

## Drug doesn't significantly lower risk of major heart problems in dialysis patients

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In one of the largest and longest trials involving patients with kidney failure, a study led by an international team of researchers found that cinacalcet—a drug commonly prescribed to patients with kidney failure and a disturbance of bone and mineral metabolism known as secondary hyperparathyroidism—does not significantly reduce the risk of death or major cardiovascular events.

The results of the trial known as EVOLVE, which enrolled nearly 4,000 [kidney patients](#) from several continents and stretched over five years, were mixed, researchers said.

"The results of the EVOLVE trial suggest that cinacalcet favorably alters bone and mineral metabolism, and could result in improved health and longevity for patients with end-stage renal disease," said the study's lead author, Glenn Chertow, MD, professor of medicine and chief of nephrology at the Stanford University School of Medicine. "But the trial was not definitive in determining cardiovascular benefits because so many patients discontinued taking the study drug."

Researchers did say the trial results showed possible [cardiovascular benefits](#) when certain factors were taken into account, such as an imbalance in age between study participants who were treated with cinacalcet and those who received a placebo. Those who received the drug were on average a year older; age is a major risk factor for cardiovascular disease.

"The trial is not definitive in its results; however, recognizing some of the limitations—such as the high dropout rate—it is suggestive of a cardiovascular [health benefit](#)," said co-author Geoffrey Block, MD, medical director of Denver Nephrology.

The study will be published online Nov. 3 in the [New England Journal of Medicine](#) and will also be presented at the American Society of Nephrology annual meeting in San Diego the same day.

Patients on [kidney dialysis](#) are among the most frail and chronically ill, with high mortality and [hospitalization rates](#). This makes recruitment and retention of such patients in clinical trials particularly challenging, the study stated.

Earlier studies suggested that cinacalcet, one of several drugs used to treat secondary hyperparathyroidism, may also help to prevent or ameliorate cardiovascular disease. Cinacalcet is manufactured by Amgen Inc., a biotechnology firm located in Thousand Oaks, Calif., which sponsored the EVOLVE trial.

Because secondary hyperparathyroidism and associated disorders are linked with death, fractures and cardiovascular disease, physicians have prescribed the drug in the hopes of preventing cardiovascular events in patients undergoing dialysis. Its side effects include nausea and gastrointestinal distress.

"Secondary hyperparathyroidism develops when the kidneys are unable to maintain the balance of certain minerals, including phosphorus and calcium," Chertow said. "In this setting, the bones do not mineralize normally, and blood vessels and other tissues can become calcified."

Cardiovascular disease is exceptionally common among patients with chronic kidney disease, including those treated with dialysis, among

whom rates of death due to cardiovascular disease are more than 10 times higher than in the general population, the study stated. The objective of the study was to determine whether the use of cinacalcet in patients undergoing hemodialysis would reduce the rates of death and major cardiovascular events, including myocardial infarction, hospitalization for unstable angina, heart failure and peripheral vascular events, all of which were considered endpoints for the study.

Determining the appropriate treatment course for people with advanced chronic kidney disease, particularly those on dialysis, can be challenging. Patients with [kidney failure](#) require either kidney transplantation or dialysis; the latter typically requires three- to four-hour sessions of blood cleansing three times per week. In addition, patients on hemodialysis take about 19 prescription tablets daily and often suffer gastrointestinal disturbances and other side effects.

"The burden of hemodialysis treatment is considerable, and most patients take several prescription medications, often several times per day," Chertow said. "Cinacalcet is not a perfect drug. It has been shown to be safe and the gastrointestinal side effects are not prohibitive, but when someone is taking 20 pills a day, it is difficult to justify the 21st unless it makes an important difference."

The trial, which was originally designed to last four years, was extended to nearly five and a half years in an attempt to reach the required number of endpoints. Between Aug. 22, 2006, and Jan. 31, 2008, researchers recruited 3,883 patients on hemodialysis with secondary hyperparathyroidism from the United States, Europe, Latin America, Russia, Australia and Canada. These patients were then randomized to either a treatment course with cinacalcet or placebo and were followed for up to 64 months.

The primary analysis of the trial showed that the relative risk of death or

a major cardiovascular event was reduced by 7 percent in [patients](#) treated with cinacalcet, a statistically non-significant result. Adjusting for age, or a combination of age and other clinical features of the study population—such as diabetes or a history of heart disease—the risk reduction was 12 percent and was nominally statistically significant, the study said.

**More information:** The trial, which was sponsored by Amgen Inc., was led by an academic executive committee of researchers from several institutions who supervised the trial design and implementation. Four Amgen researchers were among the co-authors of the study.

Chertow was the only Stanford author. He reported receiving consulting fees from Amgen.

Provided by Stanford University Medical Center

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