A Pound of Prevention? Assessing the Value of New Cholesterol-Lowering Drugs

Although cardiovascular disease has been decreasing for decades, it remains the leading cause of death in the United States. Further progress will require both optimal application of proven approaches and the development of new ways to prevent and treat atherosclerosis. Inhibitors of proprotein convertase subtilisin/kexin 9 (PCSK9), which substantially reduce cholesterol levels, are an exciting new approach based on insights from genetics and rational drug development (1). However, the U.S. Food and Drug Administration–approved PCSK9 monoclonal antibodies, alirocumab (2) and evolocumab (3), came to market priced at $14 000 per year—more than 100 times the cost of a generic statin. An ounce of prevention might be worth a pound of cure, but how much is a pound of prevention worth?

The 50% reduction in cholesterol levels from PCSK9 inhibitor use suggests that these drugs should reduce major adverse cardiovascular events: cardiovascular death, acute myocardial infarction, and ischemic stroke (4). Two large randomized trials of PCSK9 inhibitors in patients with clinically evident atherosclerotic disease who were already receiving statins showed reductions in cardiac events of 14% (2) to 20% (3), and both trials combined showed a 5% decrease in all-cause mortality (778 vs. 818 deaths).

Are these modest, yet important, reductions in cardiac events enough to justify the high cost of PCSK9 inhibitors? Several economic simulation models have examined this key question (5). All published models project that lifetime medical costs will be much higher in patients prescribed a PCSK9 inhibitor; all models also project that life expectancy will be prolonged, assuming that the short-term effects of PCSK9 inhibitors can be extrapolated over a lifetime of use. At list prices of $14 000 per year, however, the economic value of PCSK9 inhibitors was well over the generous willingness-to-pay threshold of $150 000 per life-year added, and far from the "good value" threshold of $50 000 per life-year added in every model (5).

Since these initial economic analyses were performed, the final results of the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) study were published (3), and manufacturers of PCSK9 inhibitors lowered prices (6). Kazi and colleagues (7) updated their economic model of PCSK9 inhibitors to incorporate these developments. The starting point for the updated analysis was a population of patients with clinically evident atherosclerotic cardiovascular disease (that is, patients who required secondary prevention) who had elevated low-density lipoprotein cholesterol (LDL-C) levels (mean, 2.67 mmol/L [103.2 mg/dL]) while receiving maximally tolerated statin therapy. The authors simulated the long-term outcomes of adding either alirocumab or ezetimibe to statin therapy versus continuing statin monotherapy. They projected that adding ezetimibe, at a cost of $1411 per year, to statin therapy would have an acceptable cost-effectiveness ratio of $81 000 per quality-adjusted life-year (QALY). In contrast, they projected that adding alirocumab, at a cost of $7187 per year, to statin therapy would have an unacceptably high incremental cost-effectiveness ratio of $308 000 per QALY versus statin therapy alone. Compared with the strategy of adding ezetimibe to statin therapy, adding alirocumab was even less cost-effective ($997 000 per QALY). The analysis showed that all these cost-effectiveness ratios would be more favorable at lower drug prices: Generic ezetimibe at $304 per year had a cost-effectiveness ratio of $18 600 per QALY; alirocumab priced at $3484 per year would have a cost-effectiveness ratio of $150 000 per QALY.

It is important to emphasize that the value provided by a PCSK9 inhibitor in these analyses is a population-based average, not a single, fixed number. Value should be conceptualized as a dynamic relationship between medication cost and predicted patient benefit (**Figure**). At any level of benefit, value is improved by a lower drug price. Conversely, at any drug price, value is improved by identifying and treating higher-risk patients, who will obtain more absolute benefit from treatment. The 2018 cholesterol guidelines from the American College of Cardiology and American Heart Association (8) recommend that PCSK9 inhibitors be used for secondary prevention only in "very high-risk patients" who have a persistently elevated LDL-C level while receiving a maximally tolerated statin dosage, and only after first trying ezetimibe. Analyses of clinical trial data also show that more absolute benefit is obtained from applying a higher LDL-C threshold for adding a PCSK9 inhibitor to maximally tolerated statin therapy, either greater than 2.59 mmol/L (100 mg/dL) or greater than 3.37 mmol/L (130 mg/dL), rather than the 1.81 mmol/L (70 mg/dL) minimum used as an entry criterion for clinical trials.

The 2018 cholesterol guidelines rated PCSK9 inhibitors as having low economic value at mid-2018 prices (8). Recent reductions in the list price of alirocumab will lower patients' out-of-pocket costs and should improve the drug's cost-effectiveness. The analysis by Kazi and colleagues, however, suggests that reducing the cost to $5850 per year is not enough; the price would have to drop to $1138 per year or less for PCSK9 inhibitors to provide good value in secondary prevention. The marketplace will make the final judgment, but it is both economically and clinically sound to use statins as first-line therapy in all eligible patients and to consider adding nonstatin therapies, including PCSK9 inhibitors, only for very high-risk patients who have persistently elevated LDL-C levels while receiving a maximally tolerated statin dosage.

Newer biologic agents can target disease pathways more precisely and promise to improve the outcomes of many diseases, including cancer, infectious diseases, and

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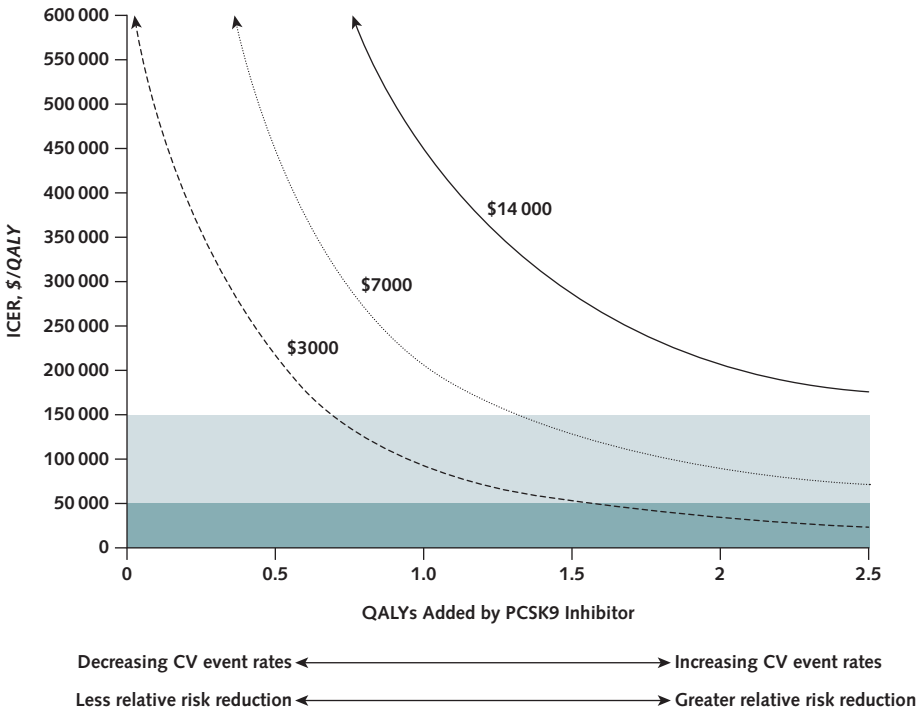
Figure. Conceptual relationship between PCSK9 inhibitors and statins with regard to clinical effectiveness, measured in QALYs added, and clinical value, measured in dollars per QALY.



The curves show the relationship between value and clinical effectiveness of 3 price points for PCSK9 inhibitor therapy. The dark green area indicates an ICER of $50 000 per QALY or less, the light green area an ICER between $50 000 and $150 000 per QALY, and the white area an ICER of $150 000 per QALY or greater. CV = cardiovascular; ICER = incremental cost-effectiveness ratio; PCSK9 = proprotein convertase subtilisin/kexin type 9; QALY = quality-adjusted life-year.

autoimmune disorders. The price tags of up to $100 000 a year for these new drugs, however, pose a major challenge to health care systems. Expensive new treatments that cure a fatal disease or eliminate disabling symptoms may well provide sufficient value to justify their high prices. Preventive therapies that slow the progression of atherosclerosis neither cure the disease nor reduce its symptoms, so their potential benefits are more limited; therefore, spending $5000 or more a year to lower cholesterol levels is harder to justify. The economics of PCSK9 inhibitors are a cautionary tale, because the price point that yields good value for patients and society is well below what manufacturers are charging. We need to find policies that reward the development of breakthrough drugs without breaking the bank.

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