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The Price of Progress: Cost, Access, and Adoption of Novel Cardiovascular Drugs in Clinical Practice

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Abstract

Purpose of Review The launch of new effective and safe cardiovascular drugs has produced large gains in health outcomes for several cardiovascular conditions. But this innovation comes at the cost of rapidly increasing pharmaceutical spending and high out-of-pocket costs.

Recent Findings In the USA, manufacturers are able to set prices according to what the market will bear rather than value to patients or society, with a complicated system of discounts and rebates obscuring the final price borne by payors. Some of these costs are passed on to patients in the form of co-payments or co-insurance, making these effective but high-cost medications unaffordable for many patients. Orphan drugs developed to treat rare diseases—for which manufactures are presented substantial financial and regulatory benefits—are particularly problematic, as they typically enter the market at very high prices compared with drugs for other indications.

Summary Systematic cost-effectiveness analyses from the healthcare sector or societal perspectives can help identify the value-based price of a medication at market entry as well as later in the lifecycle of the drug when more data on effectiveness and safety becomes available. Despite bipartisan support, legislative progress on drug pricing has been slow. Clinicians should know the cost of the drugs they prescribe frequently, use generics where feasible, and regularly discuss out-of-pocket costs with patients to pre-empt cost-related non-adherence.

Keywords Cost-effectiveness · Drug pricing · Out-of-pocket costs · Orphan drugs · Cardiovascular · Adherence

Introduction

Novel cardiovascular therapies have the potential to improve long-term outcomes in patients with cardiovascular disease (CVD), including the most severe and rare forms of CVD that previously inevitably resulted in poor health outcomes. Patients with conditions like familial hypercholesterolemia or transthyretin cardiomyopathy now have effective and safe therapeutic options [1, 2]. Even for conditions like heart failure with reduced ejection fraction, where numerous effective therapies were already available, the availability of new drugs is promising improved quality of life and prolonged survival [3]. Yet this progress has come at a price. The cost of pharmaceuticals in the USA is three times that in the UK, six times that in Brazil, and sixteen times that in India (for identical drugs) [4•, 5]. Moreover, US pharmaceutical costs are rising faster than the overall increase in healthcare spending, having increased by 33% from 2014 to 2020 [6, 7]. These high costs are often passed on to patients, many of who are then unable to afford the medications they could benefit from. In this review, we address key questions related to the economics of cardiovascular therapies in the USA. We discuss why the high cost of cardiovascular drugs is a pressing public health concern, examine key drivers of high drug costs in the USA, and propose strategies that clinicians can

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use in practice to ensure that new cardiovascular drugs reach the patients most likely to benefit from them.

Why Do the High Prices of CVD Drugs Matter?

The US response to the COVID-19 pandemic has clearly demonstrated that, even in a high-income country like the USA, healthcare resources are indeed scarce and worthy of good stewardship. From a societal perspective, high levels of pharmaceutical spending have an opportunity cost—that money cannot be spent elsewhere in the healthcare system (e.g., for screening or prevention) or in the broader economy (e.g., in public schools or on national parks). From the patients' perspective, an increasing proportion of these costs are being passed on to patients as co-payments (a fixed dollar value per prescription, typically on a sliding-scale based on drug tier) or co-insurance (as a proportion of the list price of the drug). Annual co-insurance for some drugs can reach several thousand dollars, putting effective new drugs out of the reach of many *insured* individuals [8•]. Moreover, these out-of-pocket costs may vary substantially from month-to-month depending on the structure of the benefit plan, undermining initiation and adherence. In 2017, high drug costs led to non-adherence in 11.4% of US adults [9]. In turn, cost-related non-adherence to CVD medications leads to worse health outcomes, including more frequent cardiovascular hospitalizations and, possibly, increased mortality. [10, 11•].

Out-of-pocket costs may also adversely affect health disparities. Minorities with lower income spend a greater percentage of this already limited income on healthcare [12]. Minority populations are also more likely to be uninsured or underinsured (insurance with high premiums and deductibles which limit healthcare access), and low-income groups who are uninsured or have unstable insurance have higher out-of-pocket costs [12, 13]. High out-of-pocket costs, and the resulting cost-related non-adherence, reduce uptake of novel therapies in these populations that are, on average, at higher risk for lifetime adverse cardiovascular events than high-income populations. High out-of-pocket costs, by disproportionately affecting individuals at high risk, have the potential to exacerbate disparities [14].

The costs borne by the payor are also passed back to the public as taxes (in the case of public insurance) or higher premiums (in case of private insurance). Payors respond to this increased spending with increasing patient cost-sharing and/or instituting onerous prior authorization requirements [15•]. As discussed below, many of these concerns are amplified in the case of orphan drugs developed to treat rare diseases, where, despite substantial financial and regulatory incentives, drugs frequently enter the market at a price of hundreds of thousands of dollars [16•, 17•]. As a result, effective new therapies that could dramatically improve CVD outcomes remain underused.

What Is Driving High Prescription Drug Prices in the USA?

The traditional case for high US drug prices is that they encourage pharmaceutical innovation. Research and development costs have skyrocketed, the argument goes, and high drug prices encourage the large high-risk investments needed to support the drug pipeline (the "innovation-access trade-off") [18]. While the cost of pharmaceutical innovation is obscured by weak reporting requirements, it is true that novel drugs for common CVD conditions require large multi-country trials with long follow-up, driving up development costs. However, only 10–20% of revenue of life sciences companies is invested in research and development, with much of the earliest, highest-risk research supported by government funding [4•]. The high US drug prices are the result of a system that allows pharmaceutical companies to price drugs according to what the market will bear—rather than any systematic evaluation based on the value the therapy will generate for society [19]. This is aggravated by year-on-year price unjustified increases, so that the price of a drug mid-way or later in its lifecycle may be substantially higher than the launch price [20]. It is unsurprising, then, that countries with national health systems that collectively negotiate drug prices based on a systematic health technology assessment are able to achieve substantially lower prices than in the USA. For instance, at the time of launch, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors cost $14,350 in the USA, $6,427 in the UK, and $8,700 in Finland [21]. In fact, the National Health Service in the UK, negotiating on behalf of some 90% of the population of England and Wales, negotiated a further (undisclosed) discount in the price of PCSK9 inhibitors, so that the price in the USA was effectively three times that in the UK.

How Do We Evaluate the "Value" of a Drug?

From an economist's perspective, there are a variety of metrics for evaluation of drug pricing. One crude metric is total costs, i.e., cost per prescription × number of prescriptions per year.

This reflects the total change in pharmaceutical expenditures, which varies with the uptake of the drug. But a more nuanced evaluation of value would weigh the costs against projected benefits, in a systematic cost-effectiveness analysis (CEA). Rarely, an intervention lowers costs and improves health outcomes; i.e., this intervention is superior to the

alternative being evaluated [22]. In this case, the intervention is said to be cost-saving. An example of this would be the use of generic formulations of statins for secondary prevention of atherosclerotic CVD [23]. More often, an intervention that improves outcomes also increases total spending (from the drug itself, any additional testing during follow-up, and, for drugs that improve survival, increased healthcare costs in the incremental years of life) even after accounting for the savings resulting from averted CVD events in the future. In this case, a systematic CEA can help compare the incremental costs with improved outcomes (measured in events averted, life years gained, or quality-adjusted life years or QALYs gained). QALYs incorporate quality of life (typically ranging from 0 in the case of death to 1 for perfect health) multiplied by time spent in each health state [22]. The costs and benefits can be combined into a single incremental cost-effectiveness ratio (ICER) which, as the name suggests, is the difference in cost of a new intervention with an old intervention divided by the difference in outcomes of the new intervention with the old intervention. The ICER is then compared with a cost-effectiveness threshold; an ICER below said threshold is deemed to be cost-effective (Fig. 1) [24]. Recent empiric work suggests that the implicit threshold for the USA is between $100,000 and $150,000 per QALY [25•].

For instance, at their initial launch price of $14,350, PCSK9 inhibitors (when added to ezetimibe and maximally tolerated statin therapy) were projected to have an ICER of $414,000 per QALY in patients with established atherosclerotic ASCVD and $503,000 per QALY in patients with heterozygous familial hypercholesterolemia, far exceeding the implicit cost-effectiveness threshold, suggesting a need for a 70% price reduction to meet the cost-effectiveness threshold of $100,000 per QALY gained [21, 26, 27].

Distinct from cost-effectiveness (which accounts for all costs, regardless of who pays for them) is the concept of affordability. Affordability varies by stakeholder—and compares the cost with what the stakeholder is able to pay. For instance, for an integrated health system, affordability may be the budget impact of the drug, which scales up per patient costs to the entire population. A drug that is very cost-effective in the long run may be unaffordable because of the health systems constrained budget in the short run. For instance, if all eligible patients were to receive PCSK9i (at the launch price of approx. $14,350 per patient per year), the estimated budget impact would be $568 billion [21]. But affordability from the patient's perspective refers to the out-of-pocket costs that the patient is responsible for based on the benefit structure of their insurance plan. Plainly, a drug that is cost-effective may be unaffordable to a patient if the out-of-pocket costs are high. For instance, when PCSK9i were first launched, the majority of Medicare Part D insurance plans covered PCKS9 inhibitors, but out-of-pocket costs due to cost-sharing exceeded $300 per month, or approximately

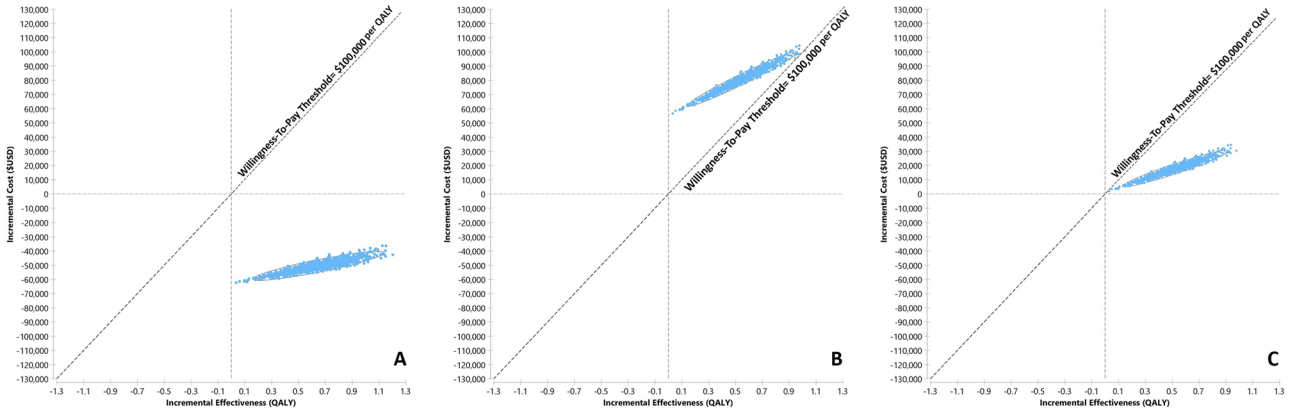

Fig. 1 Cost-effectiveness plane. The results of cost-effectiveness analyses comparing a novel therapy with the prior standard of care can be depicted on a cost-effectiveness plane. The *x*-axis represents incremental outcomes (e.g., incremental quality-adjusted life years [QALYs]) and the *y*-axis represents incremental costs when the new therapy is used compared with the standard of care. In sensitivity analyses, the exercise of estimating incremental costs and incremental QALYs is repeated by sampling each of the key input parameters from statistical distributions that represent uncertainty in these parameters. The panels below depict three hypothetical novel drugs compared with the prior standard of care. In each panel, the diagonal line represents the cost-effectiveness threshold of $100,000 per QALY gained and the ellipse depicts the 95% credible interval of the incremental cost-effectiveness ratio. In panel **A**, the new therapy improves health outcomes and lower costs, i.e., is cost saving. In this setting, the new therapy is considered the dominant or superior option and should be adopted. In panel **B**, the new therapy improves health outcomes but also increases costs, such that the incremental cost per QALY gained exceeds the cost-effectiveness threshold of $100,000 per QALY gained. Thus, the new therapy would not be considered cost-effective relative to the comparator. In panel **C**, the new therapy improves health outcomes and increases costs, but the incremental cost per QALY gained is less than the cost-effectiveness threshold of $100,000 per QALY gained, suggesting that the new therapy is likely to be cost-effective compared with the prior standard of care. In this case, the new therapy would not be considered cost-effective relative to the comparator

$5000 per year [8•]. As a result, a third of the patients who were prescribed a PCSK9 inhibitor (and received payor approval for said prescription) abandoned their prescriptions at the pharmacy during the initial years [28].

What Are Orphan Drugs and Why Are They So Expensive?

The Orphan Drug Act provides pharmaceutical companies substantial financial and regulatory incentives to develop drugs for rare diseases, i.e., conditions that affect fewer than 200,000 patients [29]. These incentives have worked; 30 of 67 drugs approved by the US Food and Drug Administration in 2015–2016 were orphan drugs [29]. Orphan drugs are now increasingly being targeted to rare cardiovascular conditions; this pathway led to the expedited approval of tafamidis for the treatment of transthyretin cardiomyopathy. However, once approved, orphan drugs often take advantage of the lack of competition and prolonged market exclusivity to enter the market at very high prices [9]. For instance, tafamidis had a list price of $225,000 at the time of market entry, making it the most expensive cardiovascular medication to enter the market until then [30]. The price far exceeds the value of health benefits, with a projected ICER of $880,000/QALY compared with usual care [16•]. A 92.5% price reduction would be necessary to meet the $100,000/QALY threshold [16•]. Orphan drugs pose several pricing challenges. Their high prices at market entry (and, frequently, high out-of-pocket costs for patients) restrict access and undermine the stated purpose of the Orphan Drug Act to expedite access to effective treatments. The lack of competition leads to substantial negotiating power for manufacturers upon approval; rebates and discounts are often small (5%) compared with other brand name drugs (20–40%) [16•, 31]. Finally, as with the case of transthyretin cardiomyopathy, the frequency of diagnosis may increase considerably after a treatment is available, so the targeted disease may not be "rare" after all [30]. Tafamidis illustrates how exorbitant pricing of orphan drugs often makes them inaccessible to the very patients who they were developed for. With the growth of precision medicine and genomics, targeted treatments for smaller groups of patients will continue to be developed. These drugs must be made affordable for the patients they are meant to treat.

How Can We Make New Cardiovascular Drugs More Accessible?

Strategies to improve access must target the numerous patient-, provider-, payor-, and health system-level barriers in our fragmented health system.

A complete review of policy interventions to improve access is beyond the scope of this review, but, briefly, new drugs would ideally be expeditiously approved, enter the market at a price commensurate with projected health and societal benefits, be prescribed to eligible patients with minimal prior authorization requirements, be available to patients at low or no out-of-pocket costs, and, upon completion of market exclusivity, be rapidly replaced by multiple high-quality generic formulations. A commonly proposed solution, i.e., to allow Medicare Part D plans to negotiate collectively with the manufacturer, would only be effective if two additional conditions are met. First, plans must know the maximum price they are willing to pay based on high-quality cost-effectiveness studies, and second, plans must have control of their formulary. For CEAs to be actionable, they must be performed by an unbiased health technology assessment organization using best-available trial and real-world data regarding safety, effectiveness, and costs, and should be updated regularly when new data become available [32•]. International reference pricing (where the US price would be based on prices in select high-income peer countries) is an alternative way to determine drug price, but such a price would be disconnected from the cost-effectiveness of the drug in the US health system. There has been bipartisan support to rein in drug prices for over a decade now, yet progress on pricing reform has been disappointing. The one recent success story that illustrates the power of CEAs has been the case of PCSK9 inhibitors. Under market pressure due to disappointingly low uptake in the first two years after market entry and following several CEAs that suggested the need for large price reductions, both the manufacturers for PCSK9i announced unprecedented 60% price reductions in 2018 [33, 34•]. This illustrated the power of CEAs in guiding value-based pricing of novel therapies.

But even as we await major policy solutions to address rising drug prices in the USA, clinicians have a key role to play in improving accessibility [35]. First, use generic formulations when available—even among insured patients, generic formulations often have substantially lower out-of-pocket costs. Second, discuss out-of-pocket costs at the time of initiating new therapies and periodically thereafter. Patients are reluctant to bring up costs with their clinicians, but appreciate it when clinicians do so [36, 37]. Because out-of-pocket costs for the same drug may vary substantially between plans and even over the course of the year, discussing them with patients on a regular basis can help pre-empt cost-related non-adherence. It also precludes clinicians from projecting our own preferences onto our patients. For instance, although direct oral anticoagulants appear to be more convenient for patients than warfarin (with fewer drug-drug and drug-food interactions and no need for regular blood draws for monitoring) and have been

shown to be cost-effective or cost-saving from the healthcare system perspective in some studies [38–40], some patients may prefer to continue to use warfarin because of substantially lower out-of-pocket costs ($48 per year for warfarin vs. $3000 per year for direct oral anticoagulants in one analysis) [41]. Third, just as clinicians increasingly recognize heterogeneity in treatment effect (i.e., that a drug may be more effective in some subgroups of patients than others), we must acknowledge heterogeneity in cost-effectiveness, so that the use of a high-cost medication may generate more value in some subgroups. For instance, adding a combination pill containing ezetimibe and bempedoic acid (a recently approved oral therapy for hyperlipidemia) to maximally tolerated statin therapy did not meet conventional cost-effectiveness thresholds in patients with established atherosclerotic cardiovascular disease (estimated ICER $186,000 per QALY gained compared with statin and generic ezetimibe) [42]. But in the subgroup of patients unable to receive statins due to severe statin-associated side effects, the ICER for the combination pill improved to $92,000 per QALY gained [42], suggesting that the drug would likely be cost-effective in this high-risk subgroup (The marked heterogeneity was because patients not receiving a statin have higher baseline low-density lipoprotein cholesterol levels, higher absolute risk of adverse events, and experience a larger reduction in cholesterol levels with bempedoic acid). Thus, being cognizant of heterogeneity in cost-effectiveness can help prioritize the use of a high-cost therapy in patients most likely to derive a large benefit. Finally, clinicians must advocate for their patients and facilitate the uptake of demonstrably cost-effective drugs. For instance, although sacubitril-valsartan was shown to be very cost-effective in patients with heart failure and reduced ejection fraction (with an ICER of $47,053 per QALY gained) [43–45], initial adoption was slow [46]. Although the low rate of adoption was partially related to highly variable out-of-pocket costs (mean of $71 per month, median $40) compared with other guideline-directed medical therapies (mean of $3 per month, median $2) for privately insured and Medicare Advantage patients, it was also a result of low prescription rates [46]. Thus, the judicious use of cost-effectiveness analyses includes both restricted use when a drug is not cost-effective, and more rapid uptake when high-quality unbiased CEAs demonstrate that a novel therapy is cost-effective.

Conclusion

While novel therapies have the potential to produce impressive improvements in health outcomes for patients with CVD, their benefits may remain unrealized if high prices limit access among patients most likely to benefit from them. In this context, well-done CEAs using best-available trial and real-world data have the potential to inform value-based pricing and uptake. The experience with PCSK9 inhibitors suggests that CEAs can help rein in drug prices and improve access. Although there is bipartisan support for major reform on drug pricing, legislative progress has been disappointing over the past decade, with orphan drugs proving particularly challenging in finding a balance between supporting innovation and ensuring access. In the meantime, clinicians have a key role to play by facilitating judicious uptake of new, high-cost therapies. Regular conversations with patients regarding out-of-pocket costs can help identify cost-related non-adherence which may be addressed by using lower-cost alternatives where available. It is incumbent upon all of us—clinicians, academics, advocates, and policy makers—to urgently address this public health issue.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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