.

PCSK9 INHIBITORS

The development of PCSK9 inhibitors provides a wonderful story of serendipity, clever epidemiology, and rational drug development. A study of a French kindred identified mutations in the PCSK9 gene that were associated with low levels of low-density lipoprotein cholesterol (LDL-C) (1). These initial observations were quickly followed by studies documenting the effect of PCSK9 polymorphisms on LDL-C levels in the general population (2), and showing that carriers of certain PCSK9 polymorphisms had significantly lower rates of atherosclerotic cardiovascular disease (3).

An understanding of the role of PCSK9 in cholesterol metabolism suggested that inhibiting its actions might lower LDL-C levels therapeutically. Several classes of drugs to manipulate the PCSK9 pathway are

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ABBREVIATIONS AND ACRONYMS

ICER = incremental cost-effectiveness ratio

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin/kexin type 9

QALY = quality-adjusted life-year

RCT = randomized controlled trial

currently under development; monoclonal antibodies directed at PCSK9 are the first to be approved. Initial studies in humans confirmed the striking power of PCSK9 inhibitors to lower LDL-C levels, with few reported adverse effects (4,5). Two agents, evolocumab and alirocumab, have been approved for use in individuals with either atherosclerotic cardiovascular disease or familial hypercholesterolemia who have had an insufficient reduction in LDL-C levels on maximally tolerated statin therapy. Although early studies of PCSK9 inhibitors were not powered to document their effects on hard clinical outcomes, a meta-analysis suggested a striking 50% reduction in cardiovascular events (6). Large, definitive endpoint trials are now being completed, and will provide substantially more evidence about the effect of PCSK9 inhibitors on hard events: cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, and all-cause mortality (7–9). The first of these large studies has reported reductions in cardiac events on the order of 15% to 20% (7), but with no effect on either cardiovascular or all-cause mortality (**Table 1**).

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is a tool to quantitatively assess the value provided by medical interventions, and thereby assist decision-making (10). Cost-effectiveness analysis has been applied to several classes of lipid-lowering medications, and provides several key insights of relevance to the assessment of PCSK9 inhibitors.

The incremental cost-effectiveness ratio (ICER) is the summary measure of value reported by cost-effectiveness studies. Although the ICER is simple in form, it encapsulates several key concepts. An ICER is calculated as:

$$\text{ICER} = \frac{\text{Cost}_2 - \text{Cost}_1}{\text{QALY}_2 - \text{QALY}_1}$$

where Cost_1 is the total cost due to using intervention 1, Cost_2 is the total cost due to using intervention 2, and QALY_1 and QALY_2 are the quality-adjusted life-years derived from using interventions 1 and 2, respectively.

The formula for ICER underscores the key principle that effectiveness is measured by clinical outcomes, not by surrogate markers like LDL-C, blood pressure, or glucose levels. QALYs capture the 2 distinct dimensions of improved clinical effectiveness: increased life-years of survival, and improved quality of life. The ICER is typically more sensitive to changes in its denominator (effectiveness = the number of QALYs added) than to changes in its numerator (cost = the number of dollars added). In particular, as the denominator shrinks toward zero, the ICER rises towards infinity, implying that interventions that produce little to no improvement in quality-adjusted survival cannot yield an acceptable ICER.

The numerator of the ICER represents the total net medical costs of using one intervention instead of an alternative, and captures both the "upfront costs" of the interventions as well as the "downstream costs" arising from subsequent adverse effects (e.g., MIs) and clinical events (e.g., coronary revascularizations). Thus, a therapy that reduces the long-term risk of MI will generate downstream cost savings from averted hospitalizations, which may offset some of the cost added by the new intervention. Rarely, an intervention may "pay for itself" if it sufficiently reduces costly downstream events.

An ICER must be compared with a threshold of acceptability to determine whether the new intervention provides sufficient value. For example, in a health system willing to pay $50,000 per QALY, a new intervention would be considered cost-effective with an ICER of $40,000 QALY, but not of $80,000 per QALY. Although there is no explicit willingness-to-pay threshold In the United States, there is general agreement that interventions with ICERs <$50,000 per QALY provide good value, whereas interventions with ICERs >$150,000 per QALY are not cost-effective (11).

Cost-effectiveness analysis is most often performed using a simulation model, in which a hypothetical cohort of patients is assigned risks of death and nonfatal cardiovascular events based on data from trials, registries, or epidemiological studies, to approximate what such a cohort would experience in the real world. The hypothetical cohort is followed until of all its members have died, and the projected clinical events and health care costs are enumerated to estimate lifetime QALYs and lifetime medical costs. Next, the simulation is repeated assuming that the application of the study intervention will reduce the risk of fatal or nonfatal events, but may lead to additional costs and side effects. The differences in total costs and total QALYs of these 2 strategies are used to calculate the ICER for the study intervention relative to the alternative. The results of simulation models are driven by their assumptions about the event rates with and without intervention, the costs of events and of interventions, and effects on quality of life. Consequently, high-quality, unbiased, internally consistent evidence is essential for a reliable