

Responsive Gene Is Key to Efficiency of Heart-Failure Drug

By Rick Weiss
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An experimental heart-failure drug that was shelved amid doubts about its usefulness appears to be a lifesaver in patients who carry a particular version of a heart-related gene, researchers are reporting today.

About half of the U.S. population carries the version of the gene that responds to the drug -- although most blacks do not. In the new analysis, patients with the responsive version were far more likely to be alive four years later if they took the drug -- a beta blocker called bucindolol -- than people with the other version, who experienced little or no benefit.

It is too soon to say whether the drug's newly recognized niche status -- effective, but only for some people -- will make it commercially viable. It is unknown, for example, whether even those patients with the responsive gene would do better on bucindolol than on the two beta blockers already on the market for heart failure -- a serious disease that kills half its victims within five years.

But the study is notable, several doctors and researchers said, because it offers such a definitive example of a drug whose potency depends on subtle genetic differences that probably do not matter as long as people remain healthy. Some experts predict that such discoveries are poised to become a revolution in health care:

truly personalized medicine, with treatments customized to patients' genomes.

"I'm hoping there are a lot of drugs on companies' back shelves that, once you segregate their genetics, are going to have some value," said Stephen B. Liggett, a professor of medicine and physiology at the University of Maryland School of Medicine in Baltimore, who led the research.

Several experts in pharmacogenomics -- an emerging specialty that deals with the interplay of genes and drugs -- said they are encouraged by the new results.

"We know that not every patient gets a benefit from every drug, and genetic differences often probably account for those differences, so this is promising," said J. Brent Muhlestein, a professor of medicine at the University of Utah and director of cardiology research at LDS Hospital in Salt Lake City.

Muhlestein and others cautioned, however, that the road to personalized medicine has been rough, and that progress is likely to be slow.

Richard Weinshilboum, a professor of pharmacology at the Mayo Clinic College of Medicine in Rochester, Minn., said: "We need to not overpromise to the public that having this kind of information is going to solve all our problems in picking the right medication at the right dose for the right patient."

Among other issues, some companies find the economics of the new approach unattractive, because discovering that a drug is not much use in some people could put a company at a disadvantage compared with competitors that have not teased out those specifics.

For bucindolol, however -- a drug that many had written off -- gene-based prescribing could only help. Seven years ago, it was being tested in a large clinical trial in which some heart-failure patients received the drug while others received a placebo. The trial was cut short when other studies documented the life-saving value of other beta blockers. With proof that patients could benefit from those drugs, experts decided it was unethical to keep giving dummy pills to patients in the bucindolol study.

Faced with equivocal results at that point, developers gave up on the drug. But another company -- ARCA Discovery of Denver -- acquired the rights and reanalyzed the results, taking into account participants' genetic codes.

ARCA approached Liggett, who for years had studied the molecular target on which beta blockers primarily work: the beta-1 adrenergic receptor. That receptor -- a protein on the surface of heart cells -- can become overactive in heart failure, a response that beta blockers can curb. But not all beta-1 adrenergic receptors are created equal, Liggett found.

He had already shown that some people inherit a slightly altered version of that receptor protein, in which one amino acid out of 477 is different than it is in other people. In the new work, described in this week's online issue of the Proceedings of the National Academy of Sciences, he and colleagues looked at the old clinical trial to see which patients had which receptor -- information not previously analyzed. The team then examined how each group responded to bucindolol.

People with the responsive gene type who received the drug had a 36 percent reduction in hospitalizations over four years and a 38 percent increase in survival, while those with the other type saw no benefits, said Liggett, who is a paid consultant for ARCA.

About 53 percent of whites carry the responsive version, compared with 38 percent of blacks.

Michael Bristow, ARCA's president and chief executive, said the company intends to apply to the Food and Drug Administration next year for approval to market bucindolol. The plan, he said, is to help doctors use the drug wisely by noting in the labeling bucindolol's record in people with various gene types. Although analyses are still ongoing, Bristow said he believes the drug will prove to be of great value in about half of Americans and modest value in about 40 percent -- figures some experts called optimistic.

Bristow also noted that 10 percent of people carry an entirely different gene that would result in their being harmed by bucindolol, making it important that patients be tested in advance.

ARCA is working with a partner, he said, to commercialize the relevant gene tests.

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