

Elephant in the Room

Cost of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

See Article by Doshi et al

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In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Doshi et al¹ raise the issue of whether the prior authorization (PA) program requirements are particularly excessive for the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) drug class. The authors report on the burden of the PA process for PCSK9i using a unique proprietary database that includes detailed information on PA requirements for 3872 public and private insurance plans. They found that there were greater PA requirements for PCSK9i than for other brand name cardiometabolic drugs used as comparators (ezetimibe, liraglutide). Although it is often expected that government bureaucracy exceeds that in the private sector, this study found that in contrast, it was the non-Medicare plans that had 3× to 11× more fields required for PA form completion than comparator drugs. In particular, health insurance exchange plans established by the Affordable Care Act had the highest burden of criteria to fulfill the PA submission process. A high-burden PA process may be related to high rates of rejection for submitted PCSK9i prescriptions because other studies have reported that commercial payers also had the lowest PA approval rates.^{2,3}

Why are we examining the intricate details of the PCSK9i PA process and high rejection rates? The reason is clear—simply put, these drugs are expensive and at a level not previously seen for a drug with this potentially large of a market. This is the elephant in the room. Cost-effectiveness analyses of PCSK9i have not been favorable. Multiple studies using a variety of sensitivity analyses and approaches all suggest that annual PCSK9i costs must be reduced by 60% to 70%, down to \$4000 to \$5000 in order reach currently acceptable societal thresholds for cost-effectiveness.⁴⁻⁶ Therefore, the current price does not make economic sense. When more agents of this class are on the market, there will be natural cost reductions because of market competition, however, not until 5 to 6 competitors are on the market in the distant future, can we expect this solution to materialize. An alternative solution to lower prices could involve government-imposed policies, such as, competitive bidding, reference-based pricing, or having a governmental agency that regulates pharmaceutical prices akin to the Patented Medicines Prices Review Board in Canada. Or right now, pharmaceutical companies can take the initiative to address the price in order move forward with improving access to PCSK9i.

Meanwhile, in response to excessive prices, insurance companies have felt compelled to act. Through their associated pharmacy benefits managers, they have implemented PA programs, the frequently used mechanisms to control costs for the insurance plan. By using the much-maligned PA programs, payers do create an intentional burden for new and expensive therapies for cost containment purposes. This then creates an obvious clash between the competing business interests of payers who are controlling costs and the pharmaceutical industry who

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seek the financial benefits from the sale and use of their medication—with patients and providers often caught in the middle.

The value of a drug is based on the balance of its benefits and harms, with one of the harms being costs (especially from a societal perspective). We might question whether it is right for there to be more restrictions based on the cost of a drug. It seems unfair. If PCSK9i cost \$1 per day, everyone eligible would likely be approved. However, we cannot expect most payers to simply absorb these excess costs because their priority is to financially manage their health plan for their members, and possibly, their shareholders. If we assume a payer has a fixed budget, to allocate large expenditures for PCSK9i, then other potential benefits in the health plan become displaced and not covered, otherwise known as opportunity cost. If the budget is not fixed, the money to fund the new, expensive therapy has to come from somewhere else to cover the additional costs—in a commercial plan, it may come from increased employer, or more likely, employee premiums, and in a government program, from increased taxes. None of these solutions is particularly palatable. To complicate matters, the high cost of PCSK9i has also raised awareness of the lack of transparency of the drug pricing process, variation in reimbursement practices, and the role of pharmacy benefits managers in the pricing process. This lack of transparency adds to the pre-existing frustration of patients and prescribers about the economic and access barriers to pharmaceutical benefits through their insurance plans.

With the current PCSK9i cost deemed excessive in relation to the demonstrated clinical outcomes benefits, we need a practical, near-term approach to better match the level of potential benefit to the high cost. Event rates drive value, with those at the highest risk deriving the most value. Because there is heterogeneity of risk for recurrent cardiovascular disease events among secondary prevention patients who might be eligible for PCSK9i, an alternative to reducing the drug cost is to increase value by strategically using the drugs in those most likely to benefit. Recent FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial subgroup analyses of those with a history of recurrent myocardial infarction, recent myocardial infarction, multivessel disease, and peripheral artery disease may offer such a solution for tailoring therapy to these groups at highest risk of adverse cardiovascular events.⁷ Ideally, creation of a risk score would aid prescribers in targeting and individualizing therapy choices to maximize value.

Although PA programs cause frustration for prescribers, we must consider that payers and pharmacy benefits managers may be justified in requiring documentation of the appropriate use of lower cost, yet effective therapies that would provide the most value, given that

prescribers do not always use new therapies wisely. In evaluations of current populations that might be eligible for PCSK9i, more than half of eligible patients were not receiving statin therapy, which clearly represents a deficiency in optimal risk reduction management.^{2,3} Oftentimes, excitement surrounding the uptake of new drugs drives potential overuse, even in the absence of outcomes evidence, with subsequent difficulty with reining in prescribing in all but the strictest of formularies.⁸ Abandonment of existing effective therapies may also ensue, and this seems to be the case with the excitement surrounding PCSK9i. High observed PCSK9i rejection rates may, in part, be driven by patients who do not meet currently accepted indications, including lack of statin use.² Given the suboptimal current therapy for many patients, it is reasonable to expect that payers would aim to maximize the use of less costly statins and ezetimibe using PA criteria. Therefore, paperwork, while tedious, seems to be necessary to evaluate the appropriateness of a patient's lipid-lowering therapy history. However, when the PA process requires the same high level of effort for those truly high-risk patients who are most likely to benefit from therapy as it does for the more marginal patients, the PA process can become a rather blunt and inefficient cost containment instrument for all parties involved.

Although less exciting than using a novel therapy, it is essential to return to first principles of maximizing the use of effective oral lipid-lowering agents before escalating to new, expensive therapies with less evidence. It has been estimated that if current oral lipid-lowering agents are used appropriately, that only 10% to 15% of atherosclerotic cardiovascular disease patients would actually need PCSK9i therapy.^{9,10} Large numbers of patients with cardiovascular disease can be managed without the need to resort to PCSK9i therapy. We must remind ourselves that statins are first line cardiovascular disease risk reduction drugs that have a long history of evidence showing benefit in reducing both cardiovascular events and mortality in those with ASCVD and are well tolerated in blinded clinical trials, with the added benefit of nonlipid-lowering anti-inflammatory effects. Although some may challenge that statins are well tolerated, blinded randomized control trials have documented statin tolerability while unblinded comparisons have revealed the importance of the placebo effect that may interfere with effective statin therapy through inducing nonadherence.¹¹ Studies have shown that most patients who are intolerant of one statin can often be successfully treated with an alternative statin.¹² Given this, it is also reasonable for payers to expect patients to try multiple statins and expect related documentation to ensure patients are receiving the first line fundamental therapy before considering add-on with PCSK9i.

Clinicians and payers also have a responsibility to be cautious with new drugs because they are most likely

to have unknown adverse reactions within the first few years after launch, as well as after expanded use in populations beyond those included in the original clinical trials.¹³ At the present time, we lack evidence that PCSK9is are life saving, and the magnitude of reduction in cardiovascular disease events has been considered somewhat underwhelming and out of proportion to that expected based on their substantial low-density lipoprotein-lowering effect. Furthermore, we have limited evidence on the side effects and non-low-density lipoprotein-lowering effects of the PCSK9i class. Although they seem to be well tolerated overall, including in FOURIER, the neuropsychiatric side effects remain a potential concern and warrant ongoing monitoring. We must be cognizant that we only have 1 clinical outcomes study with a PCSK9i with only a median of 2.2 years of follow-up, and as with any science, we need to have replication of results before gaining a strong class IA recommendation for use. It may be prudent to have PA criteria that closely mimic the outcomes trial to achieve the expected trial results. However, there is every reason to think that practical, streamlined, standardized paperwork that ensures optimal use of low-cost alternatives and targets use in suitable trial-like populations is entirely feasible for payers to implement to ease prescriber burden while also ensuring appropriate use.

It is because of excessive drug prices that are far removed from realistic cost-effectiveness norms that we find ourselves in this situation of discussing excessive administrative PA requirements as suggested by Doshi et al¹ and the difficult therapeutic decisions these requirements imply. This challenging situation gives us the opportunity to redouble our efforts on improving our prescribing of established effective oral lipid-lowering therapies while at the same time, advocating for an evidence-based, yet practical PA process, greater transparency in the pricing of pharmaceuticals, as well as incentives to explore drug policy that aims to improve access to effective therapies that are also affordable.

DISCLOSURES

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FOOTNOTES

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