Progress in Cardiovascular Diseases 62 (2019) 406–413

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Implications of cost-effectiveness analyses of lipid-lowering therapies: From the policy-maker's desk to the patient's bedside☆

Dhruv S. Kazi [a,b,c], Salim S. Virani [d,e,f,*]

[a] Richard A. and Susan F. Smith Center for Outcomes Research, Boston, MA, United States of America
[b] Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA, United States of America
[c] Harvard Medical School, Boston, MA, United States of America
[d] Michael E DeBakey Veterans Affairs Medical Center, Houston, TX, United States of America
[e] Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX, United States of America
[f] The Aga Khan University Medical College, Karachi, Pakistan

ARTICLE INFO

Keywords:
Cost-effectiveness
Incremental cost-effectiveness ratio
Lipid-lowering therapy
Statins
PCSK9 inhibitors

ABSTRACT

In our increasingly cost-conscious health system, patients, clinicians, hospitals, and payers all agree about the urgent need to rein in runaway healthcare costs. High pharmaceutical costs make drugs unaffordable to many patients who may benefit from them, including some insured patients who face prohibitive out-of-pocket costs. Health systems and payers can use the systematic framework of cost-effectiveness analysis and estimated budgetary impact to prioritize the adoption of new therapies and technologies. In this review article, we discuss basic principles of cost-effectiveness research for practicing clinicians, the concept of cost-effectiveness versus affordability, other considerations relevant to resource allocation, and limitations of cost-effectiveness research. We use the example of lipid lowering therapies to discuss application of cost-effectiveness research in informing health care policy, its use for health care systems and in the development of clinical practice guidelines, and its implications for clinicians and patients. As clinicians and patients become more cognizant of the cost-implications of new therapies, professional societies can help improve the quality of decision-making by incorporating unbiased value statements into their expert guidelines.

Published by Elsevier Inc.

Contents

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular diseased; CAD, coronary artery disease; CHEERS, consolidated health economic evaluation reporting standards; COR, class of recommendation; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; QALY, quality adjusted life years; 16, United Kingdom; 17, United States.

☆ The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

* Corresponding author at: Health Services Research and Development (152), Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd., Houston, TX 77030, United States of America.
E-mail address: virani@bcm.edu (S.S. Virani).

https://doi.org/10.1016/j.pcad.2019.10.006
0033-0620/Published by Elsevier Inc.

Background

Much has been written about the fact that the United States (US) spends an inordinate amount of money on healthcare.[1] In 2017, the US spent about 18% of its gross domestic product on healthcare, amounting to $10,224 per person. After adjusting for purchasing power, this was twice as high as the average healthcare expenditure of all high-income countries. Nevertheless, the fact that the US spends a lot more on healthcare than its peers does not automatically imply the US spends "too much" on healthcare. The world's largest economy may choose to spend more on healthcare as a reflection of its principles and priorities.[2–4] Perhaps we value healthcare more than other countries, believe that our health system yields gains that justify the cost, or choose to provide financial incentives for healthcare innovation. In that case, our health expenditures, however high, would not be considered excessive.

The evidence, however, suggests otherwise.[5] Despite the high levels of per capita healthcare spending, health outcomes in the US lag behind those of our peer countries. Furthermore, national averages conceal substantial geographic and demographic differences: underserved populations (such as rural, black, poor, or LGBTQIA+ populations) having substantially worse outcomes than other more privileged sections of the population.[6,7] Many US adults remain uninsured or underinsured, and do not have access to the high-cost innovation that our health system supposedly incentivizes. The US price of prescription drugs is three times that of the same drugs in the United Kingdom (UK), and even insured patients in the US face prohibitively high (and somewhat unpredictable) out-of-pocket costs for prescription drugs.[8] High out-of-pocket costs are an important barrier to long-term adherence to medications, so newer medications that are more efficacious than older medications in clinical trials may have lower effectiveness in the real world because older treatments frequently have lower out-of-pocket costs and therefore higher long-term adherence.[9] Health systems that care for a disproportionate number of underinsured or uninsured patients frequently teeter on the brink of insolvency, and payers themselves have had enormous challenges keeping up with soaring healthcare expenditures that are rising faster than the general economy. Finally, there is also the increasing bipartisan concern that rising healthcare costs are siphoning away money better spent elsewhere in the economy such as public education, environmental sustainability initiatives, or even recreation (the concept economists refer to as "opportunity cost"). This has led to growing cost-consciousness among all stakeholders, and an increasing demand for a systematic framework to optimally allocate scarce healthcare resources. Although the field of cost-effectiveness research has existed for several decades and its role is deeply entrenched in other health systems like the UK, Canada, and Australia, it is only now gaining prominence within the US health system. Recent successful efforts to use cost-effectiveness data to argue for large reductions in medication prices has further contributed to the growing stature of cost-effectiveness research in the US.[10,11]

In this manuscript, we review the core principles of cost-effectiveness analysis and its application to the management of dyslipidemia. We distinguish between cost-effectiveness (a measure of efficiency) and affordability (a reflection of the health system's budget constraint). We examine available economic evaluations of lipid-lowering therapies from the US health system perspective. Finally, we make a strong case for the use of high-quality cost-effectiveness analyses in informing health policy (such as drug pricing and uptake), and recommend that future practice guidelines from professional societies summarize available high-quality economic evaluations for diagnostic and therapeutic strategies and incorporate these cost considerations into their recommendations.

Principles of cost-effectiveness research cost-effectiveness 101

In order to optimally allocate scarce healthcare resources, one must be able to quantify the efficiency of various available alternatives. Efficiency in this setting is defined as how much improvement in health is produced by a given amount of spending. A commonly used metric for measuring cost-effectiveness is the incremental cost-effectiveness ratio or ICER.[12] As the name suggests, the ICER is defined as the incremental health gain per unit increase in spending. Thus, if *C1* and *O1* represent the total healthcare costs and resulting health outcomes of a patient receiving the current standard of care, and *C2* and *O2* represent the total healthcare costs and resulting health outcomes of a patient receiving a new therapy, then the ICER for the new therapy relative to the current standard of care would be defined as:

$$\text{ICER} = \frac{\text{C2} - \text{C1}}{\text{O2} - \text{O1}}$$

Some important observations follow from the above definition.

First, the ICER is a relative construct. The cost-effectiveness of a therapy is always defined *relative to its comparators*. A high-quality cost-effectiveness analysis must therefore include all potential alternatives for the population being studied. For instance, an evaluation of a new lipid-lowering agent among patients with established atherosclerotic cardiovascular disease (ASCVD) must include all other lipid-lowering therapies that may be used in that population. If there are several potential interventions, each intervention is compared with the next best intervention. Because cost-effectiveness evaluations are sequential (with each intervention compared with the next best intervention), failure to include a legitimate comparator can distort the ICER values generated and result in misallocated resources.

Second, the numerator should include all relevant healthcare costs, not just the cost of the current and new therapy being evaluated, but any downstream costs.[13] For instance, a new lipid-lowering agent may be substantially more expensive but it may produce fewer side-effects and, being more effective in reducing low-density lipoprotein cholesterol (LDL-C), result in fewer major adverse cardiovascular events (MACE, a composite of cardiovascular death, myocardial infarction [MIs], and ischemic stroke) downstream. The savings from averted MACE may offset some of the increased costs of the drug. On the other hand, if patients live longer due to the new agent, they may consume more of other kinds of healthcare (e.g., medications for diabetes or treatment for an unrelated malignancy), which may increase healthcare spending. Cost-effectiveness analyses must account for all these

changes in costs that result from the use of a new therapy. Most cost-effectiveness analyses are performed from the healthcare sector perspective and therefore include all healthcare-related expenditures regardless of who pays for them (e.g., including out-of-pocket costs). Cost-effectiveness analyses may also be performed from a societal perspective, in which case they include any related expenditures outside the healthcare system such as those related to decreased economic productivity related to the disease (e.g., missed days from work due to a hospitalization or withdrawal from the labor market to care for an unwell family member). These costs are measured in the local currency for single-country analyses, or in some standardized currency to facilitate comparison when performing multiple-country analyses, adjusting for differences in inflation over time or purchasing power across countries where relevant. In this case, healthcare costs accrued in the control arm (i.e., among patients receiving the current standard of care) and those accrued in the intervention arm are estimated separately, and the difference between the two (C2–C1) entered into the numerator of the ICER calculation.

Third, the denominator should capture all health outcomes of interest. This may take the form of counts of MACE, life-years, or quality-adjusted survival. The quality-adjusted life year (QALY) has gained traction as a useful metric of health outcomes as it can capture the benefits of interventions that improve survival, quality-of-life, or both. To estimate QALYs, the quality-of-life of a health state is estimated on a scale from 0 to 1 where 0 represents death and 1 represents perfect health. A detailed description of the tools used to elicit quality-of-life estimates and the limitations of QALYs as an outcome metric is beyond the scope of this discussion, but the interested reader is referred to a very readable summary produced by the Second Panel for Cost-Effectiveness in Health and Medicine.[14] Assume that an individual lives for five years with a quality of life of 0.7 and then dies. In this case, the individual is assumed to have accrued 5*0.7 = 3.5 QALYs. One's quality-of-life may wax and wane over time (for instance, declining during a year in which one has a stroke, but recovering partially with rehabilitation), and these can be captured over time to generate an aggregate estimate of QALYs. QALYs accrued in the control arm (in this case, among patients receiving the current standard of care) and those accrued in the intervention arm are estimated separately, and the difference between the two (O2–O1) entered into the denominator of the ICER calculation.

Fourth, both costs and outcomes must be measured over an appropriate analytic horizon.[15] Ideally, one would measure all clinical and economic consequences over the patients' lifetime. Using shorter-than-lifetime horizons can have the perverse effect of disadvantaging interventions where the costs are front-loaded but benefits accrue over time (e.g., implantable defibrillators). Alternatively, short horizons may not capture any delayed side effects associated with the intervention. On the other hand, long-term horizons may increase the uncertainty in the estimated ICER because they involve extrapolating effectiveness and safety data from short-term trials. Long-term horizons may also be less palatable to decision-makers who may be more drawn to shorter horizons that align with political cycles. Our approach for cardiovascular interventions and policies has therefore been to use the lifetime horizon in the base case (while attempting to fully capture the ensuing uncertainty from extrapolation of available shorter-term evidence), and using 10- or 20-year horizons in sensitivity analyses. We discourage the use of analytic horizons shorter than 10 years in ASCVD analyses, where population-level benefits often accrue over time.

Finally, ICER is simply a measure of economic efficiency of an intervention relative to the comparator (in dollars per QALY gained). In order to interpret the ICER, it must be compared with a cost-effectiveness threshold that reflects how much the health system is willing to pay for health interventions. An intervention with an ICER less than the threshold would be considered economically favorable. For instance, if a health system were willing to pay $50,000 per QALY gained, an intervention with an ICER of $40,000 per QALY gained relative to the current standard would be considered cost-effective whereas one with an ICER of $200,000 per QALY gained would not. Thus, defining a cost-effectiveness threshold is central to the interpretation of ICERs. Because of its political reluctance to embrace cost-effectiveness analyses in the past (out of an unfounded fear of rationing of healthcare resources), the US does not have a well-defined cost-effectiveness threshold. The American Heart Association and the American College of Cardiology adapted the World Health Organizations CHOICE framework to propose that interventions with ICERs < $50,000 per QALY gained should be considered "high-value" whereas those with ICERs ≥ $150,000 per QALY gained should be considered "low-value", with those with intermediate ICERs be considered "intermediate-value".[16] Although these thresholds, and the WHO CHOICE framework from which they were derived,[17] are somewhat arbitrary and are frequently criticized as being both too high and not high enough (depending on stakeholder interests), they are presently the most widely used approach for interpreting ICERs. Our current practice is to use $100,000 per QALY gained as the threshold for our base case analyses and vary this between $50,000 and $150,000 per QALY gained in sensitivity analyses.

The interested reader is also encouraged to view a series of short but engaging and informative videos on this topic created by UCSF Professor Emeritus James G. Kahn (total viewing time approximately 45 min).[18]

Cost-effectiveness versus affordability

At this stage, it is important to distinguish between cost-effectiveness and affordability. Cost-effectiveness is a measure of efficiency, reflecting how much health can be generated for any given amount of healthcare spending. In contrast, affordability refers to the net change in healthcare spending should an intervention be adopted at the population level.

$$\text{Budget Impact} = \text{Net cost per patient} * \text{Number of patients treated}$$

Consider an expensive drug for a rare disease that has an ICER of $300,000 per QALY gained relative to the current standard of care. Such a drug may have a minimal budget impact because only a handful of patients may be eligible for treatment. It would not be considered cost-effective because of its high ICER but may be affordable because of its minor budget impact given the very small number of eligible patients. An expensive drug for treating Hepatitis C may be cost-effective (because it avoids downstream liver transplants), but a safety-net health system that cares for a disproportionate number of patients with Hepatitis C may not be able to commandeer the dollars needed to treat all its patients based on its limited pharmaceutical budget. Such a drug would be cost-effective but unaffordable. Finally, a novel lipid-lowering therapy that has an ICER of $400,000 per QALY gained with a potential eligible population of 10 million US adults would be neither cost-effective nor affordable.

Thus, cost-effectiveness and affordability are related but distinct properties of an intervention. If one had no budget constraint, one would adopt every intervention that meets the cost-effectiveness threshold. In reality, all health systems face budget constraints, and investment decisions must consider both efficiency (cost-effectiveness) and affordability (budget impact).

Other considerations relevant to resource allocation

The remainder of this review will focus on the cost-effectiveness and affordability of lipid-lowering agents. However, it is important to remember that optimal resource allocation may require the decision maker to bear in mind other considerations as well. One important

factor that determines allocation of resources is concerns about health equity. For instance, one may be willing to invest in additional resources to address disparities related to access, adherence, and health outcomes. For instance, a health system may choose to invest additional resources in a hard-to-reach section of the population that does not engage in prevention. While such programs may appear to be less cost-effective than traditional healthcare system-delivered programs, they may still be considered worthwhile investments in a health system that values a reduction in health disparities. Similarly, advocacy by patient groups may engender political buy-in disproportionate to the immediate gains that such investments may yield. One may argue whether incorporating equity considerations or political expediency perversely distorts our resource allocation decisions or simply reflects our priorities as a society.[19] In any case, these considerations undeniably hold substantial sway over our fragmented healthcare system, even in the face of growing influence of high-quality cost-effectiveness analyses.

Cost-effectiveness of lipid-lowering agents

For the purpose of this discussion, we categorize the use of lipid-lowering agents into primary prevention (i.e., among individuals at risk for but without evidence of established ASCVD) and secondary prevention (i.e., among individuals with established ASCVD). The gestalt is that the cost-effectiveness of any intervention for primary prevention is directly related to baseline risk of ASCVD in the studied population and effectiveness of the intervention (the higher the baseline risk of ASCVD or more effective the intervention, the greater the net clinical benefit, and hence the better the cost-effectiveness of said intervention), and inversely related to the cost (higher the cost, worse the cost-effectiveness).

Statins for Primary Prevention

There have been numerous high-quality cost-effectiveness analyses examining the role of generic and branded statins for primary prevention of ASCVD.[20] Contemporary analyses all agree that, in a world of low-cost generic statins, their use for primary prevention is cost-effective across a range of underlying risk.[21] In a microsimulation model of US adults aged 45 to 75 years, a 10-year ASCVD risk threshold ≥7.5% (as used in the ACC/AHA cholesterol treatment guidelines) was projected to be a high-value intervention (ICER, $37,000/QALY), but more lenient treatment thresholds would be optimal using cost-effectiveness thresholds of $100,000/QALY (≥4.0% risk threshold) or $150,000/QALY (≥3.0% risk threshold). The optimal ASCVD threshold was sensitive to changes to statin price and the risk of statin-associated diabetes, i.e., the more expensive the statin and the higher the risk of statin-associated diabetes, the higher the risk threshold at which statins would be cost-effective. Interestingly, several studies have now shown that a key determinant of the value of the cost-effectiveness of generic statins for primary prevention is the amount of "disutility" the patient derives from having to take a daily pill.[21,22] The implications are that when using low-cost generic statins among appropriately selected patients, the only patients who appear to not have a net clinical benefit are those for whom taking a pill every day is substantially burdensome, in which case the net loss of quality-of-life from the daily pill will outweigh the benefit in patients who are at low- to intermediate-risk for ASCVD. This highlights the continued role of shared decision making when initiating statin therapy for primary prevention.

Non-statin agents for primary prevention

There are few contemporary high-quality studies examining the cost-effectiveness of non-statin therapies for primary prevention. Among patients with heterozygous familial hypercholesterolemia [FH] (who typically have an untreated LDL-C ≥ 190 mg/dL and are therefore among the highest risk subgroup within primary prevention), the addition of ezetimibe to statin therapy is likely to be cost-effective only if generic ezetimibe is used (unpublished data; generic ezetimibe price costs approximately $300 per year, compared with $1400 a year for branded ezetimibe).[10,23] In the same population, the addition of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) to statin therapy (at 2019 US prices) would have an ICER between $100,000 and $150,000 per QALY gained (unpublished data).[10]

Secondary prevention

Patients with established ASCVD are at substantially higher risk of ASCVD events (on average 6–7 MACE per 1000 person-years). They therefore derive a larger net clinical benefit from lipid-lowering therapy (on average) than patients without established ASCVD. In other words, for any given drug, its use for secondary ASCVD prevention is, on average, more cost-effective than its use for primary prevention. This does not argue against investing in primary prevention, it simply implies that if we had a limited pot of money, we would first invest it in getting all our secondary prevention patients on lipid-lowering therapy.

However, the story gets even more interesting for statin therapy. Because several high-intensity statins now have generic formulations that are very inexpensive, and because there is incontrovertible evidence of their effectiveness and safety in reducing morbidity and mortality among patients with established ASCVD, statins are in fact cost saving when used for secondary prevention. In other words, the savings that would accrue from future reductions in MIs and ischemic strokes would more than offset the cost of initiating statin therapy in this population. The use of statins in this population is what economists refer to as a "dominating option", i.e., it costs less and generates more health than the alternative (no statin therapy). Predictably, the cost-effectiveness of ezetimibe and PCSK9i is also a function of baseline risk (being more cost-effective in subgroups of patients who have higher-than-average risk). When PCKS9 inhibitors were launched in 2015, their wholesale acquisition cost was $14,350 per year, and their use in secondary prevention was projected to be not cost-effective. Since then, the manufacturers have announced a large (and, in the US market, unprecedented) 60% price reduction, so that the drugs now cost $5850 per year. In light of newer data suggesting that these drugs may be more effective at reducing non-fatal events than fatal events (with a reduction in MACE but no statistically significant improvement in survival over the duration of the clinical trials), it is likely that PCSK9i do not meet the $150,000 per QALY threshold even in high-risk secondary prevention despite the recent price reductions.[23]

In the REDUCE-IT, patients with elevated triglyceride levels despite the use of statins, treatment with 2 g of icosapent ethyl twice daily produced a significant reduction in risk of ischemic events, including cardiovascular death.[24] This trial included 70.7% patients with established cardiovascular disease and 29.3% patients with diabetes and one additional risk factor. A recent study from a national cohort of patients from the Department of Veterans Affairs showed that 14.5% and 17.1% of patients with ASCVD and diabetes would meet eligibility criteria for REDUCE-IT, with significant cost implications based on average wholesale price and Medicaid pricing.[25] A formal economic evaluation is ongoing, but there are concerns about the increase in pharmaceutical spending because a large number of US adults will likely be eligible for this therapy.[25–27]

Application of cost-effectiveness analyses

Implications for health policy

The primary function of cost-effectiveness analyses is to optimize resource allocation at the level of the health system. In countries with well-established governmental agencies for health technology

assessment, cost-effectiveness analyses are a part of the regulatory approval process. The National Institute for Health and Care Excellence in England and Wales determines not only whether a new drug is effective and safe, but also whether it would be cost-effective at the price being proposed by the manufacturer. This gives the agency implicit power to negotiate drug prices for the English and Welsh National Health Services (which constitute approximately 90% of the healthcare market in these countries). Similar health technology assessment agencies exist in Europe, Canada, and Australia, and increasingly in wealthier nations in Asia. The US, on the other hand, has been reluctant to embrace the use of cost-effectiveness analyses. In fact, the Patient Centered Outcomes Research Institute, established under the Affordable Care Act, was explicitly barred by the US Congress from developing or using a cost-effectiveness threshold in its evaluations. Despite this entrenched suspicion of cost-effectiveness analyses, various stakeholders in our fragmented health system are increasingly demanding a systematic framework to estimate the "value" of a new drug or device so that this information can be used to determine its price. The most striking example of this has been the 60% price reduction of PCSK9i that was announced by both manufacturers in 2018. Alirocumab and evolocumab were launched in 2015 at a wholesale acquisition cost of $14,350 per patient per year, a price at which their ICER was greater than $400,000 per QALY gained. But initial uptake was poor: payers created onerous prior-authorization requirements out of concerns related to total budget impact and patients abandoned prescriptions at the pharmacy because of high out-of-pocket costs.[28–30] In one analysis, out-of-pocket costs for Medicare Part D beneficiaries receiving a PCSK9 inhibitor and a statin was estimated to be $4997 per year.[8] In response to pressure from payers (armed with cost-effectiveness analyses arguing for substantial price reductions) and patients (who were voting with their feet by abandoning prescriptions), manufacturers announced a 60% price reduction for the drugs. This large price reduction for a biologic therapy is unprecedented in the US, where biologic prices typically increase 10–12% year-on-year during the lifetime of a drug's market exclusivity period. Importantly, one of the manufacturers has reduced the list price of the drug (rather than offering a larger discount), which translates to lower copays for Medicare Part D beneficiaries (who must pay a co-pay on the list price before discounts). The PCSK9 inhibitor experience has shown the power of timely high-quality cost-effectiveness analyses in helping reduce prices of and increase access to new therapies. Importantly, in line with the National Academy of Medicine's recommendation that the effectiveness and safety of drugs should be evaluated over their entire lifecycle, the cost-effectiveness of drugs should also be updated as new data emerge regarding effectiveness, safety, and price.[23]

Implications for health systems

Given the compelling evidence of the cost-saving nature of statins for secondary prevention, health systems should invest in increasing uptake of statins in this population, which still remains suboptimal.[31–33] Strategies may include identifying patients not currently on high-intensity statins, re-challenging patients previously identified as being statin intolerant, and eliminating all co-pays for statin therapy for these patients.

In addition to the cost of a new drug and its cost-effectiveness relative to the current standard of care, health systems must also be cognizant of the impact of adopting an expensive therapy like PCSK9i on their total expenditures. This is particularly true in fragmented systems where the future savings from averted MIs and strokes do not accrue to the same entity that is paying out for the new therapy at the present time (for instance, where pharmaceutical and hospital budgets are siloed). The rise of accountable care organizations may encourage payers to make investments in prevention, though the empirical evidence supporting this hypothesis is limited. One way for health systems to mitigate the economic effect of new, expensive therapies is to target these therapies to patients most likely to benefit from them. For instance, a sequential approach to lipid-lowering, in which PCSK9i are only prescribed to patients who continue to have elevated LDL-C despite maximal therapy with statins and ezetimibe, would dramatically reduce the number of patients eligible for PCSK9 inhibitor therapy compared with a strategy in which PCSK9 inhibitor therapy is initiated before trying ezetimibe.[34–37] For example, one of the recent simulation studies in the VA health care system[36] showed that the use of evidence-based statin therapy along with ezetimibe will drop LDL-C levels below 70 mg/dL in two-thirds of the patients with history of acute coronary syndrome, comparable to the active arm of the ODYSSEY Outcomes trial.[38]

Implications for Clinical Guidelines

Based on the methodology described above, the ACC/AHA guidelines have begun incorporating cost-effectiveness analyses into the guideline documents. Apart from providing a Class of recommendation (COR) and a level of evidence (LOE) for a therapeutic option, the guidelines also provide a separate "value statement" based on available cost-effectiveness analyses for a particular therapy. The 2018 AHA/ACC Multisociety cholesterol guideline[39,40] made two value statements in the guideline document (one pertaining to the use of PCSK9i for secondary ASCVD prevention and one for the use of PCSK9i in patients with FH without evidence of clinical ASCVD). As discussed above and as noted in the 2018 cholesterol guideline document, the cost-effectiveness of a therapy not only depends on the cost of a therapy (which is a moving target), it also depends on the clinical benefit from that therapy (relative risk reduction associated with the therapy and the baseline event rates in the population of interest when compared to the population studied in the RCT).

Based on the studies described above and using mid-2018 list prices for PCSK9i, the panel concluded that at mid-2018 list prices, PCSK9i have a low cost value (ICER > $150,000 per QALY) for patients with secondary ASCVD prevention when added on to statin therapy. It is important to note that there are several variables at play here. First, both outcomes studies of PCSK9i[38,41] were of relative short duration (median follow-up = ~2.2 years for FOURIER and 2.8 years for ODYSSEY-Outcomes) and therefore, there is considerable uncertainty related to whether long-term use of these therapies would lead to greater relative risk reduction than what was observed in these outcomes trials. Second, although no mortality benefit was seen in the FOURIER trial[41] and mortality benefit was seen in ODYSSEY Outcomes study[38] as a nominal finding; especially in those with baseline LDL-C ≥ 100 mg/dl; all models studied in the ICER analyses quoted in the section above assume eventual reduction in mortality from the use of PCSK9i due to a reduction in MACE. Third, cost is a moving target. Therefore, therapies may become cost-effective as prices for PCSK9i come down, some of which has already happened with both PCSK9i as discussed above. In that respect, most cost-effectiveness noted that the price of PCSK9i would need to come down between 70 and 85% to meet conventional cost-effectiveness thresholds discussed above.[39,40] Fourth, the 2018 cholesterol guideline identifies a "very high-risk ASCVD" group as patients with either multiple major ASCVD events or those with one major ASCVD event plus multiple high-risk conditions. Several of these patient phenotypes (for e.g. those with recent MI, >1 MI, multi-vessel CAD, presence of symptomatic PAD, polyvascular disease, and persistently elevated LDL-C levels)[42–46] have been shown to identify patient subgroups who seem to derive a higher absolute risk reduction compared with an average trial participant in the two outcomes trials of PCSK9i. It is therefore quite possible that the interplay of substantial price reduction (moving the numerator in ICER in favorable direction) and identifying a "very high-risk" ASCVD population (increasing the clinical benefit and moving the denominator in favorable direction) could potentially make PCSK9i

cost-effective in select secondary ASCVD patients who are deemed to be very high-risk based on clinical criteria. This was also highlighted in a recent statement from the National Lipid Association.[47]

As opposed to ASCVD patients, only two studies examined the use of PCSK9i in patients with heterozygous FH. One of the studied models found low value (ICER = $503,000 per QALY added) when PCSK9i were used.[10] The second study reported intermediate value (ICER = $75,900 per QALY added) with the use of PCSK9i in heterozygous FH.[48] Therefore, the value statement in the 2018 AHA/ACC Multisociety guideline on the management of blood cholesterol noted an uncertain value for PCSK9i at mid-2018 list prices when added to maximally tolerated statin and ezetimibe therapy.

Implications for clinicians and patients

A large body of evidence demonstrates that adherence to medications declines when patients incur high out-of-pocket costs.[9,49] In the US, patients may face substantially different out-of-pocket costs for two drugs in the same class, and out-of-pocket costs for any given drug can vary substantially month-to-month (e.g., based on the phase of Medicare Part D coverage).[8] Clinicians are therefore encouraged to regularly discuss out-of-pocket costs with their patients, with the aim of early identification of cost-related non-adherence. While generic drugs typically have lower out-of-pocket costs than branded formulations, even this appears not to be universally true. Regular communication about costs can help encourage patients to discuss cost issues with their clinician in a timely manner, so the medication regimen can be altered appropriately.

Limitations

Cost-effectiveness analyses must make assumptions about the long-term effectiveness and safety of the intervention being evaluated, even when only short-term data are available. Similarly, budget impact analyses must estimate uptake of the product among patients eligible for it. Thus, there is substantial uncertainty in estimated ICER and budget impact, particularly early in the product's life cycle, when the evidence is most sparse. It is important to note that the uncertainty in these economic valuations is far greater than the statistical uncertainty captured in the 95% confidence intervals of the effect size seen in clinical trials. Policy makers must use the limited information that is available to make decisions regarding drug approval and pricing. An important role of cost-effectiveness analysis is to quantify this uncertainty, to identify whether uncertainty in any of the underlying assumptions or input parameters would materially alter estimates of the ICER. This is achieved by performing sensitivity analyses where the value of one or more input parameters (or structural assumptions in the model) are varied while holding all others constant and examining the change in the ICER. For a new drug that has not been priced yet, one could ask the question: What would the price have to be for the drug to meet traditional cost-effectiveness thresholds? For instance, cost-effectiveness analyses of PCSK9i relative to ezetimibe among patients with established ASCVD showed that the price of PCSK9i would have to decline 70–80% from their launch price to meet a threshold of $100,000 per QALY gained. In another example, when a drug-related adverse event is not clearly understood, one may ask the question: How frequent or severe would the adverse event have to be to completely neutralize the clinical benefit from the drug (or make it cost-ineffective)? When low-cost statins are available, they are cost-effective for primary prevention regardless of any (reasonably-sized) increased risk of hypothetical adverse events; the primary driver of cost-effectiveness is whether or not the patient has any disutility from taking a daily pill.[22,50] Thus well-done sensitivity analyses can be enormously informative to policy makers and clinicians, and by highlighting gaps in knowledge, can help identify key priorities for future research.

Because of the numerous assumptions that go into a cost-effectiveness analysis, an investigator can make assumptions favorable (or unfavorable) to the intervention being evaluated, systematically biasing the results. Because of the complexity of the analytic approach, these assumptions may go unnoticed by the untrained reviewer. The CHEERS checklist has been developed to evaluate the quality of a cost-effectiveness analysis.[51] As with other forms of clinical and policy research, it is critical that cost-effectiveness analyses are thoroughly vetted by unbiased reviewers with expertise in cost-effectiveness analysis as well as subject-matter expertise in the field of interest.

Future directions

Three ongoing developments foretell the growing influence of cost-effectiveness analyses. First, professional societies are increasingly incorporating cost-effectiveness into clinical guidelines, thus reflecting the consensus among clinicians and patients that considerations related to healthcare expenditures are directly relevant to clinical decision-making. Second, there is increasing interest among cost-effectiveness researchers to move the field away from theoretical estimations of clinical and economic outcomes to more practical, updated, and context-specific estimates of cost-effectiveness that can be used by policy-makers and guideline writing committees. Cost-effectiveness researchers are also systematically using sensitivity analyses to highlight key gaps in knowledge and, in doing so, helping identify priority areas for future research. Finally, in the absence of a government-supported health technology assessment agency in the US, the Institute for Clinical and Economic Review has had some early success in bringing together various stakeholders, commissioning high-quality cost-effectiveness analyses from academic investigators, and influencing drug pricing.[52]

Conclusions

In our increasingly cost-conscious health system, patients, clinicians, hospitals, and payers all agree on the urgent need to rein in runaway healthcare costs. High pharmaceutical costs make drugs unaffordable to many patients who may benefit from them, including some insured patients who face prohibitive out-of-pocket costs. Health systems and payers can use the systematic framework of cost-effectiveness analysis and estimated budgetary impact to prioritize the adoption of new technologies, though such decisions should also consider the implications for health equity. Clinicians should be aware of the costs of the drugs they prescribe and regularly discuss out-of-pocket costs with patients as such discussions may lead to early identification of cost-related non-adherence. As clinicians and patients become more cognizant of the cost implications of new therapies, professional societies can help improve the quality of decision-making by incorporating unbiased value statements into their expert guidelines.

Sources of funding

Dr. Virani is supported by research funding from the Department of Veterans Affairs Health Services Research & Development (IIR 16-072), World Heart Federation, and Tahir and Jooma Family. Dr. Kazi is supported by the NHLBI (R01 HL141823; MPI: Moran, de Ferranti) to evaluate screening strategies for FH and received funding from the Institute for Clinical and Economic Review to evaluate the economics of PCSK9i.

Declaration of competing interest

Dr. Virani has received honorarium from the American College of Cardiology (Associate Editor for Innovations, acc.org). He also serves on the steering committee for the Patient and Provider Assessment of Lipid Management (PALM) registry at the Duke Clinical Research Institute (no financial remuneration).

Dr. Kazi: none to report.

References

1. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. JAMA 2018 Mar 13;319(10):1024-1039. https://doi.org/10.1001/jama.2018.1150.
2. Fuchs VR. How and why US health care differs from that in other OECD countries. JAMA 2013 Jan 2;309(1):33-34. https://doi.org/10.1001/jama.2012.125458.
3. Fuchs VR. Critiquing US health care. JAMA 2014 Nov 26;312(20):2095-2096. https://doi.org/10.1001/jama.2014.14114.
4. Fuchs VR. Economics, values. and health care reform Am Econ Rev 1996 Mar;86(1):1-24.
5. Moses 3rd H, Matheson DH, Dorsey ER, George BP, Sadoff D, Yoshimura S. The anatomy of health care in the United States. JAMA 2013 Nov 13;310(18):1947-1963. https://doi.org/10.1001/jama.2013.281425.
6. Chetty R, Stepner M, Abraham S, et al. The association between income and life expectancy in the United States, 2001–2014. JAMA 2016 Apr 26;315(16):1750-1766. https://doi.org/10.1001/jama.2016.4226.
7. Yeh RW, Normand SL, Wang Y, Barr CD, Dominici F. Geographic disparities in the incidence and outcomes of hospitalized myocardial infarction: does a rising tide lift all boats? Circ Cardiovasc Qual Outcomes 2012 Mar 1;5(2):197-204. https://doi.org/10.1161/CIRCOUTCOMES.111.962456 [Epub 2012 Feb 21].
8. Kazi DS, Lu CY, Lin GA, et al. Nationwide coverage and cost-sharing for PCSK9 inhibitors among medicare part D plans. JAMA Cardiol 2017 Oct 1;2(10):1164-1166. https://doi.org/10.1001/jamacardio.2017.3051.
9. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med 2014 Sep 16;161(6):400-407. https://doi.org/10.7326/M13-2942.
10. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA 2016 Aug 16;316(7):743-753. https://doi.org/10.1001/jama.2016.11004.
11. Kazi DS, Penko J, Coxson PG, et al. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. JAMA 2017 Aug 22;318(8):748-750. https://doi.org/10.1001/jama.2017.9924.
12. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA 2016 Sep 13;316(10):1093-1103. https://doi.org/10.1001/jama.2016.12195.
13. Basu A. Estimating costs and valuations of non-health benefits in cost-effectiveness analysis. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. Cost Effectiveness in Health and Medicine. 2nd ed. New York: Oxford University Press; 2017.
14. Feeny D, Krahn M, Prosser LA, Salomon JA. Valuing health outcomes. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. Cost Effectiveness in Health and Medicine. 2nd ed. New York: Oxford University Press; 2017.
15. Basu A, Maciejewski ML. Choosing a time horizon in cost and cost-effectiveness analyses. JAMA 2019 Feb 21. https://doi.org/10.1001/jama.2019.1153 [Epub ahead of print].
16. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. J Am Coll Cardiol 2014 Jun 3;63(21):2304-2322. https://doi.org/10.1016/j.jacc.2014.03.016 [Epub 2014 Mar 27].
17. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ 2015 Feb 1;93(2):118-124. https://doi.org/10.2471/BLT.14.138206 [Epub 2014 Dec 15].
18. https://www.youtube.com/watch?v=b9PHwhyxIQI&list=PLPdSQGGMt89e4_ObAbU8F8ZASfgAoNVH9.
19. Marseille E, Kahn JG. Utilitarianism and the ethical foundations of cost-effectiveness analysis in resource allocation for global health. Philos Ethics Humanit Med 2019 Apr 3;14(1):5. https://doi.org/10.1186/s13010-019-0074-7.
20. Kazi DS, Penko JM, Bibbins-Domingo K. Statins for primary prevention of cardiovascular disease: review of evidence and recommendations for clinical practice. Med Clin North Am 2017 Jul;101(4):689-699. https://doi.org/10.1016/j.mcna.2017.03.001.
21. Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. JAMA 2015 Jul 14;314(2):142-150. https://doi.org/10.1001/jama.2015.6822.
22. Heller DJ, Coxson PG, Penko J, et al. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. Circulation 2017 Sep 19;136(12):1087-1098. https://doi.org/10.1161/CIRCULATIONAHA.117.027067 [Epub 2017 Jul 7].
23. Kazi DS, Penko J, Coxson PG, Guzman D, Wei PC, Bibbins-Domingo K. Cost-effectiveness of Alirocumab: a just-in-time analysis based on the ODYSSEY outcomes trial. Ann Intern Med 2019 Jan 1. https://doi.org/10.7326/M18-1776 [Epub ahead of print].
24. Bhatt DL, Steg PG, Miller M, et al. Ballantyne CM; REDUCE-IT investigators. Cardiovascular risk reduction with Icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019 Jan 3;380(1):11-22. https://doi.org/10.1056/NEJMoa1812792 [Epub 2018 Nov 10].
25. Jia X, Akeroyd JM, Nasir K, et al. Eligibility and cost for icosapent ethyl based on the REDUCE-IT trial. Circulation 2019 Mar 5;139(10):1341-1343. https://doi.org/10.1161/CIRCULATIONAHA.118.038691.
26. https://icer-review.org/announcements/additive-cvd-topic/.
27. Khera R, Valero-Elizondo J, Saxena A, Virani SS, Krumholz HM, Nasir K. National population and cost implications of treatment with icosapentyl ethyl in the United States: an assessment based on the REDUCE-IT trial. doi: https://doi.org/10.1101/466649.
28. Navar AM, Taylor B, Mulder H, et al. Association of prior authorization and out-of-pocket costs with patient access to PCSK9 inhibitor therapy. JAMA Cardiol 2017 Nov 1;2(11):1217-1225. https://doi.org/10.1001/jamacardio.2017.3451.
29. Myers KD, Farboodi N, Mwamburi M, et al. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. Circ Cardiovasc Qual Outcomes 2019 Aug;12(8), e005404. https://doi.org/10.1161/CIRCOUTCOMES.118.005404 [Epub 2019 Jul 23].
30. Nasir K, Angraal S, Virani SS. PCSK9 inhibitors prior authorization. Circ Cardiovasc Qual Outcomes 2019 Aug;12(8), e005910. https://doi.org/10.1161/CIRCOUTCOMES.119.005910 [Epub 2019 Jul 23].
31. Pokharel Y, Tang F, Jones PG, et al. Adoption of the 2013 American College of Cardiology/American Heart Association cholesterol management guideline in cardiology practices nationwide. JAMA Cardiol 2017 Apr 1;2(4):361-369. https://doi.org/10.1001/jamacardio.2016.5922.
32. Hira RS, Cowart JB, Akeroyd JM, et al. Risk factor optimization and guideline-directed medical therapy in US veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. Am J Cardiol 2016 Oct 15;118(8):1144-1149. https://doi.org/10.1016/j.amjcard.2016.07.027 [Epub 2016 Jul 29].
33. McBride CL, Akeroyd JM, Ramsey DJ, et al. Statin prescription rates and their facility-level variation in patients with peripheral artery disease and ischemic cerebrovascular disease: insights from the Department of Veterans Affairs. Vasc Med 2018 Jun;23(3):232-240. https://doi.org/10.1177/1358863X18758914 [Epub 2018 Mar 30].
34. Cannon CP, Khan I, Klimchak AC, Reynolds MR, Sanchez RJ, Sasiela WJ. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. JAMA Cardiol 2017 Sep 1;2(9):959-966. https://doi.org/10.1001/jamacardio.2017.2289.
35. Virani SS, Akeroyd JM, Nambi V, et al. Estimation of eligibility for proprotein convertase Subtilisin/Kexin type 9 inhibitors and associated costs based on the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk): insights from the Department of Veterans Affairs. Circulation 2017 Jun 20;135(25):2572-2574. https://doi.org/10.1161/CIRCULATIONAHA.117.028503 [Epub 2017 May 2].
36. Virani SS, Akeroyd JM, Nambi V, et al. Applicability and cost implications for proprotein convertase Subtilisin/Kexin type 9 inhibitors based on the ODYSSEY outcomes trial. Circulation 2019 Jan 15;139(3):410-412. https://doi.org/10.1161/CIRCULATIONAHA.118.034993.
37. Virani SS, Akeroyd JM, Smith Jr SC, et al. Very high-risk ASCVD and eligibility for nonstatin therapies based on the 2018 AHA/ACC cholesterol guidelines. J Am Coll Cardiol 2019 Aug 6;74(5):712-714. https://doi.org/10.1016/j.jacc.2019.05.051.
38. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-2107. https://doi.org/10.1056/NEJMoa1801174.
39. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 2019 Jun 25;73(24):e285-e350. https://doi.org/10.1016/j.jacc.2018.11.003 [Epub 2018 Nov 10].
40. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019 Jun 18;139(25):e1082-e1143. https://doi.org/10.1161/CIR.0000000000000625 [Epub 2018 Nov 10].
41. Sabatine MS, Giugliano RP, Keech AC, et al. FOURIER steering committee and investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017 May 4;376(18):1713-1722. https://doi.org/10.1056/NEJMoa1615664 [Epub 2017 Mar 17].
42. Sabatine MS, De Ferrari GM, Giugliano RP, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease. Circulation 2018 Aug 21;138(8):756-766. https://doi.org/10.1161/CIRCULATIONAHA.118.034309.
43. Bonaca MP, Nault P, Giugliano RP, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk). Circulation 2018;137(4):338-350.
44. Jukema JW, Szarek M, Zijlstra LE, et al. Patients with Recent Acute Coronary Syndrome and Polyvascular Disease Derive Large Absolute Benefit from Alirocumab: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019 Mar 12. https://doi.org/10.1016/j.jacc.2019.03.013 [Epub ahead of print. pii: S0735-1097(19)33921-X].
45. Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. Circulation 2019 Jul 9;140(2):103-112. https://doi.org/10.1161/CIRCULATIONAHA.118.038840 [Epub 2019 May 23].
46. Jia X, Al Rifai M, Birnbaum Y, Smith Jr SC, Virani SS. The 2018 cholesterol management guidelines: topics in secondary ASCVD prevention clinicians need to know. Curr Atheroscler Rep 2019 Apr 2;21(6):20. https://doi.org/10.1007/s11883-019-0784-8.
47. Robinson JG, Jayanna MB, Brown AS, et al. Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. J Clin Lipidol 2019 May 16. https://doi.org/10.1016/j.jacl.2019.05.005 [pii: S1933-2874(19)30181-3. Epub ahead of print].
48. Gandra SR, Villa G, Fonarow GC, et al. Cost-effectiveness of LDL-C lowering with evolocumab in patients with high cardiovascular risk in the United

States. Clin Cardiol 2016 Jun;39(6):313-320. https://doi.org/10.1002/clc.22535 [Epub 2016 Apr 19].
49. Choudhry NK, Avorn J, Glynn RJ, et al. Post-myocardial infarction free Rx event and economic evaluation (MI FREEE) trial. Full coverage for preventive medications after myocardial infarction. N Engl J Med 2011 Dec 1;365(22):2088-2097. https://doi.org/10.1056/NEJMsa1107913 [Epub 2011 Nov 14].
50. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation 2011 Jul 12;124(2):146-153. https://doi.org/10.1161/CIRCULATIONAHA.110.986349 [Epub 2011 Jun 27].
51. Husereau D, Drummond M, Petrou S, et al. CHEERS task force. Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health 2013 Mar–Apr;16(2):e1-e5. https://doi.org/10.1016/j.jval.2013.02.010.
52. Freund D, Choi J. Is ICER NICEr? Pharmacoeconomics 2018 Apr;36(4):385-386. https://doi.org/10.1007/s40273-018-0617-6.