

Just Price for PCSK9 Inhibitors: No less, No More

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PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitor scientific translation from bench to bedside over the past decade has been rightfully highlighted as one of the top success stories in cardiovascular disease (CVD) management in recent years.¹ Despite this newer therapeutic class undeniably resulting in proven improvement in CVD outcomes, its widespread adoption has faced an uphill battle in recent years. For example, leveraging large national insurance data sets, recent studies have reminded us that approximately half of those prescribed eventually get preapproved. For both patients and physicians, these barriers are disheartening.^{2,3} What is the rationale behind the existing rigid preauthorization process and such high rejection rates? According to many, the reason is clear: simply put, these are relatively expensive for a drug with such a potentially large market. This is the “elephant in the room.”⁴

In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, although the 2% absolute and 15% relative CVD risk reduction over a 2.2-year period is widely celebrated, at the same time, we need to acknowledge that these benefits are not miraculous.⁵ The gains on top of standard of care depend on the eye of the beholder, because it appears substantial to some and modest to others. For those in the business of allocating healthcare resources, on the basis of back of the envelope crude estimates, even assuming half of current suggested prices, a \$700 000 price tag to prevent one cardiovascular event is a daunting proposition.

In the past, our cardiovascular community, unlike our peers in oncology, has largely been immune to the dogmatic conversations of considering cost in our management

decisions. However, now in 2018, in the midst of (1) proven benefit as well as high price tags of PCSK9 inhibitors, (2) genuine expectations of fulfilling our obligations toward the deserving patients' rightful needs, (3) increasing awareness of financial toxicity on families from out-of-pocket costs as a real adverse effect of our medical decisions, and (4) being reminded of opportunity cost where a higher yield can be realized by investing in higher-value health care, there is no more hiding for us.

Rightfully so, the question of how we relate PCSK9 inhibitors' price to worth remains a highly contentious issue. Although there is no one right way to reach this conclusion, many among us concur that like everything else in life related to financial decisions, one needs to consider incremental costs (spent versus saved) for some level of benefit. These conversations can get even more convoluted, especially without clear insights on real-world need assessment, and to put it more crudely, what should we expect to pay and what are we getting back in return?

The efforts by Ko and colleagues in this issue of the *Journal of the American Heart Association (JAHA)* are admirable for providing thoughtful perspectives by leveraging real-world data on potential therapeutic eligibility in the entire Ontario province of Canada and its subsequent cost/benefit implications.⁶ Applying the “what-if” principle, the authors suggest that, based on the FOURIER trial criteria, nearly 1 in 2 patients with established CVD in Ontario would be eligible for PCSK9 inhibitors. Implying the cardiovascular risk reduction observed in the FOURIER trial, the authors estimated recommended PCSK9 inhibitors could deter >1000 primary cardiovascular events in the next 3 years, with a potential downstream costs savings of ≈\$43.9 million. However, these benefits come with a hefty price tag. Even with the annual cost in Canada being nearly half of that in the United States (\$8000 versus \$14 000), to all these eligible candidates, cost will be ≈\$1.5 billion Canadian dollars.⁶ In short, to realize \$1 in savings, the provision insurance health system in Ontario needs to invest \$34 dollars in a 3-year time frame.

The findings of the current study raise several points worthy of discussion. First, the current study's modeling assumptions point to a situation in which PCSK9 inhibitors are allotted indiscriminately. In the real world, their use will generally be contingent on a graded escalation of therapy on

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the basis of clinical sensibility. In this report, with 1 in 5 of these patients not receiving a statin, less than half of those prescribed statins were on a high-intensity dose. It has been suggested that the overall health system impact will be significantly less with less costly escalation of other lipid-lowering medications (eg, high-intensity statins and ezetimibe); as suggested in existing clinical guidelines, this may reduce the number of eligible patients by half.⁷

Second, despite extensive evidence with class IA recommendations for proven mortality benefit, oral dosing, low cost, an excellent safety profile, and no major barriers to access, statin adoption among individuals with established CVD, a group that derives the greatest benefit from statins, remains suboptimal and a major challenge. According to contemporary data, ≈ 6 in 10 patients with CVD report statin use, with high-intensity statins used by less than one third of all statin users.⁸ On the basis of these insights, it is unlikely that even with liberal assumptions we will ever observe close to 50% PCSK9 inhibitor adoption among eligible candidates in real-world situations.

I believe that on the basis of these 2 considerations, the budget impact is extremely unlikely to be more than one fourth of the suggested \$500 million/year. Irrespective, even with this conservative assumption of PCSK9 inhibitor uptake in 12% of patients with atherosclerotic CVD in the province of Ontario, with a price tag of \$125 million dollars, equivalent to a staggering 1% of the entire province medication spending in 2015 (\$12.4 billion), this is a substantial short-term budgetary concern.

Third, the authors assumed only a narrow time frame of 3 years while considering the benefits and budget implication. A more prolonged frame, such as extending to 5 to 10 years, may significantly increase the cost impact; however, there is a possibility of narrowing the significant high cost/benefit ratio. Furthermore, viewing costs within the narrow constraints of healthcare outcomes or cost savings obtained per dollar spent is a simplistic approach without accounting for societal and long-term considerations. One widely used alternate method is a cost-effective analysis to ball park incremental costs per quality-adjusted life years gained with a particular treatment over the population's lifetime.

In this regard, last year was pretty hot for PCSK9 inhibitors. Three back-to-back investigations published last summer determined that at current prices, widespread adoption on the basis of FOURIER trial eligibility will not be cost effective from the broader societal and private insurance perspective.^{9–11} The sobering reminder of the accompanying editorial, “the path forward currently requires only 1 intervention: lower the cost,”¹² is not much different from the message conveyed by the current study by Ko et al.⁶

One thing is clear, irrespective of how we slice or dice the cost/benefit pie, we are likely going to reach the same

conclusions: current PCSK9 inhibitor prices are impractical. What are our options moving forward? In my humble opinion, rather than continue to bemoan the issue of affordability, we need a conversation about how we can derive value for our main stakeholders, namely patients and health systems, while being fair to the industry and encouraging innovation, rather than just cost containment, which likely will occur in due course.

As we eagerly await market and policy solutions, who is going to lead the charge for defining value for these agents with health care? I humbly query the potential role of physician organizations, such as the American Heart Association, the American College of Cardiology, and the American Society of Preventive Cardiology? Although we are all immensely grateful for their much-needed advocacy to enhance critical patient access to these therapies, I believe these physician-led organizations have shied away from leading the conversation on the “just price” of PCSK9 inhibitors.

One can argue that our medical organizations currently do not have sufficient policy influence to alter the way access or investment decisions for these novel therapeutics are made. However, I believe that these challenges provide a tremendous opportunity for our medical societies to take the leadership, act as a neutral third party, and convene and lead a realistic conversation about pharmaceutical pricing among the wide range of stakeholders.

A major task would be to develop a transparent and replicable method reflecting societal value on how we want to spend on our healthcare resources. Whether cost-benefit analysis, as shown in the current study, as well as prior cost-effective analysis framework are adopted, it is important to realize the tradeoffs on the opportunity cost will play a pivotal role in negotiations. A single-minded and uncompromising focus on these methods to inform reimbursement decisions will certainly encounter a hostile reception. The goal of these efforts should center around the notion that payments need to be fair. Rather than making our own assumptions on value, we need the public to drive the dialogue about the economic value on preventing CVD while balancing the deliberations on opportunity costs at the same time. If we truly believe that our joint interest centers around patient-centric care, then let us allow their input and understanding to drive consensus on these critical issues. This will also counter the prevalent resistance by industry towards cost-effectiveness estimates related to these emerging therapeutic interventions.

Furthermore, our management guidelines need to broaden our consideration beyond the narrow focus on efficacy and effectiveness and perhaps also have a broader societal perspective balancing costs and benefits. It is critical that these agencies realize that if we continue to ignore these budgetary impacts, access will unfortunately worsen for many deserving patients, especially with many other expensive treatments on the horizon.

It is time these medical organizations place a greater emphasis on value, and overcome existing reluctance to recommend target prices that matches magnitude of benefit derived from these interventions. I sincerely hope the next guidelines, rather than developing bland treatment recommendations that are isolated from ground realities, will be mindful of the value proposition of these therapies. For example, until better pricing is achieved, sensible adoption in a group at much higher risk that can subsequently derive a higher absolute benefit will provide a better return of investment in CVD risk management with these costly interventions. On the basis of a recent subanalysis from the FOURIER trial focusing on PCSK9 inhibitors among the highest-risk groups, such as those with recent acute coronary syndrome, those with symptomatic peripheral arterial disease, or those who are post-myocardial infarction with at least 1 high-risk feature, may result in a bearable budgetary burden on health systems.^{1,13}

In summary, if we truly aspire to create a sustainable health system, there must be room for those who raise uncomfortable questions about what will we get for what we pay? For this, Ko et al deserve our deepest appreciation for providing insights on existing gaps between the price and value derived from PCSK9 inhibitors.⁶ If these studies can successfully facilitate conversations among stakeholders to agree on the just price for 1-2% absolute CVD risk reduction, no less, no more, I am confident that the cost of PCSK9 inhibitors will no longer be the top story in 2019.

Disclosures

Advisory Board member for Regeneron.

References

1. Blumenthal RS, Nasir K, Martin SS. Realizing value with proprotein convertase subtilisin/kexin type 9 inhibitors are we closer to finding the sweet spot? *Circulation*. 2018;138:767–769.

2. Navar AM, Taylor B, Mulder H, Fievitz E, Monda KL, Fievitz A, Maya JF, Lopez JAG, Peterson ED. Association of prior authorization and out-of-pocket costs with patient access to PCSK9 inhibitor therapy. *JAMA Cardiol*. 2017;2:1217–1225.
3. Hess GP, Natarajan P, Faridi KF, Fievitz A, Valsdottir L, Yeh RW. Proprotein convertase subtilisin/kexin type 9 inhibitor therapy: payer approvals and rejections, and patient characteristics for successful prescribing. *Circulation*. 2017;136:2210–2219.
4. Jackevicius CA. Elephant in the room: cost of proprotein convertase subtilisin/kexin type 9 inhibitors. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004425.
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
6. Ko D, Khan AM, Kotri G, Austin PC, Wijeyesundera HC, Koh M, Chu A, Jackevicius CA, Lawler P, Tu JV. Eligibility, clinical outcomes, and budget impact of PCSK9 inhibitors adoption: the CANHEART PCSK9 study. *J Am Heart Assoc*. 2018;7:e010007. DOI: 10.1161/JAHA.118.010007.
7. Virani SS, Akeroyd JM, Nambi V, Heidenreich PA, Morris PB, Nasir K, Michose ED, Bittner VA, Petersen LA, Ballantyne CM. Estimation of eligibility for PCSK9 inhibitors and associated costs based on the FOURIER trial: insights from the Department of Veterans Affairs. *Circulation*. 2017;135:2572–2574.
8. Salami JA, Warraich H, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, Virani SS, Blankstein R, Khera A, Blaha MJ, Blumenthal RS, Lloyd-Jones D, Nasir K. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol*. 2017;2:56–65.
9. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. *JAMA*. 2017;318:748–750.
10. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, van Hout B, Villa G, Qian Y, Somaratne R, Sabatine MS. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2:1069–1078.
11. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated cost-effectiveness assessments of PCSK9 inhibitors from the perspectives of the health system and private payers: insights derived from the FOURIER trial. *JAMA Cardiol*. 2017;2:1369–1374.
12. Bonow RO, Harrington RA, Yancy CW. Cost-effectiveness of PCSK9 inhibitors: proof in the modeling. *JAMA Cardiol*. 2017;2:1298–1299.
13. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kavevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozlu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease. *Circulation*. 2018;137:338–350.

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