Increasing the Adoption and Diffusion of a Novel Pharmacological Therapy That Is Both Mortality Reducing and Cost-Effective

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For novel, effective therapeutics to improve the quality of care for Americans with heart disease, rapid dissemination of clinical trials and clinical guidelines should lead to adoption and diffusion in populations that will benefit. Keeping healthcare providers knowledgeable about new therapeutic options has the potential to reduce the time between knowledge generation and helping patients. As a practical matter, however, many barriers to adoption and diffusion of new therapies exist. Overcoming some of those barriers is important for improving quality.

One such barrier is called therapeutic inertia,[1] or continuing an older clinical treatment despite less efficacy and failing to start a new medication that has proven more effective.[2] Inertia is thought to be a result of both patient and provider factors. From the patient perspective, changing medications can be confusing, especially when patients have grown accustomed to an older medication over the course of years. Often, fear exists about new adverse effect profiles and medication schedules, and a lack of understanding about relative risks and benefits results in reluctance to change therapies.[1] Providers may share some of these fears, and they may hesitate to encourage patients to try new medications in this setting. In addition, the need to taper old and titrate new medications can present a barrier to therapeutic change, particularly when compliance and follow-up plans are not clear.[1]

Other barriers, however, are more controversial and complex. For example, clinical trials may lead to approval from the Food and Drug Administration after validation in a specific population. But in broader populations, the therapy could be less effective, or even ineffective or harmful. Even when new therapies are clearly effective relative to older alternatives, cost-effectiveness and the net impact on healthcare expenditures pose difficult societal tradeoffs.

For example, costs have likely played a role in suboptimal access to novel PCSK9 (proprotein subtilisin-kexin type 9) inhibitors. PCSK9 inhibitors were approved for use in adults with persistent elevations in low-density lipoprotein therapy cholesterol, despite titration of statin therapy, and for those with familial hypercholesterolemia. Although PCSK9 inhibitors cause dramatic decreases in low-density lipoprotein cholesterol levels through a novel biological mechanism and reduce important clinical end points,[3] <1% of PCSK9-eligible patients actually receive prescriptions for the medications.[4]

This poor uptake of PCSK9 inhibitors may be related to high prices. In response to prices that initially exceeded $14 000 per year, health insurers and pharmacy benefit managers used mechanisms to reduce prescription rates, primarily via the use of prior authorizations and cost-sharing mechanisms resulting in high copayments. In that setting, in the first year of PCSK9 inhibitor availability, about half of prescriptions received approval and only about two thirds of approved prescriptions were filled because of high copayments.[5] The reasons for rejected prior authorizations could range from inadequate provider documentation to restrictive policies. Either way, these prior authorizations likely have decreased access. Similar studies have demonstrated higher rates of prescription abandonment for expensive specialty medications with higher out-of-pocket costs, particularly when they exceeded a copayment of $200/month.[6]

In 2015, the New England Comparative Effectiveness Public Advisory Panel deemed PCSK9 inhibitors clinically efficacious but not cost-effective at the introductory list price,[7] based on a decision-analytic model[8] developed by the Institute for Clinical and Economic Review. The model was updated after publication of clinical outcomes trials but did not change the determination that the prices of the medications were still too high to be cost-effective.[9,10] In July 2018, Sanofi-Regeneron decreased the price of alirocumab by about two thirds.[11] In response, the pharmacy benefit manager

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Express Scripts replaced prior authorizations for alirocumab with a simpler provider attestation of clinical need.[12] In October 2018, Amgen followed by announcing similar reductions in the price of evolocumab.[13] The 2018 guidelines on treatment of blood cholesterol explicitly consider cost-effectiveness when discussing the role of PCSK9 inhibitors.[14] Given the demonstrable efficacy but high prices of PCSK9 inhibitors, the recent price decreases may increase the adoption and diffusion of these breakthrough cardiovascular medications, improving clinical outcomes in real-world practice.

Although angiotensin-receptor/neprilysin inhibitors (ARNIs) are similar to PCSK9 inhibitors in the sense that they are novel and expensive, they are otherwise different. Unlike PCSK9 inhibitors, sacubitril/valsartan was deemed cost-effective (although it narrowly failed a test of net budget impact) by the California Technology Assessment Forum, based on an Institute for Clinical and Economic Review report.[15] For patients with systolic dysfunction and class II to IV heart failure, sacubitril/valsartan reduces the risk of death[16] and is cost-effective.[15] In that context, heart failure guidelines list replacement of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers with ARNIs as a class 1 indication.[17]

Yet, despite all this, adoption and diffusion of ARNI for patients with systolic dysfunction and heart failure has been also slow.[18] Improving use of ARNI for these patients is a critical public health goal, and it can save lives. Furthermore, as a cost-effective medication, ARNI does not pose as many of the same problematic societal and budgetary considerations as PCSK9 inhibitors. As such, understanding how to broaden access to ARNI is critical.

Into that important space, we now have new, innovative work by Luo et al[19] that appears in this issue of the *Journal of the American Heart Association* (*JAHA*). The methods in this analysis are clever for several reasons. First, this is a use of a clinical quality registry (Get With The Guidelines–Heart Failure) to address an important public health issue related to drug policy and access. Second, the authors merge data from different sources, including quality ratings from the Hospital Compare database of the Centers for Medicare and Medicaid Services, data from the Dartmouth Atlas of Health Care, and data from the American Hospital Association survey. With these merged data, the authors attempt to understand better what types of hospitals are associated with higher and lower proportions of ARNI use. Those types of conclusions may be helpful in public policy efforts to increase access to this mortality-reducing, cost-effective medication.

This work confirms the concern that adoption and diffusion of ARNI in clinical practice has been slow, showing only 6.1% of eligible patients receiving ARNI prescriptions at hospital discharge. In their insightful discussion, the authors postulate several reasons for the slow adoption of ARNI therapy, including therapeutic inertia, drug pricing, and the impact of insurance coverage and barriers to insurance approval, such as prior authorizations. Although there are some legitimate concerns about initiation of ARNI therapy during hospitalization, as the authors note, newer analyses mitigate many of those concerns. Furthermore, it seems inconceivable that these types of clinical concerns could lead to 73 of 210 hospitals (34.8%) prescribing no ARNI to eligible patients.

Although it is possible that therapeutic inertia plays a role in the low rate of ARNI adoption seen, there are several characteristics of ARNI therapy that may mitigate some of these concerns. The relationship of ARNIs to the well-known angiotensin-converting enzyme inhibitors may alleviate some patient concerns about switching therapies, and the specialization of heart failure providers likely reduces some of the therapeutic concerns around cross-titration. Taken together, this may result in mitigation of some of the factors that traditionally drive therapeutic inertia. It is, therefore, feasible that a more important driver of poor ARNI adoption lies in the pricing of the drug and its subsequent effect on insurance coverage. That would be unfortunate because ARNI is cost-effective. To improve value in health care, we should scrutinize prices for medications that are not cost-effective as a method to improve access and work to decrease other barriers (like prior authorizations) for medications that are costly but cost-effective.

This work also provides other important new insights. Patients were more likely to receive ARNI at discharge at for-profit hospitals rather than nonprofit hospitals. The reason for this is not clear and raises hypotheses for future work. Hospitals in the West were more likely to provide ARNI to eligible patients than hospitals in the Northeast, which could be related to either provider factors or perhaps insurance policy because commercial insurance policies vary by state. Understanding the sources of this variation could lead to plausible hypotheses about how to increase access to ARNI and other novel, cost-effective therapies.

Surprisingly, ARNI prescription was not associated with other quality metrics that the authors obtained through data linkage of multiple databases. A composite measure of non–heart failure quality metrics from Hospital Compare was inversely associated with ARNI prescriptions; hospitals with higher scores seem to discharge fewer inpatients on ARNI. In addition, rate of ambulatory follow-up after hospitalization was not independently associated with ARNI prescription. As the authors note, follow-up after discharge is a validated metric of quality of care in heart failure. In particular, patients discharged from hospitals that see more patients with heart failure within 7 days have lower 30-day readmission rates.[20] This validation was published in 2010, before ARNI was available in general clinical practice. But these results suggest

that different domains of hospital-level quality may exist. Hospitals that are effective at care transitions, for example, may be different than hospitals with proactive systems of care that facilitate prior authorizations for novel medications.

Why then do similar patients receive expensive but cost-effective medications at some hospitals but not at others? This analysis raises several possibilities. More than a third of hospitals in this work prescribe no ARNI for eligible patients at hospital discharge. Perhaps systems of care differ in terms of facilitating the completion of prior authorizations. Alternatively, clinical culture may lead to physicians to be more persistent in pursuing prior authorizations at some hospitals but not others. Either way, as a matter of quality and improving public health, determining the cause behind hospital- or physician-level differences in pursuing prior authorizations may be essential in identifying important modifiable factors. Because prior authorizations are often used for medications that are expensive, it is useful to focus attention on the way in which novel drugs are assigned prices in the United States.

One important aspect of pharmacologic pricing mechanisms in the United States is that the value of a drug, defined by the benefit derived from the prescription medication compared with the cost of that medication, is not necessarily considered. Value-based drug pricing, a mechanism traditionally used by single-payer health systems, such as the United Kingdom's National Health Service, is a concept by which coverage of a new drug is determined by whether its price aligns with the incremental therapeutic value it provides, as measured by quality-adjusted life years. This type of model is more challenging in a system that has multiple healthcare payers, as prescription drugs are purchased by multiple buyers (ie, health insurers).[21] However, New York's state Medicaid program has started to use this concept in determining a fair price to use in negotiations with drug makers.[22] Furthermore, CVS Health recently announced that it had launched a new insurance design in which certain drugs would not be covered if, after price negotiation, their cost-effectiveness did not meet a reasonable standard.[23] Even some drug manufacturers have embraced this model in select cases, as these value-based negotiations often result in improved patient access and, therefore, the ability to recoup losses of lower prices with increased volume of specialty drug sold.[24]

A key advantage of value-based pricing is that it could establish evidence-based consensus between insurers and manufacturer on a benchmark for the relationship between incremental benefit and cost, potentially improving patient access. Although hospital-level factors, including region and for-profit status, were also associated with ARNI prescription rates, many characteristics of hospitals examined by the authors in the analysis by Luo et al[19] were not associated. As such, these unmeasured characteristics of hospitals, variation we do not yet understand, may influence likelihood of receiving ARNI.

Given the complexities of drug pricing in the United States, variation in state-level insurance policies as well as hospital infrastructure and physician culture around prior authorizations should be investigated in future research. Historically, drug companies have set prices and insurance companies have determined how to respond with prior authorizations. Providers may vary in terms of their resources and determination to respond to prior authorizations, and patients may vary in terms of their ability to advocate for themselves or afford large copayments.

This interesting work by Luo et al[19] reminds us about the chaotic ways in which drug manufacturers and insurance companies interact on drug pricing. Irresponsibly high drug prices can both impair access to care and contribute to unsustainable increases in the overall cost of health care. Conversely, overly restrictive prior authorizations deny patients critical, cost-effective treatments. In this setting, value-based pricing could improve access. In the case of sacubitril/valsartan, a life-saving medication that is also cost-effective has not been adopted meaningfully in clinical practice. Whether because of drug pricing and prior authorization, or simply because of therapeutic inertia, this lack of adoption is unfortunate. We providers need to redouble our efforts at diffusion of cutting-edge clinical knowledge with new therapies. Furthermore, any rational system of drug pricing needs to distinguish between expensive medications and medications that exceed cost-effectiveness thresholds. Expensive but cost-effective medications still improve value.

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