Received: 21 December 2017 | Revised: 5 February 2018 | Accepted: 6 February 2018

DOI: 10.1002/clc.22924

WILEY CLINICAL CARDIOLOGY

REVIEW

PCSK9 inhibitor valuation: A science-based review of the two recent models

Seth J. Baum[1] | Christopher P. Cannon[2]

[1]Department of Integrated Medical Sciences, Florida Atlantic University, Charles E. Schmidt College of Medicine, Florida

[2]Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

Correspondence
Seth J. Baum, MD, FACC, 7900 Glades Road, Suite 400, Boca Raton, FL 33434
Email: sjbaum@fpim.org

Low-density lipoprotein cholesterol (LDL-C) has been extensively evaluated. Prospective cohort studies, randomized controlled trials, biology, pathophysiology, genetics, and Mendelian randomization studies, have clearly taught us that LDL-C causes atherosclerotic cardiovascular disease. The newest class of drugs to lower LDL-C, the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, have been found to safely reduce LDL-C approximately 60% when added to high-intensity statin therapy. Because their cost is much greater than that of the currently available agents, their value has been questioned. In late August, 2017, two groups assessed the value of this class of drugs looking at cost-effectiveness; however, the Institute for Clinical and Economic Review and Fonarow and colleagues found disparate results when assessing PCSK9 valuation. Herein, we review the evolution of LDL-C from hypothesis to fact, and then attempt to adjudicate the 2 models, shedding light on the complex modeling process. We find that models of cost-effectiveness are helpful adjuncts to decision making, but that their conclusions depend on many assumptions. Ultimately, clinician judgment regarding their clinical benefit, balanced by some estimation of cost, may be more productive to target the right patients for whom the benefits can be well-justified.

KEYWORDS

Coronary Artery Disease, Familial Hypercholesterolemia, Low-Density Lipoprotein Cholesterol, Myocardial Infarction, Stroke

1 | A BRIEF HISTORY OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE CAUSATION

To fully grasp the current debate regarding valuation of proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mabs), one must appreciate the history of low-density lipoprotein cholesterol (LDL-C). Cholesterol was discovered over 200 years ago, but it was not until 1913 that a Russian medical student, Nikolai Anitschkow, demonstrated the association of cholesterol and atherosclerosis.[1] Twenty-six years later, Michael Macheboeuf identified distinct lipoproteins, but again the pathogenic/cholesterol connection lagged.[2] Then, in 1939, Carl Müller identified the first cases of familial hypercholesterolemia (FH), introducing genetics as a participant in cholesterol regulation.[3] His patients had extremely high cholesterol, fatty collections beneath their skin, and early onset heart disease. The cholesterol-atherosclerosis link was bolstered. A decade later, in 1949, John Gofman took the cholesterol story to a more granular level by using analytic ultracentrifugation to separate disparate lipoprotein particles.[4] One was low-density lipoprotein (LDL). Gofman did not stop there; he demonstrated that patients with FH had not just high cholesterol levels, but more precisely, extremely elevated LDL-C. It was not until the 1960s that LDL-C became systematically studied.[5]

The Framingham Heart Study, which started in 1948, was the first of such analyses. Subsequently, numerous other prospective cohort studies demonstrated concordant associations of LDL-C and atherosclerotic cardiovascular disease (ASCVD); the higher the LDL-C the more prevalent the ASCVD, whereas the lower the LDL-C, the

less prevalent. These trials fueled more conclusive ones, the randomized controlled trials. The Scandinavian Simvastatin Survival Study, published in 1994, was a turning point for LDL's causal association with ASCVD.[6] In this placebo-controlled trial, over 5.4 years there was a compelling 30% relative risk reduction in cardiovascular (CV) mortality, an absolute 9% reduction (i.e., number needed to treat [NNT] = 11) in the composite triple endpoint of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke, and a 30% reduction in all-cause mortality. The Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis of 26 trials documented that for every millimole per liter reduction in LDL-C, a consistent 22% relative risk reduction in ASCVD events followed,[8] which became the backbone of the American College of Cardiology (ACC)/American Heart Association (AHA) 2013 cholesterol guidelines.[9] Over the past decade, we have also seen a uniformity of results in Mendelian randomization studies evaluating LDL-C and ASCVD.[10] Consistently, mutations that cause high LDL-C result in a higher prevalence of ASCVD, whereas mutations causing low LDL-C result in the opposite. In 2017, the European Atherosclerosis Society published a consensus statement that concluded: "Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD."[11]

2 | PCSK9, FROM DISCOVERY TO DRUG

In 1973, amid our burgeoning appreciation of LDL's role in atherosclerosis, Brown and Goldstein published their seminal work describing the role of the LDL receptor.[7] Their model helped clinicians and scientists not only better understand familial hypercholesterolemia (FH), but also pursue more appropriate therapeutics to lower LDL-C and thereby diminish ASCVD risk. Their discoveries led to a Nobel prize in 1985. In 2003, Abifadel identified the gene for PCSK9, residing on the short arm of chromosome 1.[12] Nearly concurrently, Abifadel also demonstrated PCSK9 gain of function mutations causing high LDL-C, increased ASCVD, and FH.[13] Subsequently the opposite was identified, which was PCSK9 loss of function mutations leading to low LDL-C and decreased ASCVD.[14] The stage was set for intensive further research into PCSK9 as a key LDL-C regulator and a potential therapeutic target. Though PCSK9 is released by hepatocytes as a zymogen, it rapidly undergoes intra-endoplasmic reticulum autocatalysis to become the active protein that binds hepatocyte LDL receptors. This binding curtails the repetitive recycling of LDL receptors, leading to higher circulating LDL-C.[15] Thus, blocking PCSK9 promised to lead to greater numbers of hepatic LDL receptors, lower LDL-C, and fewer ASCVD events. In 2007, industry scientists solved PCSK9's crystal structure, and in 2010 human studies with PCSK9 mab were initiated.[16,17]

Just 5 years later, enough convincing data had accrued from multiple phase 2 and 3 studies such as the ODYSSEY trials: LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy), FH I and II (Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy), HIGH FH (Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia); and COMBO 1 (Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia), LAPLACE (LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy), RUTHERFORD (Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study), DESCARTES (Durable Effect of PCSK9 Antibody Compared with Placebo Study), and TESLA (Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities), for the Food and Drug Administration (FDA) to approve 2 PCSK9 mabs, alirocumab and evolocumab.[18–24]

3 | FDA APPROVAL OF ALIROCUMAB AND EVOLOCUMAB, WHAT ARE THE INDICATIONS

In 2015, the FDA approved the PCSK9 mabs alirocumab and evolocumab. Evolocumab received approval for homozygous FH, whereas both drugs were approved for heterozygous FH and clinical ASCVD. The stipulations for use required that eligible patients were taking maximally tolerated statin therapy yet still required additional lowering of LDL-C. On its face, these criteria seemed self-evident. What ensued proved otherwise.

Within the first 6 months following approval, denial rates for these medications were unprecedented, topping 80% in some analyses of claims.[25] The prior authorization (PA) and appeal processes were also exceptionally burdensome. A thorough evaluation of PCSK9 mabs claims and denials ensued. Evidence accrued illustrating flaws in the utilization management process, inconsistent adjudication, and a faulty initial review process.[26,27] Perhaps most concerning of all were case reports in the *New York Times*, Reuters, Bloomberg, and the *Wall Street Journal* of incontrovertibly inappropriate PCSK9 mab denials.[28–31]

In response to such overwhelming evidence, the American Society for Preventive Cardiology (ASPC) crafted an initiative including members from other societies—the FH Foundation, the American Association of Clinical Endocrinology (AACE), the National Lipid Association (NLA), and the American College of Cardiology (ACC)—to hold a series of town hall meeting designed to acquire input from all stakeholders involved in PCSK9 mab therapies. Patients, politicians, payers, clinicians, the media, and others were invited. A comprehensive paper was subsequently published, which defined the 5 central designations in the PCSK9 mab package inserts and produced simple, user-friendly, single page PA and appeal letters.[32] Clarifying and streamlining the process of prescribing these agents was the intent of this open-access paper and its attachments. To date, nearly 1000 clinicians have attended these town halls or utilized the consensus paper. Still, access to PCSK9 mab remains problematic.

4 | FOURIER AND THE NEW CV EVENT REDUCTION INDICATION

FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) was designed to assess the effect of evolocumab on clinical outcomes. It randomized 27,564 high-risk individuals on high-intensity statin therapy with LDL-C ≥ 70 mg/dL to either placebo or evolocumab.[33] Evolucumab produced a 59% LDL-C reduction and led to a 15% reduction in the primary endpoint of cardiovascular death, nonfatal MI, or stroke, unstable angina, and coronary revascularization. The key secondary endpoint of CV death, nonfatal MI, and nonfatal stroke was reduced by 20%. At 3 years, there was an absolute risk reduction of 2% in both primary and key secondary endpoints, translating into an NNT over 3 years of 50. The findings were consistent with the CTTC's results. Additionally, from a safety perspective, no adverse signals were found in FOURIER, even in the realm of neurocognitive events as demonstrated in the large parallel study, EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects).[34]

With these data, the FDA granted a new indication for CV event reduction for evolocumab in late 2017; however, regarding utilization, little seems to have changed.

5 | INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW: ITS MISSION AND INFLUENCE ON PCSK9 MAB UTILIZATION

The Institute for Clinical and Economic Review (ICER) is an organization that states on its website[35]: "ICER is driven by a mission to conduct evidence-based reviews of health care interventions, such as drug, devices and diagnostics, that help patients, doctors, and everyone else in the health care system know what works. For every report, ICER follows a process that includes numerous opportunities for stakeholders to engage and be involved throughout its development." Although this is a noble mission that does not appear to speak about costs, their reports focus on the dollar value of medical interventions.

ICER's non–peer-reviewed PCSK9 Inhibitor New Evidence Update focused on their interpretation of FOURIER. Some findings were scientifically valid and deserve recognition.[36] ICER acknowledged FOURIER's excellent quality and convincing demonstration of the lack of safety concerns. It also acknowledged that other drugs, such as ezetimibe, can reduce CV events by lowering LDL-C as seen in the IMPROVE IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin [Ezetimibe/Simvastatin] vs Simvastatin [P04103]) trial.[39] Finally, ICER invited individuals and groups to express their opinions regarding the implications of FOURIER. This process not only required a significant time commitment from those of us who spoke with ICER, but also from ICER itself. For these reasons, they should be commended.

However, we believe that ICER made 4 key miscalculations in their analysis. The first and most consequential was their C+ rating: "We considered a B+ rating (incremental or better), but the uncertainty introduced by the non-significant trend towards increased cardiovascular mortality in years 2+ of the trial (HR 1.12, 95% CI 0.88-1.42) led us to the more conservative assessment." ICER's C+ rating claims that compared with the standard of care in high-risk patients, evolocumab is comparable or better, whereas a B+ rating would have recognized that FOURIER proved evolocumab to be incremental or better." It is hard to dispute that FOURIER's results demonstrate evolocumab to be at least incremental to or better than standard of care, an easy ICER B+ rating.

ICER said that their reason for downgrading the PCSK9 mab class hinged partly on FOURIER mortality data from a landmark analysis, which includes only a portion of the data. A landmark analysis excludes patients with events before the start of the landmark curves and does not include all patients or all events. As such, it is observational and not fully randomized. Therefore, though valuable, it cannot be relied on to make any definitive assessments. Furthermore, the overall mortality data are neutral. This is expected, because no prior intervention when added to statins has reduced mortality, not high-intensity statins or ezetimibe, or most recently anacetrapib.[8,40,41] Only when compared with placebo have statins shown a mortality benefit. To make a scientific claim about these partial mortality results of only 2-year plus analysis is not scientific. Additionally, the trial was not powered for mortality. It was too short to demonstrate a mortality benefit, and the confidence intervals for mortality were too large to infer any scientific conclusion. Most importantly, mortality cannot be the only endpoint that proves a drug's effectiveness. Consider this: the 2013 ACC/AHA cholesterol guidelines hinge on CTTC results.[8,9] Only 3 of the 26 trials in the CTTC demonstrated mortality benefits. They were powered to do so, far longer in duration than FOURIER, and placebo controlled. The 23 remaining trials compared different doses or types of statins and demonstrated reductions in nonfatal events, not mortality. Statin therapy as recommended in the 2013 ACC/AHA cholesterol guidelines is based entirely on these trials, the overwhelming majority of which failed to show mortality benefits of statins. Thus, adopting ICER's mortality-reliant logic in appraising FOURIER would demand that we dismiss the relevance of all statin trials supporting higher vs lower doses, and negate the 2013 ACC/AHA cholesterol guidelines.

ICER also downplayed the importance of nonfatal MI and stroke. It is now recognized that reductions in nonfatal MI and stroke ultimately translate into downstream mortality benefits. Perhaps more important though is the fact that such events can result in not only life-altering morbidities for patients, they can also permanently adversely affect patients' relatives/caretakers. To reiterate, mortality cannot be the sole endpoint considered; other infirmities do evoke grave consequences. Finally, there is an irony in ICER's insistence that mortality reduction is a prerequisite to support the B+ rating that they refused to grant this drug class. Mortality could not be demonstrated in FOURIER in part because the trial was brief, its brevity being the consequence of an unexpectedly high residual ASCVD risk in the placebo arm. FOURIER thus proves that ASCVD patients need more intensive therapies because their residual risk remains unacceptably high. In a way, FOURIER's lack of a mortality benefit demonstrates just how important it is for appropriate high-risk patients to take the PCSK9 mabs.

The explanation for poor uptake of a PCSK9 mab was also distorted in the ICER report. Their statement, "Uptake of the PCSK9 inhibitors has been slow, with their high cost and limited data on hard CV disease outcomes dampening enthusiasm for the drugs" has limited support. Instead, multiple studies, even cited in their update, have demonstrated flaws in utilization management, adjudication, and initial review processes.[25–27] Various sources have cited barriers in accessing the PCSK9 mab. Doctors enthusiastically prescribe these medicines but are stymied by time-consuming oppressive obstacles. The media has spotlighted individual cases, whereas others have examined large datasets. The *New York Times*, for example, revealed the case of a 41-year-old man with severe FH. Having had a first MI at age 17 years, followed by coronary artery bypass surgery, multiple stents, and the need for prolonged LDL apheresis, this gentleman had a persistent LDL-C well over 200 mg/dL on maximally tolerated statin therapy, ezetimibe, and a bile acid sequestrant.[28] He was an indisputable candidate for a PCSK9 mab. Yet it took a year and the help of a *New York Times* expose to get him the medicine he needed and deserved. The FH Foundation demonstrated that even in FH patients with ASCVD and extremely high LDL-C on maximally tolerated statin therapy, there is an unacceptably high number of PCSK9 mab denials.[27] Others have studied large claims databases, demonstrating the lack of disparity in drug rejections among those on diverse statin regimens, with or without diabetes, and even with or without ASCVD (using prescription antiplatelet therapy as an ASCVD proxy).[26] The approval process, therefore, appears to be unpredictable. The FH foundation, ASPC, AACE, and others have published these findings in well-respected peer-reviewed journals.[32] A consistency of conclusions provides further credence to the claim that the process of drug approval/denial is seriously flawed.

6 | MODELING COST-EFFECTIVENESS OF MEDICATIONS

The purpose of economic models assessing drugs is to derive two metrics, QALY and ICER (N.B. ICER the metric is different from ICER the Institute).[38] These terms, though different, are frequently inappropriately interchanged. QALY, Quality Adjusted Life Years, is a number expressing two variables, quality and quantity of life. Its value hinges on another metric, Utility. Utility is the numeric expression of an individual's health. It ranges from 0 to 1; 0 being death, and 1, perfect health. The average US citizen has a utility of 0.825, meaning he or she enjoys 82.5% of perfect health. A QALY therefore expresses both the quality and time added to one's life by a novel therapy. A QALY is calculated by multiplying the extra time derived from a therapy by the Utility a person experiences during that time.

An ICER, or Incremental Cost Effectiveness Ratio, provides the relationship between the cost and benefit of two different interventions. ICER is a monetary figure, while QALY is not. The formula to derive an ICER is $(c1\text{-}c2)/(q1\text{-}q2)$, where c1 is the average healthcare cost of treatment for patients on a new drug, and c2 is the average healthcare cost of treatment on standard therapy. Q1 is the new drug's QALY, while Q2 is the QALY with standard care. ICER, the incremental cost effectiveness ratio, is the cost of a new therapy required to provide a person with an additional year of perfect health. A calculated ICER is compared to an "acceptable" ICER threshold to determine whether a novel therapy is worth its price tag. Unfortunately, this "acceptable" value is subjective; there is yet to be an agreed-upon number. In first world countries, WHO recommends 3 times of the GDP be used as the threshold.[39] For example, in the US, that is approximately $150,000, although the threshold can vary from $50,000 to $200,000. To better grasp an ICER's implications, one must examine the model itself, and the inputs used to draw conclusions on a therapy's cost effectiveness and in so doing, derive an ICER.

7 | REVIEW OF RECENT COST-EFFECTIVENESS MODELS OF PCSK9 INHIBITORS

There have recently been 2 models of cost-effectiveness of PCSK9 inhibitors published, with an update to 1 analysis. They differ greatly in their conclusions; 1 noted these agents would not be cost effective, whereas the other suggested they were close to current thresholds for acceptable cost–benefit.

The ICER analysis (Kazi et al.[42]) relied on the Coronary Heart Disease Policy Model published 30 years ago.[43] This is in contradistinction to the model employed by Fonarow et al.,[44] which is based on Gandra et al.,[45] Toth et al.,[46] and the Repatha Health Technology Assessment (HTA) submissions, including the one to National Institute for Health and Care Excellence in the United Kingdom.[47] Even at the time of their original publication, the authors recognized this model's limitations stating, "The specific forecasts could be inaccurate, however, as a consequence of erroneous assumptions or misestimated baseline data."

An important input to the cost-effectiveness models is the baseline event rate. These differed greatly in the 2 analyses: Kazi et al. used an event rate of 3.7% for MI, stroke, and CV death, whereas Fonarow et al. used 6.4%. When Fonarow et al. considers revascularization in his model, the event rate rises to 9.7%.[42,44] ICER chose to use an event rate derived from clinical trials, and also elected to exclude recurrent events. Fonarow et al. selected real world numbers and included recurrent events as they have real world implications. Fonarow et al. used National Health and Nutrition Examination Survey and MarketScan data to construct their model. It has been well-established that event rates are uniformly lower (one-half to one-third) in clinical trials than in the real world. As the intent of these pharmacoeconomic models should be to determine whether PCSK9 mabs are cost effective outside of clinical trials and in the real world, it stands to reason that an optimal event rate should be real world. Event rates produce a large effect on a drug's value; low rates make it harder to demonstrate value whereas high rates do the opposite. Thus, the large disparity of event rates between these models is consequential. Inputting a spuriously low event rate diminishes the value of the medication under study.

8 | CHOOSING THE EVENTS THEMSELVES, ANOTHER POWERFUL PLAYER

In addition to selecting a given event rate to demonstrate treatment effect, the other substantial driver of model output, one must also

select the events themselves. Kazi et al. chose nonfatal MI, nonfatal cerebrovascular accident (CVA), and death. Fonarow et al. added hospitalizations for coronary revascularizations. The latter events not only drive up healthcare costs for payers, but also take a significant toll on patients and their caregivers. Again, in a real-world vein, adding such hospitalizations as events makes sense. Other inputs in the models, though less impactful on the final output, also require our attention.

The source of utility values for MI and CVA differed between the studies. Kazi et al. chose values from a Global Burden of Disease dataset, reflecting third-world figures. Fonarow et al. chose first world or United States data. Considering just MI and CVA, ICER assigned utility values of 0.96 and 0.88, respectively. As the average US citizen has a utility of 0.825, such values are hard to justify.[48] It is difficult to imagine how a stroke victim can enjoy a higher utility, or quality of life than that of an average healthy individual. Equally implausible is suggesting that a heart attack victim has a nearly perfect quality of life, far exceeding that of an ordinary American. Disutility, the immediate and transient impact of an event, was similarly minimized by Kazi et al. For MI, their assigned disutility was 0.005, whereas for CVA it was 0.01. MI and CVA were thus considered by Kazi et al. to have essentially no meaningful immediate impact, again a supposition that runs counter to the experience of clinicians and family members who have cared for heart attack and stroke patients.

Another input into the cost-effectiveness models is the baseline LDL-C. Kazi et al. used 104 mg/dL, the mean LDL-C, whereas Fonarow et al. used this scenario, but also one with a higher value, as more often seen in clinical practice (mean = 130 mg/dL). Neither model employed scenarios in which LDL-C was very high, as is typically the case in those with FH. The age of modeled patients also varied between the 2 studies. Kazi et al. used an age range of 40 to 84 years, whereas Fonarow et al. used ≥18 years. By omitting younger patients, Kazi et al. failed to consider those with FH, many of whom have events between 18 and 40 years old. Omitting those over 84 years also fails to recognize another subset at extremely high risk for ASCVD events, the very elderly.

Finally, the choice of incremental cost-effectiveness ratio threshold varied between the 2 studies. In their base cases, Kazi et al. selected $100,000 per quality-adjusted life year (QALY), whereas Fonarow et al. chose $150 000 per QALY. Though the merits of one number vs another are debatable, Kazi et al. has acknowledged that in first-world countries, an incremental cost-effectiveness ratio threshold of $150 000 per QALY can be appropriate. The higher the incremental cost-effectiveness ratio, the easier it is for a drug to have value. Thus, the choice of incremental cost-effectiveness ratio is not inconsequential. Fonarow and colleagues ran several scenario analyses utilizing different incremental cost-effectiveness ratio thresholds. They also did this with other variables. By doing so, their analysis helps better inform clinicians about the nuances inherent in medical practice. When caring for patients, clinicians use population data as a guide, yet understand that each patient is unique. The multiple scenarios presented by Fonarow et al. help illustrate the importance of considering each patient in his or her own light. Their models promote more of a personalized or precision approach to patient.

9 | PRICE TO ACHIEVE COST EFFECTIVENESS

The Kazi et al. model concluded that an annual drug price of $4215 would be needed to achieve cost-effectiveness at a threshold of $100 000/QALY. Fonarow et al. concluded that an annual net drug price of $9669 would be required to reach cost-effectiveness at a $150 000/QALY threshold. As the current list price for the PCSK9 mab is approximately $14 500, it would appear that Fonarow et al. believes evolocumab is priced too high. A careful read of their article will reveal, however, that they have already reached that benchmark. The exact price paid by pharmacy benefit managers is not publicly disclosed. Assuming an average 29% rebate cited (PCSK9 mab rebates may be higher), the drug price would be around $10 000, but if it is closer to 50%, evolocumab would be very well-priced. Additionally, though some may argue that the Canadian cost of CV events differs from that of the United States and therefore should not be used as a comparator, in Canada, the list price is ~$7000 Canadian dollars, thus not much different from their model's calculated threshold.

In summary, using different inputs and assumptions, the 2 articles arrived at very different conclusions. This illustrates how these models are heavily influenced by the assumptions that go into the models, and the Kazi et al. model has many questionable assumptions. Hence, we cannot rely on these as a final and absolute assessment of value.

10 | CONCLUSION

Over the past 30 years, great strides have been made in managing ASCVD. Perhaps most consequential has been the confirmation that LDL-C causes ASCVD. We now have 4 classes of drugs that reduce LDL-C with large randomized trials demonstrating a reduction in ASCVD risk, reaffirming the central importance of lowering LDL-C. Two years ago, the PCSK9 mabs alirocumab and evolocumab were FDA approved for specific indications with their very potent LDL-C lowering, and most recently 1 agent has been approved for reduction of CV events. Unfortunately, their uptake has been slow, and a key reason for this has been the unprecedented pushback from payers and the pharmacy benefit managers (PBMs). (A recent pushback on PBMs has been made by the proposed Berkshire Hathaway/Amazon/J.P. Morgan consortium, but it is much too early to understand what generalizable impact this may have). The ICER group has played a significant role in fostering this challenge, asserting that these medications are not valuable enough at their current price. Modeling the valuation of medications is an imperfect science, one based on assumptions that can vary widely, as seen in the large differences between the 2 recent publications from Kazi et al. and Fonarow et al..

In the end, we must return to clinical medicine, wherein we need to examine a drug's clinical benefit for an individual patient. The newer, more costly therapies should be targeted to those who will benefit most, and only after other less expensive therapies have failed to meet risk-reduction goals. Rather than using models to block access for all patients, payers should work jointly with clinicians, who can identify those patients who will benefit most. In so doing, we will assure the

most cost-effective use of this important new class of drugs, and others that will surely follow, to help reduce the risk from CV disease.

Conflicts of interest

Seth J. Baum, MD, FACC, research/consulting/scientific advisory boards: Amgen, Regeneron/Sanofi, Esperion, Madrigal, Gemphire, Akcea, Merck, AstraZeneca, Boehringer-Ingelheim, Lilly; speaking: Amgen, BI/Lilly. Christopher P. Cannon, MD, FACC, research grants from: Amgen, Arisaph, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Takeda; consulting fees from Alnylam, Amgen, Amarin, Arisaph, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Kowa, Lipimedix, Merck, Pfizer, Regeneron, Sanofi, and Takeda.

ORCID

Seth J. Baum http://orcid.org/0000-0001-9045-6607

REFERENCES

1. Buja LM. Nikolai N. Anitschkow and the lipid hypothesis of atherosclerosis. *Cardiovasc Pathol*. 2014 May–Jun;23(3):183–184. https://doi.org/10.1016/j.carpath.2013.12.004. Epub January 3, 2014.
2. Robert E Olson. Discovery of the lipoproteins, their role in fat transport and their significance as risk factors. *J Nutr*. February 1, 1998; 128(2):439S–443S. https://doi.org/10.1093/jn/128.2.439S.
3. Müller C. Nutrition classics. Archives of Internal Medicine, Volume 64, October 1939: Angina pectoris in hereditary xanthomatosis. *Nutr Rev*. 1987 April;45(4):113–115.
4. Richard J Havel. Introduction: John Gofman and the early years at the Donner Laboratory. *J Clin Lipidol*. 2007 May;1(2):100–103. https://doi.org/10.1016/j.jacl.2007.03.003.
5. Endo A. A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86:484–493.
6. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
7. Brown MS, Goldstein JL. Plasma lipoproteins: teaching old dogmas new tricks. *Nature*. November 12–18, 1987;330(6144):113–114.
8. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
9. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S1–S45.
10. Jansen H, Samani NJ, Schunkert H. Mendelian randomization studies in coronary artery disease. *Eur Heart J*. 2014;35:1917–1924.
11. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472.
12. Abifadel M, Rabès JP, Devillers M, et al. Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Hum Mutat*. 2009;30:520–529.
13. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34: 154–156.
14. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.
15. Zhang DW, Lagace TA, Garuti R, et al. Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation. *J Biol Chem*. 2007;282:18602–18612.
16. Piper DE, Jackson S, Liu Q, et al. The crystal structure of PCSK9: a regulator of plasma LDL cholesterol. *Structure*. 2007;15:545–552.
17. Cunningham D, Danley DE, Geoghegan KF, et al. Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia. *Nat Struct Mol Biol*. 2007;14:413–419.
18. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:16:1489–1499.
19. Kastelein JJ, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hyper- cholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. *Cardiovasc Drugs Ther*. 2014;28:281–289.
20. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal anti- body, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord*. 2014; 14:121.
21. Giugliano RP, Desai NR, Kohli P, et al; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380:2007–2017.
22. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126:2408–2417.
23. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370: 1809–1819.
24. Raal FJ, Honarpour N, Blom DJ. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015; 385,341–350.
25. PCSK9 inhibitors: payer dynamics. Symphony Health Solutions website. https://symphonyhealth.com/wp-content/uploads/2017/03/-PCSK9-Inhibitors-Payer-Dynamics-Feb-2017.pdf. Accessed November 2017.
26. Baum SJ, Chen CC, Rane PB, et al. Characteristics of patients approved and denied access in PCSK9i therapy by payers. Paper presented at: 66th Scientific Session of the American College of Cardiology; Washington, DC; March 17–19, 2017. Abstract 1258-435.
27. Knowles JW, Howard WB, Karayan L, et al. Access to non-statin lipid-lowering therapies in patients at high risk of atherosclerotic cardiovascular disease. *Circulation*. 2017;135:2204–2206.
28. Kolata G. Study shows promise for expensive cholesterol drugs, but they are still hard to obtain. *New York Times*. November 15, 2016. https://www.nytimes.com/2016/11/16/health/cholesterol-drugs-pcsk9-inhibitors.html? _r=0. Accessed March 15, 2017.
29. Berkrot B. Amgen cholesterol drug reduces artery-clogging plaque in study. Reuters website. http://www.reuters.com/article/us-hearta mgen- cholesterol-idUSKBN13A27Q. Published November 15, 2016. Accessed March 15, 2017.
30. Chen C, Cortez M. Amgen's Repatha unclogs arteries in good sign for future sales. https://www.bloomberg.com/news/articles/2016-11-15/amgen-s-repatha-unclogs-arteries-in-good-sign-for-future-sales. Published November 15, 2016. Accessed March 15, 2017.
31. Reddy S. A cholesterol drug tug-of-war. Wall Street Journal. June 20, 2017. http://online.wsj.com/public/resources/documents/print/WSJ_-A011-20170620.pdf. Accessed September 21, 2017.

32. Baum SJ, Toth PP, Underberg JA, et al. PCSK9 inhibitor access barriers—issues and recommendations: Improving the access process for patients, clinicians and payers. *Clin Cardiol*. 2017;40:243–254.
33. 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;376:1713–1722.
34. Giugliano RP, Mach F, Zavitz K, et al; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377:633–643.
35. Institute for Clinical and Economic Review. https://icer-review.org. Accessed November 2017.
36. Institute for Clinical and Economic Review. PCSK9 inhibitors: new evidence update. https://icer-review.org/material/pcks9-inhibitors-neu. Accessed September 21, 2017.
37. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
38. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010;13(5):509–518.
39. World Health Organization, Policy and practice: cost effectiveness thresholds pros and cons. http://www.who.int/bulletin/volumes/94/12/15-164418/en/. Accessed September 21, 2017.
40. Heron M, Anderson RN. Changes in the leading cause of death: recent patterns in heart disease and cancer mortality. *NCHS Data Brief*. 2016;(254):1–8.
41. HPS3/TIMI55–REVEAL Collaborative Group; Bowman L, Hopewell JC, Chen F, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377:1217–1227.
42. 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;318:748–750.
43. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health*. 1987;77:1417–1426.
44. Fonarow GC, Keech AC, Pedersen TR, et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2:1069–1078.
45. 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;39:313–320.
46. Toth PP, Danese M, Villa G, et al. Estimated burden of cardiovascular disease and value-based price range for evolocumab in a high risk, secondary-prevention population in the US payer context. *J Med Econ*. 2017;20:555–564.
47. Carroll C, Tappenden P, Rafia R, et al. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: an evidence review group perspective of a NICE single technology appraisal. *Pharmacoeconomics*. 2017;35:537–547.
48. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010;13:509–518.

How to cite this article: Baum SJ, Cannon CP. PCSK9 inhibitor valuation: A science-based review of the two recent models. *Clin Cardiol*. 2018;41:544–550. https://doi.org/10.1002/clc.22924