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PCSK9 Inhibitors: A Technology Worth Paying For?

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Abstract

Food and Drug Administration in the United States has approved the (PCSK9) inhibitors alirocumab and evolocumab as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease requiring additional lowering of LDL-C. Evolocumab has also been approved for homozygous FH. Long-term outcomes studies are pending. The drugs are expensive, costing over $12,000 a year. There is concern that these drugs may not provide good value. While this can be studied with cost-effectiveness analysis, this will be challenging to do, especially when considered for therapy in young people which may be life-long. While inexpensive preventative therapies are cost-effective in the young, expensive therapies may not meet a societal willingness-to-pay threshold as the costs are high and accrue immediately, while the benefits may be decades in the future.

In mid-2015 the Food and Drug Administration in the United States approved the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab.[1] Approval was based on the surrogate marker LDL cholesterol reduction rather than on evidence of cardiovascular benefit. Favorable outcomes trials have been published, but the main long-term cardiovascular event trials remain to be completed.[2, 3] Both drugs have been approved by the FDA as adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease requiring additional lowering of LDL-C. Evolocumab has also been approved for homozygous FH. The drugs are expensive, costing over $12,000 a year. The major issues concern whether this type of therapy prolongs life and whether it is a good value. The point of view of the patient, health care system and society will influence value assessment.

PCSK9 facilitates degradation of the LDL receptor in the hepatocyte.[4] PCSK9 inhibitors are monoclonal antibodies that inactivate PCSK9 and are given by injection. PCSK9 inhibition decreases degradation of the LDL receptor, thus increasing the number of functioning LDL receptors on hepatocytes and lowering the number of LDL particles in the blood.[4] Reduction of LDL-C with statins, which inhibit cholesterol synthesis, and more recently with ezetimibe, which inhibits intestinal cholesterol absorption, results in a decrease in

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cardiovascular events.[5, 6] The PCSK9 inhibitors act in a complementary fashion, with resultant dramatic lowering of LDL-C, in the presence of these other therapies.[2, 3]

How can we determine if these drugs provide good value, and for whom? The issues to be considered are noted in the table.[7] The first consideration is the clinical setting, encompassing patients who cannot take statins (statin intolerance) or do not have a sufficient response to statins and ezetimibe. This could be a small group of people who do not respond to statins or who have a clear adverse reaction to statins, such as a myopathic response with muscle pain and CPK elevation.[8] However, it could be a much broader group of people who either cannot achieve sufficiently low levels of LDL cholesterol or who subjectively feel that they cannot tolerate statins. These patients could be either primary prevention patients who have never had a cardiovascular event or secondary prevention in patients who have had an event. It should be expected that patients will be on therapy for life. This could potentially include a large number of patients with FH who could be on this therapy for decades. Mendelian randomization studies suggest a 1 mmol/dl (about 40 mg/dl) lower LDL-C over a lifetime reduces risk of atherosclerotic cardiovascular disease by 50%.[9]

The cost-effectiveness of PCSK9 inhibitors will depend on the comparison group. This could be patients on statins, no lipid-lowering therapy due to unresponsiveness or intolerance, or other pharmacologic therapy, e.g. ezetimibe. In each case, the alternative therapy will cost a small fraction of the cost of PSCK9 drugs. The choice of comparator is critical to understanding PSCK9 effectiveness and cost-effectiveness, as is the clinical setting. For instance, if a group of patients with familial hypercholesterolemia who do not respond to statins but do respond to PCSK9 inhibtion could be defined, then the effect will be large, but the timeframes may be long. On the other hand, as an add-on to patients with established vascular disease who remains at risk due to insufficient effect on LDL-C with statins, the effect may be smaller, but in this setting the effects may be noted more rapidly.

Perhaps the most important issue is life expectancy in the absence of PCSK9 inhibition, and by how much mortality will be reduced by the PCSK9 inhibitor. To date this is unknown, but can be modeled based on the effect of statins on lipid levels and on mortality. Even with decades of clinical trial data to guide us, the effect of statins on life expectancy requires mathematical models which extrapolate data from these clinical trials to the period beyond observation within trials. Life expectancy can be converted to quality adjusted life years by multiplying life years by utility. The effect of these drugs on life expectancy is probably the greatest unknown, especially when the drugs are contemplated for young people who may be on them for decades.

PCSK9 inhibition may also reduce non-fatal cardiovascular events. For secondary prevention, this is relatively straight-forward as events can be examined during the course of a clinical trial, that is over a period of about five years. After the trial period the effect on event rates requires modeling, as the drug could continue to offer the reduced incidence of events noted in the trial, presumably until death. If the event rates in clinical trials continue to show effectiveness with the difference in hazard of events continuing to the conclusion of the observation period, then the reduced incidence of events with therapy could be carried forward after the trial period. If the event rates initially part and then remain in parallel in

later years of the trial, then it would be appropriate to assume no further effect of therapy after the trial period. Non-fatal events such as stroke and acute myocardial infarction will both shorten life expectancy and change the health state by reducing utility. No matter what is observed within a trial, modeling based on reasonable but not necessarily empirically evident observation will be needed.

Overall cost should be from a societal perspective. The cost of PCSK9 inhibitors will be relatively straightforward to estimate using Redbook wholesale acquisition cost (WAC) or a similar measure.[10] However, it becomes difficult to estimate several years into the future as there may be downward pressure of pricing from payers or consumers as well as from competition. It seems likely that usage and cost of these drugs will change considerably over the next several years. The broader costs of medical care to be taken into consideration for PCSK9 cost-effectiveness studies can be approached by applying standarized costs to resource use as noted above. It will be reasonable to consider only hospitalization and the PCSK9 drug costs, as other health care costs can reasonably be assumed to be similar between arms. The hospitalization costs can be estimated from the number of events, as considered in the paragraph above. However, this approach becomes increasingly untenable as patients are considered further into the future and event rates and costs become more uncertain.

The really difficult issues related to PCSK9 cost effectiveness relate to the consideration of giving these drugs to young people as primary prevention, patients who will then potentially take them for many years, perhaps even from childhood and over the ensuing lifespan. Many of these young people have familial hypercholesterolemia which could potentially be defined genetically, providing the opportunity for more limited and accurate patient selection. Familial hypercholesterolemia is a common disease, and not all patients will have sufficient LDL-C lowering with statins. Increasing numbers will be identified by recommended universal cholesterol screening at age 9–11 years and by Cascade screening of identified index cases.[11] We do not have efficacy and safety data which would support such a tailored therapeutic approach at present. We do not know the likely effect of PCSK9 inhibition on survival, event rates or cost. This offers opportunity for modeling, but little data to base it on. Thus, the decision to consider PCSK9 therapy in young people and considering lifetime therapy is already upon us, with insufficient literature to guide decision making.

Cost-effectiveness studies alongside clinical trials have often ignored the costs related to lost productivity or the benefits of prolonged productivity. The effect of therapy upon productivity may be grouped with indirect costs. Indirect costs are often ignored in costs-effectiveness analysis due to difficulty in estimating them. Given the difficulty in estimating lost productivity and that most patients in trials of several years duration are generally older, this is not unreasonable. However, lost productivity is critical when considering lifetime therapy in young people. Our goal is to keep people healthy and productive. If we effectively prevent cardiovascular events by low cost interventions, e.g. tobacco control legislation, then the societal gain becomes considerable by preventing events that otherwise would have occurred in the prime of life while working and raising a family. Such interventions are quite

compelling and remain the focus of groups such as the American Heart Association and the United States Department of Health and Human Services.[12, 13]

The issues become much more difficult, with productivity gains unable to make up for the cost when therapy is expensive. This is true in part because gains decades into the future are discounted, but the cost of expensive preventive therapy begins to accrue immediately. If in a 20 year-old with familial hypercholesterolemia and with LDL- c >> 160 mg/dl we begin a PCSK9 inhibitor at $12,000 a year for 30 years, the cost by age 50 without discounting will be $360,000. If there is an absolute event rate reduction of 5%, then the cost would be $7,200,000 to prevent an event. If the person in whom we prevent an event gains 10 years of life expectancy, then the cost becomes $720,000 per life year gained. If this person loses 20 productive years at $100,000 a year, this is considerable. However the loss in productivity will occur in the future. If therapy begins at age 20 and prevents an event at age 50, the discounted productivity at 3% annually for $100,000 a year would be $40,000 a year. By 50 years this would be about $20,000 a year. The prolongation of life some 30 years in the future would also be similarly discounted. While there is much uncertainty in this “back of the envelope” calculation, it is not likely that PCSK9 inhibitors for primary prevention in young people, as currently priced, to provide an incremental cost-effectiveness ratio within a society willingness-to-pay threshold.[14] This calculus may prevent widespread adoption of PCSK9 inhibition as currently priced for primary prevention in young people.

There has been one attempt to evaluating the cost-effectiveness of PCSK9 inhibition.[15] This was based on a simulation using the CVD policy model.[16] Consistent with the difficulties outline above, the ICERs for both FH and secondary prevention were >$500,000 per QALY saved. More definitive results will require cost-effectiveness alongside the current outcome trials, once these trial data become available. The good news, in the fullness of time, is that less expensive approaches to PCSK9 inhibition are likely to be developed and such a scientific advance may well offer life-saving therapy many people.

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Table 1

Issues Concerning the Cost-Effectiveness of PCSK9 Inhibitors

1) Overall perspective
2) Selection of appropriate patients
3) Choice of comparator group
4) Incremental effect of PCSK9 on life expectancy compared to the control
5) Incremental effect of PCSK9 on non-fatal events
6) Effect of non-fatal events on health status
7) Incremental cost of PCSK9
8) Cost savings by preventing events
9) Cost savings by preservation of productivity
10) Incremental direct costs due to prolongation of life