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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

TABLE 1 Effect of PCSK9 Inhibitors on Outcomes in RCTs

	Randomized		All-Cause Mortality		CVD Mortality		MI	
	PCSK9 Inhibitors	Control	PCSK9 Inhibitors	Control	PCSK9 Inhibitors	Control	PCSK9 Inhibitors	Control
24 small RCTs (6)	6,187	3,972	19*	21	12	13	19†	19
SPIRE (8)	13,720	13,718	120	117	37	30	192	210
FOURIER (7)	13,784	13,780	444	426	251	240	468	639
ODYSSEY (9)	9,000	9,000	N/A	N/A	N/A	N/A	N/A	N/A
Total	42,691	40,470	583	564	300	283	679	868

Values are n unless otherwise indicated. *p = 0.015. †p = 0.03.

CVD = cardiovascular disease; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibitors in Subjects With Elevated Risk; MI = myocardial infarction; N/A = Not available; PCSK9 = proprotein convertase subtilisin/kexin type 9; RCT = randomized controlled trial; SPIRE = Studies of PCSK9 Inhibitors and the Reduction of Vascular Events.

model. The methods for performing cost effectiveness studies are somewhat technical, but there are well-accepted standards (10).

An alternative approach to economic evaluation is to collect data from cohorts of actual patients, rather than simulate outcomes in hypothetical patients. The highest-quality data on economic outcomes are derived from randomized clinical trials (RCTs) that collect data on health care utilization and cost alongside of the clinical outcome data (12,13). Nevertheless, trial-based analyses are subject to the limitations of the parent RCT, and often have low statistical power and short follow-up, so some projections may be needed to fully account for the long-term effectiveness and cost.

BUDGET IMPACT ANALYSIS

The budget impact of a new technology, defined as the number of treated patients multiplied by the incremental cost per patient, is distinct from its cost-effectiveness. Importantly, because treatments that are cost-effective almost always cost more money, they may still have a large budget impact. Indeed, total health care expenditures may be increased to the point of unaffordability if a costly treatment is used by a large segment of the population. In contrast, an expensive treatment for a rare disease may have relatively minimal budget impact because it is used for only a handful of patients. Both cost-effectiveness and budget impact of new technologies are important considerations for sustainable health systems.

INSIGHTS FROM ECONOMIC EVALUATION OF STATINS

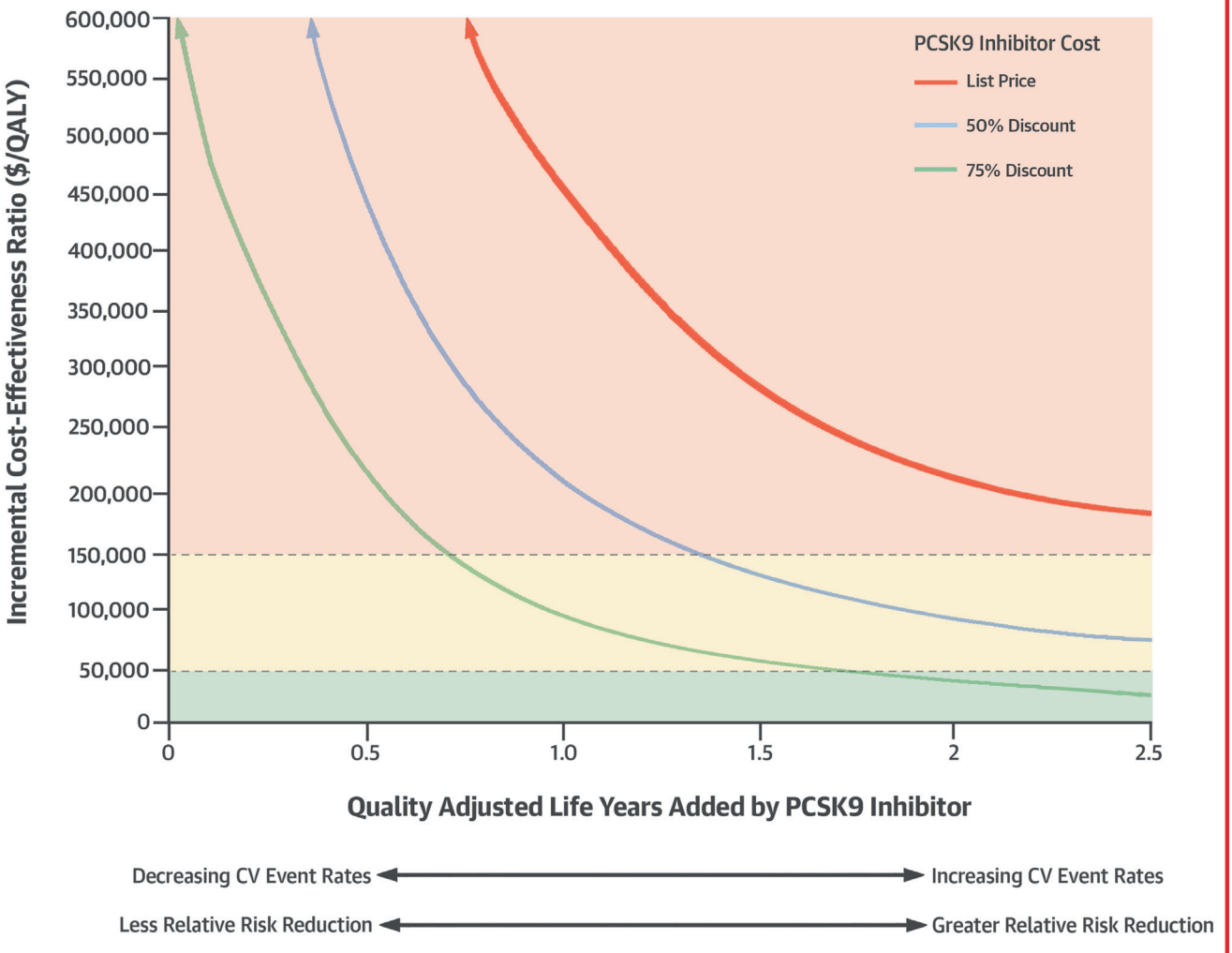
Therapies to treat elevated LDL-C have been repeatedly evaluated using cost-effectiveness analysis (14,15). The classic study by Goldman et al. (14) showed that the ICER for statins varied >100-fold, depending on the patient population treated. The ICER for using lovastatin (then costing $561 per year) as primary prevention varied from $13,000 to $1,500,000 per life-year added, depending on the patient's underlying risk of developing clinical atherosclerosis. Statin therapy was consistently more cost-effective when used as secondary prevention, with ICERs <$15,000 per life-year added. This insight—that the same treatment provides more value when used for secondary prevention than for primary prevention—has been repeatedly confirmed: treating higher-risk patients results in more QALYs added for the same drug cost, providing more "bang for the buck." This inverse relationship between the ICER and clinical effectiveness (**Central Illustration**) arises because the same relative risk reduction yields greater absolute benefits (more QALYs) in higher-risk patients. Lowering the cost of the new intervention shifts this curve downward, but does not abolish the inverse relationship between clinical effectiveness and the ICER. The availability of high-intensity, low-cost, generic statins has made it possible to treat lower-risk patients cost-effectively, and may have led to improved survival and cost savings in the highest-risk subgroups (16,17).

ECONOMIC EVALUATIONS OF PCSK9 INHIBITORS

All published economic evaluations of PCSK9 inhibitors have used simulation models, because no major RCT has included a prospective economic evaluation. These models differ in their structure, assumptions, and results (**Table 2**).

Kazi et al. (16) applied the well-established Cardiovascular Disease Policy Model to project the clinical and economic consequences of using either PCSK9 inhibitors or ezetimibe in addition to statins for primary and secondary prevention of cardiovascular disease. They relied on the reported 58% to 65% reductions in LDL-C levels reported by short-term studies of PCSK9 inhibitors, and assumed that

CENTRAL ILLUSTRATION **Economics of PCSK9 Inhibitors**



Hlatky, M.A. et al. J Am Coll Cardiol. 2017;70(21):2677–87.

Relationship between the incremental cost-effectiveness ratio (ICER) **(vertical axis)**, in dollars per quality-adjusted life-year (QALY) added, and the clinical effectiveness of PSCK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy **(horizontal axis)**. The horizontal axis is labeled with both the underlying cardiovascular (CV) risks of the treated population **(top scale)** and the relative risk reduction in cardiovascular events from PCSK9 inhibitor therapy **(bottom scale)**. The vertical axis includes **dotted lines** at $50,000/QALY and $150,000/QALY to indicate ICERs that are generally considered to be "high value" (**green area**), "intermediate value" (**yellow area**), and "low value" (**orange area**). The **top curve** shows the relationship between the ICERs and QALYs added at a cost of $14,000 per year (list price) for PCSK9 inhibitors, the **middle curve** shows this relationship if the price of PCSK9 inhibitors were discounted by 50% (to $7,000 per year), and the **bottom curve** shows this relationship if the price were discounted by 75% (to $3,500 per year).

lowering LDL-C would reduce coronary heart disease to the same extent as found in the pooled data from large RCTs of statins: a relative risk of 0.76 per mmol/l reduction in LDL-C. They also assumed that PCSK9 inhibitors would continue to be effective for the rest of the patients' lifetimes, at a cost of $14,350 per year. Based on these assumptions, they projected that use of PCSK9 inhibitors for 5 years in all U.S. adults for whom they are indicated would add $592 billion in drug spending, while saving about $28 billion (a 5% offset) in averted cardiovascular events. They calculated that PCSK9 inhibitors had a lifetime ICER of $414,000 per QALY relative to ezetimibe in secondary prevention populations, and an ICER of $503,000 per QALY in primary prevention for individuals with heterozygous familial hypercholesterolemia (16). They did not directly calculate the ICER for PCSK9 inhibitors compared with statins, but the published

results suggest it would be $316,000 per QALY when used for secondary prevention.

Kazi et al. (18) recently updated their model to include the initial outcome data from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibitors in Subjects With Elevated Risk) trial. They assumed that mortality would eventually be reduced to the same degree as other cardiovascular events, and calculated the ICER to be less favorable than in their earlier projections, namely $450,000 per QALY added in secondary prevention populations. This result was sensitive to the assumed late mortality reduction: the ICER would be $1,795,000 per QALY if there were no direct effect on cardiovascular death, as found in the FOURIER trial (18). They noted that the price of PCSK9 inhibitors would have to be reduced to ≤$4,215 per year for them to be cost-effective at a threshold of $100,000 per QALY.

Gandra et al. (19) came to strikingly different conclusions using a model developed by consultants for Amgen, the manufacturer of evolocumab. They assumed that patients would have the higher event rates found in the Reduction of Atherothrombosis for Continued Health registry, and that PCSK9 inhibitors would reduce risk in proportion to the degree of LDL-C lowering found in the pooled statin RCTs. Based on these assumptions, they projected that, in secondary prevention, a PCSK9 inhibitor would add $197,000 per patient in lifetime medication costs and save $56,000 per patient (a 28% offset) from averted events, yielding an ICER of $141,700 per QALY relative to statin therapy alone. In primary prevention for patients with heterozygous familial hypercholesterolemia, they projected greater clinical effectiveness at similar incremental costs, yielding a more favorable ICER of $76,000 per QALY relative to statin therapy alone.

The basic model of Gandra et al. (19) has been used in 2 other published economic evaluations (20,21). Toth et al. (20) used data from patients in the United Kingdom to estimate population risk, and projected that use of PCSK9 inhibitors would increase life-time medical costs, with an ICER of $194,400 per QALY compared with statin therapy. Fonarow et al. (21) adapted this model to incorporate data from the FOURIER trial, and assumed that the reductions in cardiovascular events would translate into mortality reductions after 5 years. They estimated that medical costs would increase by $105,398 per patient, with a gain of 0.39 QALYs, leading to an ICER of $268,600 per QALY for PCSK9 inhibitors compared with statins.

Arrieta et al. (22) analyzed the economic effects of PCSK9 inhibitors from a health care system perspective in a hypothetical cohort of patients treated for primary or secondary prevention. They assumed that the health system would negotiate a price discount on PCSK9 inhibitors ($12,048 per year), and that treatment would reduce cardiovascular events by 53% (7). They projected that the higher lifetime drug costs of PCSK9 inhibitor therapy ($237,700 per patient) would be minimally offset by savings from prevented cardiovascular events ($5,800 per patient, or 2.4%), yielding an ICER of $348,800 per QALY. They also projected that health systems would lose money by using PCSK9 inhibitors, and commented that in the fragmented health care system in the United States, health systems would have little incentive to "invest" in PCSK9 inhibitors because patients would be likely to move to other health plans before any benefits appeared.

Arireta et al. (23) updated their model to incorporate the results of the FOURIER trial and to assume the price of PCSK9 inhibitors would drop by 43% after patent expiration (23). The updated ICER was relatively unchanged at $337,700 per QALY.

The economic evaluation of PCSK9 inhibitors by Jena et al. (24) used a cost-benefit framework, in which survival gains were converted to dollars at a rate of $150,000 per life-year added. In cost-benefit analysis, the benefits (in dollars) are directly compared to the costs (in dollars) to assess value. In a secondary prevention scenario, with risk reductions in proportion to the degree of LDL-C lowering, they calculated the "total social value" of a year of PSCK9 inhibitor therapy would be $11,600, not enough to justify paying $14,000 per year for the medication. The benefits and costs would be equal (implying an ICER of $150,000 per QALY) if the drug price were reduced to $11,600 per year.

The results of these economic models vary considerably—with studies sponsored by manufacturers of PCSK9 inhibitors reporting more favorable results—but they all agree in several key respects. All models project that PCSK9 inhibitors will greatly increase lifetime medical costs, and that any cost savings from preventing cardiovascular events would offset only a small fraction of the cost added by the drug. All models project improved survival from use of PCSK9 inhibitors, but differ in the underlying risk of the treated population, and hence in the number of QALYs added by therapy. Most of the variation in the ICERs in these models arises from differences in how they estimated pre-treatment cardiovascular risk and projected the absolute mortality reductions expected from PCSK9 inhibitor therapy (**Table 2**). Even with optimistic assumptions, all models found relatively unfavorable ICERs for PCSK9 inhibitors, primarily because of the currently high prices of these drugs.

TABLE 2 Major Economic Models of PCSK9 Inhibitors as Secondary Prevention

Model Characteristic	Kazi et al. (16)	Kazi et al. Update (18)	Gandra et al. (19)	Toth et al. (20)	Fonarow et al. (21)	Arrieta et al. (22)	Jena et al. (24)
Sponsor	New England Comparative Effectiveness Public Advisory Council, Arnold Foundation	University of California, San Francisco	Amgen	Amgen	Amgen	None	Amgen
Study design	State-transition Markov Model (CVD Policy Model)	State-transition Markov Model (CVD Policy Model)	State-transition Markov Model	State-transition Markov Model	State-transition Markov Model	State-transition Markov Model	Cost-benefit analysis
Time horizon	Lifetime	Lifetime	Lifetime		Lifetime	Lifetime	20 yrs
Perspective	U.S. health system	U.S. health system	U.S. payer	U.S. health system	U.S. "societal"	U.S. health system	U.S. health system
Discount rate	3%	3%	3%	3%	3%	3%	3%
Productivity losses	Not included	Not included	Not included	Not included	Included	Not included	Not included
Intervention	PCSK9 inhibitor	PCSK9 inhibitor	Evolocumab	Evolocumab	Evolocumab	PCSK9 inhibitor	PCSK9 inhibitor
Comparator	Statin + ezetimibe	Statin + ezetimibe	Statin	Statin	Statin	Statin	"Standard lipid-lowering therapy"
Population							
Cohort	NHANES	NHANES	Framingham; Reduction of Atherothrombosis for Continued Health registry	U.K.-based clinical practice	NHANES/Truven	Evolocumab trial population	NHANES/Truven
Inclusion criteria	ASCVD with LDL >70 mg/dl despite maximally tolerated statin therapy (includes individuals who are statin intolerant)	ASCVD with LDL ≥70 mg/dl despite maximally tolerated statin therapy	ASCVD with LDL >70 mg/dl despite maximally tolerated statin therapy	ASCVD with a prior CV event, LDL ≥70 mg/dl despite maximally tolerated statin therapy	ASCVD with LDL ≥70 mg/dl despite maximally tolerated statin therapy	Patients who would have been eligible for a trial in the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) study	Elevated LDL-C >190 mg/dl or pre-existing ASCVD with LDL-C >70 mg/dl despite optimal "standard" therapy
Baseline demographics							
Mean age, yrs	61	66	62	67	66	58	Not reported
Proportion men	62%	61%	66%	60%	61%	52%	Not reported
Mean LDL-C, mg/dl	109	104	141	103	104	120	Not reported
Control event rate, baseline yr	3.02	3.6	2.78	12.3	6.4	1.73-5.71, variable by age	
Effectiveness							
Relative risk reduction	0.76/mmol/l reduction in LDL-C	0.76-0.83	0.69-0.71/mmol/l reduction in LDL-C	0.69-0.71/mmol/l reduction in LDL-C	0.80-0.90	0.47	0.50-0.57
Annual costs	2015 USD	2017 USD	USD/yr		2017 USD	USD/year	2015 USD
PCSK9 inhibitor	14,350	14,542	14,139	14,139	14,523	12,048	Not included
Ezetimibe	2,878	3,818	Not included	Not included	Not included	Not included	Not included

Continued on the next page

EVIDENCE GAPS AND MODEL UNCERTAINTIES

Simulation models require many assumptions, and there are several key evidence gaps that have large effects on the projected cost-effectiveness of PCSK9 inhibitors. The long-term effect of treatment on survival is by far the most critical uncertainty, because there are few clinical data on the long-term efficacy of PCSK9 inhibitors. The models handled this in 2 different ways: 1) they assumed that mortality will be reduced in proportion to the degree of LDL-C reduction; or 2) they assumed that mortality will be reduced to the same degree as seen for other cardiovascular events in short-term trials, particularly FOURIER (4).

It is a strong assumption that any drug that lowers LDL-C will reduce mortality. The relationship

TABLE 2 Continued

Model Characteristic	Kazi et al. (16)	Kazi et al. Update (18)	Gandra et al. (19)	Toth et al. (20)	Fonarow et al. (21)	Arrieta et al. (22)	Jena et al. (24)
Results*							
Life-yrs gained	8.68×10^6	6.09×10^6	1.29	Not reported	0.41	0.88	0.07/yr treated
QALYs gained	7.92×10^6	5.56×10^6	1.12	0.68	0.39	0.66	Not evaluated
Cost-effectiveness							
Incremental costs, drug	$3,273 \times 10^9$	$2,486 \times 10^9$	197,113	Not reported	139,375	237,718	Not evaluated
Incremental costs, other	9×10^9	14×10^9	−38,806	Not reported	−33,977	−5,800	−$1,200 per year of treatment
Incremental costs, total	$3,282 \times 10^9$	$2,500 \times 10^9$	158,307	127,088	105,398	231,918	Not reported
ICER relative to ezetimibe	414,000	450,000	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
ICER relative to statin	316,000	339,000	141,700	190,400	268,600	348,800	Not reported
Key sensitivity analyses	Drug price	Drug price	CVD rates	Baseline LDL-C, cohort defined by incident event	CVD event rate, late mortality reduction, drug price	Drug price	Uptake rates
Price at which PCSK9i has an ICER							
≤$50,000 per QALY	2,261	Not evaluated	Not evaluated	Not evaluated	5,578	2,297 (est)	Not evaluated
≤$100,000 per QALY	4,536	4,215	Not evaluated	9,064	7,623	4,250	Not evaluated
≤$150,000 per QALY	6,810	Not evaluated	Not evaluated	11,990	9,669	6,214 (est)	11,600
Budget impact	$125 billion/yr	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Conclusions	Not cost-effective at current prices	Not cost-effective at current prices	Is cost-effective	Good value with discounts >20%	Not cost-effective at current prices	Not cost-effective at current prices	"Substantial value"

*Results for Kazi (16) and Kazi update (18) are for the U.S. population; results for other models are per person.

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; FH = familial hypertension; ICER = incremental cost-effectiveness ratio; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; QALY = quality-adjusted life-year; USD = U.S. dollars; other abbreviations as in Table 1.

between LDL-C-lowering and risk reduction used by several models was taken from a meta-regression analysis of the results of large statin RCTs (25,26), which was performed because of the significant heterogeneity in relative risk reductions among RCTs. The average LDL-C reduction seen in a trial is a proxy for the potency of the statin regimen used, so the meta-regression analysis suggests that more potent statins reduce risk to a greater extent than less-potent statins do. It is plausible that the effect of statins on mortality may be partly mediated through mechanisms other than LDL-C lowering, because several other drugs that lower LDL-C have not reduced mortality (27,28). It is therefore a leap of faith to assume that lowering LDL-C by other means will be just as effective in reducing risk as lowering LDL-C by a statin. At present, there is little direct evidence for the assumption that PCSK9 inhibitors reduce mortality (**Table 1**), but several large RCTs are ongoing, and longer-term follow-up of FOURIER (4) may eventually show a reduction in mortality. Because preventing fatal events generates more lifetime QALYs and improves the long-term ICER, reliable trial data on this question will be critical to establish the cost-effectiveness of PCSK9 inhibitors.

A subtler additional key assumption of all the cost-effectiveness models is that the effects of PCSK9 inhibitors will continue, undiminished, over a lifetime of therapy. This assumption may be optimistic for several reasons. First, adherence to regular injections was high in RCTs, but is likely to be lower in more real-world patients, particularly because of high drug copayments (see the following text). Second, the efficacy of monoclonal antibody therapy may decline over time if neutralizing antibodies develop with continued use. Neutralizing antibodies developed at 1 year in 48% of patients treated with the PCSK9 inhibitor bococizumab, with titers high enough in some to negate the effect of the drug on LDL-C (29). Although bococizumab is substantially more antigenic than either alirocumab or evolocumab, even fully human antibody therapies may lead to

neutralizing antibodies with continued use (30), particularly if therapy is interrupted. Any reduction in the long-term efficacy of PCSK9 inhibitors would lead to less favorable cost-effectiveness.

All cost-effectiveness models assumed that PCSK9 inhibitors will not lead to any serious adverse events. Other newly approved biological agents have developed late safety events more frequently than small-molecule drugs (31), which may not become evident for several years after approval, with more time for some adverse events to become manifest in a larger, less-selected population. Any late adverse effects of PCSK9 inhibitors would lower their cost-effectiveness by the "double-whammy" of increasing costs and reducing effectiveness.

Finally, all but 1 model (23) assumed that the list prices of PCSK9 inhibitors would remain at their current levels in the future. It is possible that competition from newer agents might lower list prices, which would improve their cost-effectiveness. However, prices of other biological agents have generally increased over time, not decreased, even in the face of new competitors (see the following text). Price reductions many years in the future would also have less of an effect on the ICER because future costs and benefits are discounted at 3% per year in cost-effectiveness models (e.g., after 15 years, $100 would be equivalent to only $66).

POLICY ISSUES

PCSK9 inhibitors have been developed in the context of dramatic changes in the pharmaceutical industry. New biological agents and other "specialty pharmaceuticals" have been rationally designed to target specific molecular pathways, such as the monoclonal antibodies trastuzumab (Herceptin, Genentech, San Francisco, California) for breast cancer, and imatinib (Gleevec, Novartis, East Hanover, New Jersey) for chronic myelogenous leukemia. Almost all new specialty pharmaceuticals were developed to treat rare or uncommon diseases, and all carry very high price tags, some well over $10,000 per month. The costs of specialty pharmaceuticals are rising rapidly (32), and may soon comprise more than one-half of all drug spending in the United States.

Whereas small-molecule drugs face competition from generics soon after patent expiration, monoclonal antibodies and other biological agents face little competition from "biosimilars," which have a more difficult route to development, testing, and regulatory approval. Thus, the effective period of market exclusivity extends well beyond the duration of the initial patent. Even when biosimilars do come on the market, they typically cost only 15% to 20% less than the original product, in contrast to generic small-molecule drugs that usually cost 85% to 90% less than the branded product (33). Most cardiovascular drugs are small molecules, and most drug classes contain >3 competing agents and several generics. In particular, there are 7 statins approved in the United States, with many generic competitors. Consequently, the cost of statins has decreased to quite low levels: the wholesale acquisition price for a year's supply of 80 mg of atorvastatin is now under $125.

PCSK9 inhibitors represent a new paradigm for treating chronic cardiovascular diseases with a biological agent, and pose different policy issues than using biologics to treat cancer or inflammatory diseases. First and foremost, nearly 10 million U.S. adults might be eligible for PCSK9 inhibitor therapy (16,34), far more than the numbers of patients treated with other specialty drugs. Second, PCSK9 inhibitors are not a cure for atherosclerosis, but a preventive, lifelong therapy for individuals who may live 20 years or more. This extended therapy contrasts with short-course treatments like sofosbuvir, which cures hepatitis C, or most cancer therapies, which are given for a few months to patients with limited life expectancies.

Millions of patients treated for decades with PCSK9 inhibitors costing $14,000 per year will have a huge budget impact—more than a trillion dollars—which has rightly drawn the attention of policymakers and the concern of payers. Schulman et al. (35) have estimated that if just 5% of eligible adults 40 to 60 years of age with high LDL-C levels were started on a PCSK9 inhibitor, everyone's health insurance premium would increase by $124 per year.

There are 2 approaches to improving the cost-effectiveness and reducing the budget impact of PCSK9 inhibitors: 1) lowering the cost of the drug; and 2) restricting its use to the highest-risk patients most likely to benefit.

Pricing of specialty pharmaceuticals, including PCSK9 inhibitors, bears little relationship to the actual costs of developing and manufacturing the drug, and is much more determined by the manufacturer's sense of what the market will bear (36). Moreover, the prices of these agents have historically continued to rise after introduction to the market. The progressive rise in the price of Gleevec, from $30,000 per year in 2001 to $120,000 per year in 2016, cannot be attributed to recovering the sunk costs of research and development. Similarly, the prices of the top-selling

anti-inflammatory agents have risen sharply over the past decade, despite the introduction of competitors.

It is also well known that drug prices in the United States are considerably higher than in any other country, even though the U.S. market is larger. Governments in other countries directly negotiate lower prices for drugs: in the United Kingdom, the list price is £4,423 per year for evolocumab, and £4,388 per year for alirocumab (about $5,700 and $5,649 per year, respectively), not including the additional negotiated "simple discount" (37,38). Large integrated systems and pharmacy benefit managers in the United States have probably also negotiated discounts for PCSK9 inhibitors, but these transactions are shadowy and secretive. If a consensus emerges among physicians and health plans that these drugs are overpriced, that may lead to price reductions or larger discounts. The "value proposition" for PCSK9 inhibitors will clearly depend on the actual prices paid, not just "list price."

The negotiation power of American payers and pharmacy benefits managers with manufacturers is at least partly contingent on being able to use 1 PCSK9 inhibitor exclusively. This tactic is threatened by a patent infringement lawsuit filed by Amgen against Sanofi and Regeneron, which, if successful, would leave only 1 PCSK9 inhibitor in the U.S. market. The U.S. Court of Appeals has stayed the injunction on selling alirocumab, so at least 2 PCSK9 inhibitors will compete in the U.S. market for the immediate future (39).

The budget impact of PCSK9 inhibitors can be reduced by restricting their use to the highest-risk patients who will derive the most clinical benefit. Payers have imposed restrictions on patient eligibility for PCSK9 inhibitors, and generally require pre-approval. The precise criteria used by different payers vary, but common elements include documentation of a prior atherosclerotic cardiovascular disease event, and of the failure of a high-potency statin to reduce LDL levels sufficiently. The United Kingdom, for instance, requires LDL-C levels >135 mg/dl in secondary prevention and >193 mg/dl in primary prevention to justify use of a PCSK9 inhibitor (37,38). Initial experience with PCSK9 inhibitors shows relatively slow uptake, with many prescriptions not approved by insurers (40–42). Even when a prescription has been approved, patients may face high copayments that can easily exceed $300 per month (43), which lower the proportion of approved prescriptions that are ultimately filled (42).

Finally, accurate identification of true statin intolerance is an important clinical and economic consideration in use of PCSK9 inhibitors. Most patients who report statin intolerance will eventually tolerate a challenge with the same or a different statin (44). Kazi et al. (16) estimated that reducing the prevalence of statin intolerance from 10% to 3% would result in 974,000 fewer individuals eligible for PCSK9 inhibitor therapy, and decrease health care spending by $10.2 billion over 5 years. In addition to the economic benefits of reserving PCSK9 inhibitors for those truly unable to tolerate statins, the fact that statins have been proven to reduce long-term mortality in appropriately selected populations supports performing multiple trials of alternative statin agents and doses before prescribing a PCSK9 inhibitor for patients with statin intolerance.

CONCLUSIONS

PKSK9 inhibitors were rationally designed to reduce LDL-C levels substantially. It is unclear whether their effects on LDL-C will translate directly into lower mortality, because no large outcome trial has reported significant reductions in mortality, although follow-up has been relatively short. The list prices of PCSK9 inhibitors in the United States are over 100-fold higher than statins, and only a small fraction of their higher cost will ever be recouped by prevention of cardiovascular events, especially in lower-risk patients. The projected cost-effectiveness of PCSK9 inhibitors does not meet generally accepted benchmarks for good value, but would improve if their prices were cut substantially. For individual patients, high out-of-pocket costs may be a substantial barrier to access, and impede long-term adherence. The budgetary impact of PKSK9 inhibitors will be very large if all potentially eligible patients were treated, which poses dilemmas for policymakers, payers, and society.

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