

PHARMACEUTICALS

MEDICAL INNOVATION: ACE INHIBITORS (PHARMACEUTICAL: SMALL MOLECULE)

Physician: Dr. John Vane, Dr. Kevin Ng, Dr. Miguel Ondetti and Dr. David Cushman
Industry: Bristol-Myers Squibb

Situation

The heavy burden of heart failure

Heart failure, also called congestive heart failure (CHF), is a chronic, long-term ailment in which the heart can no longer pump enough blood to the rest of the body. The most common cause of CHF is reduced blood circulation, usually caused by blocked arteries and high blood pressure. Five million Americans suffer from congestive heart failure and up to 700,000 new cases are diagnosed every year, costing some \$40 billion in direct and indirect hospitalization costs annually.

Heart failure is a complex condition, producing a range of symptoms and resulting in a dramatically weakened heart. Further heart enlargement and weakening are caused by chemical messengers in the body such as angiotensin-converting enzymes (ACEs) that cause blood vessels to narrow, thereby increasing blood pressure and decreasing blood flow. Until recently, doctors had no way to intervene directly in the body's production of these enzymes, and thus had no ability to improve circulation quickly and effectively for patients with heart failure.

Physician-Industry Collaboration

Snake venom leads to a discovery on blood pressure

In the 1960s, a pathologist from England named John Vane was actively investigating the causes of high blood pressure. During this time, a Brazilian post-doctoral fellow, Sergio Ferreira joined Vane's group and brought with him an extract of the venom from a Brazilian viper snake that he noticed sometimes caused blood vessels to dilate, therefore potentially lowering blood pressure. Vane decided to test the effect of the venom on ACE and found it to be a potent inhibitor of the enzyme.

This prompted further interest, and Vane approached the Squibb pharmaceutical company in New Jersey (now Bristol-Myers Squibb) about conducting extensive research on how to isolate and produce peptides from the venom that might be used to lower blood pressure in humans. He and a colleague, Kevin Ng, worked closely with two Squibb scientists, David Cushman and Miguel Ondetti on a series of intravenous studies in animals, at great expense, and with little long-term promise initially. After producing some success in the animal experiments, Vane arranged for the first human trial to take place in the U.K., followed by another study in the U.S.

The intravenous so-called ACE inhibitors proved so effective at lowering blood pressure in the patients studied that Squibb worked quickly to develop an oral form of the drug that could be produced on a large scale. The first drug produced, Captopril, was approved by the FDA in 1981 and rapidly became a standard drug for treating high blood pressure and congestive heart failure.

Innovation Benefits

Transforming the treatment of congestive heart failure

Now three decades after approval, ACE inhibitors stand among the most successful and widely used drugs in the world, and have transformed the treatment of congestive heart failure and high blood pressure. They also have become some of the most studied drugs in the world: some 7,000 patients have participated in long-term ACE inhibitor trials.

Patients who use ACE inhibitors demonstrate improved heart function, improved symptoms, and show a lower death rate from all causes by 20% to 25% and a lower risk of death and hospitalization by 30% to 35%. This translates into billions of dollars each year in direct and indirect savings. Further, the drugs have contributed to a [30% relative decline](#) in the overall hospitalization rate for heart failure over the last decade and to a [6% relative decline](#) in mortality from the disease.

ACE inhibitors are now used to preserve kidney function among some diabetics and prevent strokes, and they are being studied for other uses as well, including treatment for depression.

Patient Benefits

“I haven’t felt this good in 25 years”

The Richard B. and Lynne V. Cheney Cardiovascular Institute at The George Washington University tells [a powerful story](#) about the personal impact of the improvement in treatment for heart failure:

Welford was in his late forties when he began feeling weak, as though all the energy had been drained out of him. He experienced a few dizzy spells but shrugged them off. “I was too young for something like heart failure to be happening to me,” says Welford. “I put off dealing with it for too long, until it was almost too late.”

Fortunately, he sought treatment in time. His doctors implanted a pacemaker and later a biventricular ICD. The ICD monitors his heartbeat and delivers a shock if the rhythm gets out of sync. As part of such treatment, doctors typically prescribed a regimen of ACE inhibitors to lower blood pressure and improve circulation.

“I also learned how to eat right – fruits and vegetables, no fried foods anymore. I used to love fried chicken, but now I barely miss it because I feel so much better,” says Welford. “I walk two hours every day now and have lost 40 pounds. I haven’t felt this good in 25 years.”

These days, Welford feels up to working in his yard and tinkering with cars, two favorite activities he had given up in the days when his undiagnosed heart failure was sapping his strength and energy. His wife and two sons worry sometimes that he might overdo it, but Welford assures them that he knows to stop and rest if he gets tired.

“It took a near-death experience,” he says, “but now I’m enjoying life again.”

