High Costs and Caution Yield Slow Start for New Heart Drugs

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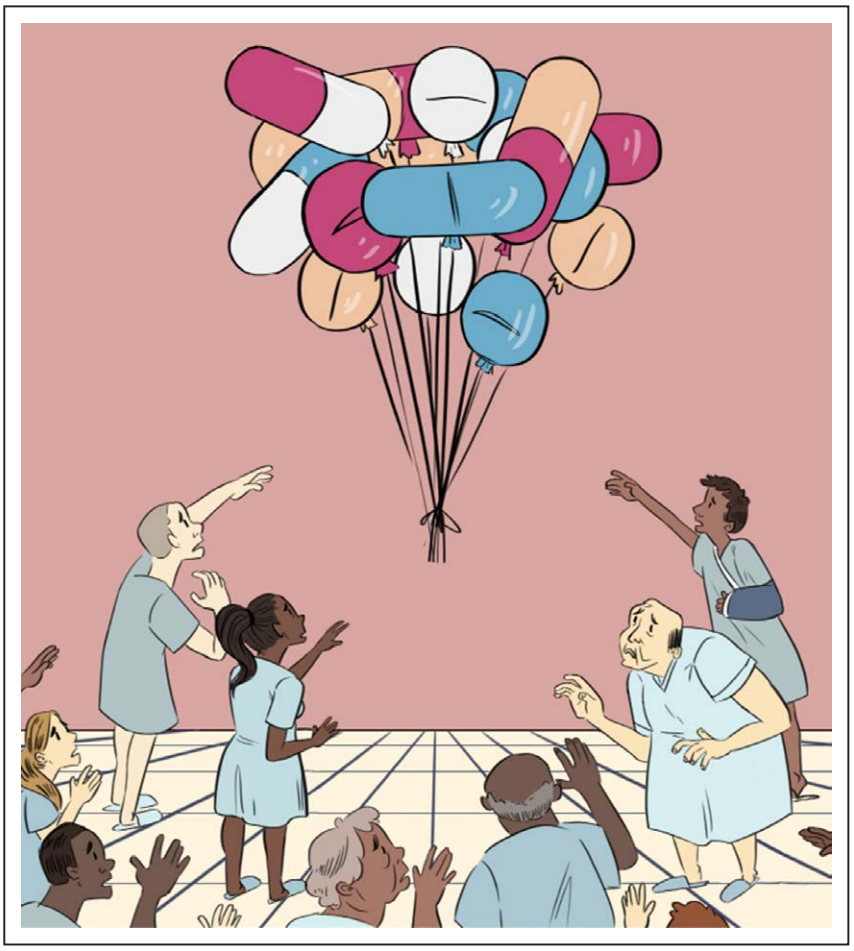
New heart medications sacubitril-valsartan and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have seen a very slow uptake despite predictions they would be blockbusters.

A variety of barriers, including the drugs' high costs, payer restrictions, and limited real-world safety and efficacy data have likely contributed to a slower-than-expected embrace of the drugs despite promising results from the drugs' clinical trials. But data are only just starting to emerge to explain these trends.



High costs and limited data on efficacy have been a barrier to access to some newer drugs for cardiovascular disease.

SLOW UPTAKE

A landmark Institute of Medicine study found that it takes, on average, 17 years for a new drug to make it from clinical trials into routine practice, noted Robert Mentz, MD, assistant professor of medicine at Duke University. He and his colleagues have several studies underway to better understand the uptake of sacubitril-valsartan and how to facilitate appropriate use.

In the first year after its July 2015 approval, only 2 of every 100 eligible hospitalized patients received the drug, according to a study Mentz and his colleagues published in *JACC: Heart Failure* earlier this year.

"We were optimistic we would see greater use over time," Mentz said. And they did see a modest uptick in use near the end of the study period to >3 in 100 patients. Moreover, the study, which analyzed data on >21 000 patients from hospitals across the country in the Get With the Guidelines-Heart Failure registry, found a wide variation in uptake across facilities, with hospital prescribing rates varying from 0.13% to 90% of eligible patients.

"When you look at numbers there are early adopters, but generally it is a bell curve," Mentz said. "There are a lot of people in the middle who want to understand the use of the drug and its challenges."

Several factors might have contributed to a slower-than-expected embrace of the drug. Evidence-based guidelines recommend that even patients who have stable heart failure with low ejection fractions

may be switched. But physicians may have had some concerns about the best way to transition patients, or how it can be used with other medications.

"Some of it is, when you have a patient who is stable on a drug over time, there is inertia," Mentz said. More data on which patients to switch, when, and how may help overcome this inertia by giving physicians a clearer path forward, he noted.

Concerns about a potential risk of dementia or macular degeneration also may have caused some clinicians to use caution with the drug, given the lack of long-term real-world data. But Sean Pinney, MD, director of advanced heart failure and heart transplantation at Mount Sinai Health System, said, given the high risk of dying of heart failure, with patients surviving on average for 5 years, the risk is likely small.

"It's theoretically possible, but I don't think the time course is long enough for anyone to develop it," he said.

Both drugs are supported by just one very large outcomes trial to date, so some providers may choose to await more trials or postmarket surveillance data to better understand the risks and benefits of the drugs. Mentz said it is important to try to balance the benefits to patients while considering potential long-term risks and collect long-term data that may help better define the risks.

"We are trying to find the right balance of getting patients on the drug if appropriate, while working to overcome challenges," he said.

ACCESS, COST BARRIERS

In addition to clinical considerations, the high wholesale costs of drugs like sacubitril-valsartan at >$4000 a year and the PCSK9 inhibitors at >$14 000 a year have created another set of barriers.

Payers have set strict limits on use of the drugs. As many as 80% of prescriptions for PCSK9 inhibitor prescriptions were initially rejected and more than half were never filled, found Ann Marie Navar, MD, PhD, a cardiologist from Duke University who presented her findings at the American College of Cardiology (ACC) meeting.

"It's been very difficult," said Dan Ollendorf, PhD, Chief Scientific Officer at the Institute for Clinical and Economic Review (ICER), a nonprofit organization that assesses drug value. "Even patients with familial hypercholesterolemia (one of the approved indications for PCSK9s) have had a lot of trouble accessing them because payers have limited access to those who absolutely need it and make people step through lower-cost options first."

The high price of PCSK9 inhibitors has been a significant driver of these strict restrictions. In September, ICER published an updated review of PCSK9 inhibitors incorporating outcomes data from the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). The new analysis found that adding evolocumab to statin therapy would cost $1.3 million per quality-adjusted life-year, far above the organization's target cost-effectiveness range of $100 000 to $150 000 per quality-adjusted life-year.

Anecdotal data suggest that it has also been difficult and time consuming to obtain approval for sacubitril-valsartan. Pinney explained that initially the nurse practitioners in his practice made numerous calls to gain approval, but he heard from other cardiologists who did not have the resources to pursue such time-consuming approvals.

"The time it took to get these prescriptions approved was onerous," he said. "Sacubitril-valsartan had a slow rollout because many cardiologists at heart centers did not have 45 minutes to get the drug approved."

Although sacubitril-valsartan's cost is also substantial, ICER's 2016 review of the drug, which can help to substantially reduce hospitalization costs and extend life expectancy, found that it was cost-effective at ≈$50 000 per quality-adjusted life-year.

"We didn't feel that some of these restrictions on [sacubitril-valsartan] were warranted," Ollendorf said. "It seems that some health systems have been painting both [PCSK9 inhibitors and sacubitril-valsartan] with the same brush given their high cost."

SYSTEM COST STRESS

The high cost of these drugs for common conditions is putting additional strain on the already cost-burdened US health system and has led to some efforts to rein in drug costs.

To prevent 1 cardiovascular adverse event, ≈70 patients would need to be treated for 2 years with evolocumab, according to the results from the FOURIER trial published in the *New England Journal of Medicine* in May. This would cost a health system ≈$2 million before the treatment prevented a single heart attack, stroke, or death.

"It puts a lot of pressure on the health system," said Ollendorf. To make PCSK9s more cost-effective, the drugs would have to be discounted 85% to 88% from the current price to $1725 to $2242 a year, according to ICER's most recent analysis.

Barriers to new drug access can also add to health system costs by requiring staff time and paperwork for both payers and practices.

"All of these things have an opportunity cost," said Pinney. "The time it takes a nurse practitioner or an office manager to spend on the phone to get a diagnostic test or therapeutic approved is time not spent with patients. It all adds cost to the system and adds to provider burnout having to deal with the bureaucracy."

But reining in drug costs might help alleviate some of the burden to the health system.

"If prices were lower, it is likely that some of those barriers would not be in place," Ollendorf said.

TAKING ON COSTS

Numerous efforts by professional societies, payers, and others are ongoing to help address rising drug costs. But many in the field say cardiologists could do more to promote drug affordability.

Not-for-profit regional insurer Capital District Physician's Health Plan, which is based in New York, has begun hiring former pharmaceutical company representatives to meet with physicians to discuss appropriate use of drugs, including Lipitor, omeprazole, and sacubitril-valsartan, and pay-for-value programs and overall care management, as well. The company's CEO, John Bennett, MD, a cardiologist, said many physicians are becoming more cost conscious, but with so much on their plates, it is not always the first thing they think about.

"Physicians have to act responsibly and think about the best interest of their patients," Bennett said. "The most lifesaving drug is useless if patients cannot afford it."

Patients not receiving the right medicine or the right doses can also contribute to higher health costs, noted Pinney.

"We should always be mindful of costs," Pinney said. "One of the best ways to reduce health care costs is to ensure that patients in need get the right drug at the right dose at the right time. If physicians do that, it could not only improve patient outcomes but also save the health care system a lot of money."

To help physicians make the best drug choices, groups like ICER provide regular reports on cost-effectiveness, and the American Heart Association (AHA) and the ACC integrate cost-effectiveness analyses into their care guidelines.

"The ACC and AHA are among the few professional societies that have decided to integrate cost-effectiveness explicitly into guideline development," Ollendorf said.

But federal policy interventions may also be needed to help address the root causes of high drug prices in the United States, which pays substantially more for drugs than comparable industrialized countries. A review published by Aaron Kesselheim, MD, JD, MPH, an associate professor of medicine at Harvard Medical School, and colleagues in *JAMA* in August 2016 found that US policies that give drug makers tight exclusivity enable drug makers to set very high prices, as do policies that prevent government payers from negotiating drug prices.

"Drug prices are higher in the United States than in the rest of the industrialized world because, unlike that in nearly every other advanced nation, the US health care system allows manufacturers to set their own price for a given product," Kesselheim and his colleagues wrote.

Pharmaceutical companies have long argued that high drug prices help defray the cost of research and drug development and may reflect the potential value of the drug to society. A recent campaign from the Pharmaceutical Research and Manufacturers of America, an organization that represents drug makers, notes that typically one third of the list price of medications is rebated to payers and others in the supply chain. It also notes that the industry provides patient assistance programs and that some drug makers have set up value-based payment agreements. For example, sacubitril-valsartan maker Novartis in February 2016 entered agreements with health insurers Cigna and Aetna that tie payments for the drug to reductions in heart failure hospitalizations among treated patients, according to a report from corporate consulting firm KPMG International.

Cardiologists can help address drug cost issues by working with payers and pharmaceutical companies to help bring down US drug costs, said Bennett.

"I've always been proud that ACC and AHA have taken the lead in promoting evidence-based guidelines and addressing health disparities," Bennett said. "I'd love to see us continue to do that by stepping up to the plate on rational pharmaceutical pricing." ■

This is part 1 of a 2-part article. See part 2 in the January 16 issue.

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