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THE MINIMAL IMPACT OF A BIG HYPERTENSION STUDY

The Evidence Gap

The surprising news made headlines in December 2002. Generic pills for [high blood pressure](#), which had been in use since the 1950s and cost only pennies a day, worked better than newer drugs that were up to 20 times as expensive.

The findings, from one of the biggest clinical trials ever organized by the federal government, promised to save the nation billions of dollars in treating the tens of millions of Americans with hypertension — even if the conclusions did seem to threaten pharmaceutical giants like [Pfizer](#) that were making big money on blockbuster hypertension drugs.

Six years later, though, the use of the inexpensive pills, called diuretics, is far smaller than some of the trial's organizers had hoped.

"It should have more than doubled," said Dr. Curt D. Furberg, a public health sciences professor at [Wake Forest University](#) who was the first chairman of the steering committee for the study, which was known by the acronym Allhat. "The impact was disappointing."

The percentage of hypertension patients receiving a diuretic rose to around 40 percent in the year after the Allhat results were announced, up from 30 to 35 percent beforehand, according to some studies. But use of diuretics has since stayed at that plateau. And over all, use of newer hypertension drugs has grown faster than the use of diuretics since 2002, according to [Medco Health Solutions](#), a pharmacy benefits manager.

The Allhat experience is worth remembering now, as some policy experts and government officials call for more such studies to directly compare drugs or other treatments, as a way to stem runaway medical costs and improve care.

The aftereffects of the study show how hard it is to change medical practice, even after a government-sanctioned trial costing \$130 million produced what appeared to be solid evidence.

A confluence of factors blunted Allhat's impact. One was the simple difficulty of persuading doctors to change their habits. Another was scientific disagreement, as many academic medical experts criticized the trial's design and the government's interpretation of the results.

Moreover, pharmaceutical companies responded by heavily marketing their own expensive hypertension drugs and, in some cases, paying speakers to publicly interpret the Allhat results in ways that made their products look better.

"The pharmaceutical industry ganged up and attacked, discredited the findings," Dr. Furberg said. He eventually resigned in frustration as chairman of the study's steering committee, the expert group that continues to oversee analysis of data from the trial. One member of that committee received more than \$200,000 from Pfizer, largely in speaking fees, the year after the Allhat results were released.

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There was another factor: medicine moves on. Even before Allhat was finished, and certainly since then, new drugs appeared. Others, meanwhile, became available as generics, reducing the cost advantage of the diuretics. And many doctors have shifted to using two or more drugs together, helped by pharmaceutical companies that offer combination pills containing two medicines.

So Allhat's main query — which drug to use first — became "an outdated question that doesn't have huge relevance to the majority of people's clinical practices," said Dr. John M. Flack, the chairman of medicine at Wayne State University, who was not involved in the study and has consulted for some drug makers.

Dr. Sean Tunis, a former chief medical officer for [Medicare](#), remains an advocate for comparative-effectiveness studies. But, as Allhat showed, "they are hard to do, expensive to do and provoke a lot of political pushback," said Dr. Tunis, who now runs the nonprofit Center for Medical Technology Policy, which tries to arrange such trials.

"There's a lot of magical thinking," he said, "that it will all be science and won't be politics."

Expensive Pills

Promising better ways to treat high blood pressure, drug companies in the 1980s introduced a variety of medications, including ones known as [calcium](#) channel blockers and ACE inhibitors.

Although there was no real evidence the newer pills were better, diuretics fell to 27 percent of hypertension [prescriptions](#) in 1992, from 56 percent in 1982. Use of the more expensive pills added an estimated \$3.1 billion to the nation's medical bill over that period.

So the National Heart, Lung and Blood Institute, part of the federal [National Institutes of Health](#), decided to compare the various drugs' ability to prevent heart attacks, strokes and other cardiovascular problems. "This was a big-bucks issue," said Dr. Jeffrey Cutler, the Heart, Lung and Blood Institute's project director for the study.

Allhat — short for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial — began enrolling patients with high blood pressure, age 55 and older, in 1994, with more than 42,000 people eventually participating. Patients were randomly assigned one of four drugs: a diuretic called chlorthalidone; an ACE inhibitor called lisinopril, which [AstraZeneca](#) sold as Zestril; a calcium channel blocker, amlodipine, sold by Pfizer as Norvasc; and an alpha blocker, doxazosin, which Pfizer sold as Cardura.

Cardura was added only after Pfizer, which had already agreed to contribute \$20 million to the trial's costs, increased that to \$40 million, Dr. Cutler said.

Early Trouble Signs

Pfizer's bet on Cardura proved a big mistake. As the Allhat data came in, patients taking Cardura were nearly twice as likely as those receiving the diuretic to require hospitalization for [heart failure](#), a condition in which the heart cannot pump blood adequately. Concerned, the Heart, Lung and Blood Institute announced in March 2000 that it had stopped the Cardura part of the trial.

What happened next provided the first signs that the Allhat evidence might not be universally embraced.

Rather than warn doctors that Cardura might not be suited for hypertension, Pfizer circulated a memo to its sales representatives suggesting scripted responses they could use to reassure doctors that Cardura was safe, according to documents released from a patients' lawsuit against the company.

And in an e-mail message unearthed in those same court documents, a Pfizer sales executive boasted to colleagues that company employees had diverted some European doctors attending an American cardiology conference from hearing a presentation on the Allhat results and Cardura. "The good news," the message said, "is that they were quite brilliant in sending their key physicians to sightsee rather than hear Curt Furberg slam Pfizer once again!"

Pfizer declined to comment on the messages.

The [Food and Drug Administration](#) waited a year before convening a meeting of outside experts to discuss Cardura's safety. At that session, some of the experts sharply challenged the conclusions of the Allhat organizers. They argued that the heart failure cases might have been false readings and that an inadequate dose of Cardura had been used in the trial.

By the end of the daylong meeting, Dr. Robert O. Temple, a senior F.D.A. official, was clearly exasperated by the experts' varying interpretations of a supposedly definitive trial.

"This is the largest and best attempt to compare outcomes we are ever going to see," he said. "And people are extremely doubtful about whether it has shown anything at all."

The committee decided that there was no need to issue an urgent warning to doctors and patients about Cardura.

Cardura sales held up in 2000. But the next year, worldwide sales fell to \$552 million, from \$795 million. Prescriptions for all alpha blockers fell 22 percent from 1999 to 2002 after having risen before then, according to one study.

Pfizer's decision to stop promoting Cardura in late 2000, after the drug lost patent protection, was a factor in the decline. But Allhat clearly was, too.

Cost-Benefit Analysis

The main Allhat results were announced in December 2002 at a news conference in Washington and published in The Journal of the [American Medical Association](#).

In the primary target outcome of the trial — the prevention of heart attacks — the three remaining drugs were proved equal. But patients receiving the Norvasc calcium channel blocker from Pfizer had a 38 percent greater incidence of heart failure than those on the diuretic. And those receiving the ACE inhibitor from AstraZeneca had a 15 percent higher risk of strokes and a 19 percent higher risk of heart failure.

Moreover, the diuretic cost only about \$25 a year, compared with \$250 for an ACE inhibitor and \$500 for a calcium channel blocker. So the diuretic was declared the winner.

But some hypertension experts accused the government of overstating the case for the diuretics, as a way to cut medical spending.

"There was a feeling there was a political and economic agenda as much as a scientific agenda," said Dr. Michael Weber, a professor of medicine at the Health Science Center at Brooklyn, part of the [State University of New York](#), who had been an investigator in the study but afterward became one of its leading critics. "They pushed beyond what the data allowed them to say."

Critics said the rules of the trial had favored the diuretics. If the first drug did not adequately lower [blood pressure](#) — as happened in more than 60 percent of cases — a second drug could be added. But that second drug was usually a type that worked better with diuretics than with ACE inhibitors.

There were also more new cases of [diabetes](#) among the patients who took diuretics, although experts argued over how meaningful that finding was.

Adding fuel to the debate, an Australian study released two months after Allhat found an ACE inhibitor superior to a diuretic. The proper lesson to draw from Allhat, some critics contended, was that what matters most is how much blood pressure is lowered, not which drug is used to do it. For these and other reasons, European hypertension experts discounted Allhat.

Allhat's proponents discounted the Australian study as less authoritative, and they dismissed the other criticisms.

Still, the arguments "muddied the waters," said Dr. Randall S. Stafford of Stanford, who studied the effect of Allhat on prescriptions. "The message," he said, "was no longer as clear to physicians."

Science Moves On

By the time the Allhat results were released, lisinopril, the ACE inhibitor, had become generic. That meant AstraZeneca and [Merck](#), which sold a version of the compound as Prinivil, had less interest in defending their drugs.

Not so Pfizer. Norvasc was the best-selling hypertension treatment in the world, with sales of \$3.8 billion in 2002, and Pfizer's second-biggest drug behind the [cholesterol](#) medication [Lipitor](#).

The company set out to accentuate the positive. In a news release after the Allhat results were announced, it said that Norvasc was found to be "comparable to the diuretic in fatal [coronary heart disease](#), heart attacks and stroke." And in a medical journal advertisement, it proclaimed "[ALL](#) HATs off" to its drug.

Neither the news release nor the ad, however, included the 38 percent greater risk of heart failure with Norvasc in the Allhat study.

Nor did [Hank McKinnell](#), then Pfizer's chief executive, mention heart failure in lauding the results during his quarterly earnings conference call with analysts a few weeks after the Allhat report was released. "Contrary to what you might have read in the press," Mr. McKinnell said, "Allhat is extremely positive for Norvasc. It will be our job to explain that to the medical community."

Dr. Paul K. Whelton, president of Loyola University Health System and the current chairman of the Allhat steering committee, said that Pfizer and other drug companies "took what was in their best interest and ran with those, and conveniently didn't mention other things."

Pfizer defends its actions. Dr. Michael Berelowitz, the head of Pfizer's global medical organization, said that in the trial's design, heart failure was merely one component of a broader measure of various cardiovascular problems. And in that broader measure, Dr. Berelowitz said, there was no difference between Norvasc and the diuretic. Also, he said, the label for Norvasc already contained a precaution about heart failure.

"Further action regarding the heart failure finding was therefore not considered necessary," he said in a statement in response to questions.

Pfizer was not the only company promoting its drugs. The drug giant [Novartis](#), for example, was spending heavily to market Diovan, a leader among a class of hypertension drugs called angiotensin receptor blockers, which were too new to

have been included in Allhat. Diovan, which had more than \$5 billion in sales last year, sells for \$1.88 to \$3.20 a pill on drugstore.com, compared with 8 to 31 cents for a diuretic.

No company, though, was spending money to promote generic diuretics. So the federal Heart, Lung and Blood Institute recruited Allhat investigators, provided them with training and sent them to proselytize fellow physicians. In all, 147 investigators gave nearly 1,700 talks and reached more than 18,000 doctors and other health care providers.

But it was a coffee-and-doughnuts operation compared with the sumptuous dinners that pharmaceutical companies used to market to doctors. Moreover, the steering committee's outreach program did not get under way until about three years after the results were published.

Dr. Stafford of Stanford said the outreach seemed to have had a slight effect on increasing the use of diuretics.

The results of Pfizer's efforts are easier to quantify. Norvasc sales continued to grow to \$4.9 billion in 2006, falling only after the drug lost patent protection in the United States in 2007.

Tangles and Strife

Tensions about industry influence reached even the study's own steering committee. Dr. Furberg, the chairman, bluntly accused some members of the committee of being agents of the industry.

One member, Dr. Richard H. Grimm Jr. of the University of Minnesota, had been receiving tens of thousands of dollars a year from Pfizer since at least 1997, according to reports that pharmaceutical companies file in that state.

In 2003, the year after the Allhat results were published, Dr. Grimm's payments from Pfizer soared to more than \$200,000 — an increase that The New York Times reported in 2007.

Dr. Grimm said in a recent interview that about half those fees in 2003 came from giving about 100 Pfizer-sponsored talks to doctors about Allhat. Dr. Grimm said he gave mainly the standard Allhat-sanctioned talk. But instead of saying diuretics were outright better than the other drugs, he said they were as good or better.

Meanwhile, Dr. Grimm had led an effort to remove Dr. Furberg from his position on the grounds that he had not been impartial.

"He had a vendetta against the calcium channel blockers," Dr. Grimm said. Dr. Furberg had been publicly questioning the safety of those drugs based on some studies he did in the 1990s. The effort to oust Dr. Furberg failed in 2001. But in August 2004, Dr. Furberg resigned as chairman, contending that there had not been enough effort to disseminate the Allhat message.

Dr. Whelton, who took over as chairman, said that the study's message was never compromised by industry ties on the steering committee.

"Curt is a wonderful guy who is a crusader," said Dr. Whelton, who did not have industry ties and was not involved in the effort to unseat Dr. Furberg. "He has certainly rubbed a lot of people, even good friends, the wrong way."

Changing Practice

Experts see several lessons to be learned from Allhat.

One is that "all trials have flaws" that leave the results open to interpretation, said Dr. Robert M. Califf, a cardiologist at Duke who served on the safety monitoring committee of Allhat.

Another is that providing doctors information is "necessary, but not sufficient" to urge them to change their practices, said Dr. Carolyn M. Clancy, director of the federal Agency for Healthcare Research and Quality, which itself conducts studies comparing different medical treatments.

And while insurers can influence practice through reimbursement policies, they did not seem to have pushed strongly for diuretics after Allhat, in part because some of the other drugs had become generic.

Even the cost-conscious medical system at the [Department of Veterans Affairs](#) did not require diuretics, because too many doctors would probably have requested exceptions, said Dr. William C. Cushman, chief of [preventive medicine](#) at the department's medical center in Memphis.

Dr. Cushman, a member of the Allhat steering committee, said diuretic use in the system was still "much lower" than he thought it should be.

Dr. Clancy said that her agency was now mainly using insurance records to judge how treatments perform. While clinical trials are the gold standard, she said, they are costly and time-consuming.

And, she added, "You might be answering a question that by the time you are done, no longer feels quite as relevant."

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