Valsartan Forestalled Diabetes But Not CV Events

BY MARY ANN MOON

Nateglinide failed to prevent the development of diabetes and related CV events in high-risk patients in a large international clinical trial.

In the same trial, the angiotensin-receptor blocker valsartan also failed to prevent CV events. However, valsartan induced an unexpected relative reduction of 14% in the incidence of diabetes, according to the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study Group.

The results were published simultaneously their at the annual meeting of the American College of Cardiology in Atlanta.

In an editorial accompanying the two reports, Dr. David M. Nathan of Massachusetts General Hospital's Diabetes Center, Boston, said, "The authors suggest that the prevention of diabetes with valsartan might make it a preferred drug as compared with antihypertensive drugs that potentially worsen glycemia."

However, this trial's single positive finding was only a "weak" reduction in diabetes with valsartan—not enough to support such a recommendation. The totality of the study findings show instead that "for now we should steer away from these two drugs" when attempting to forestall diabetes and its associated cardiovascular complications in high-risk patients, Dr. Nathan said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMe1002322]).

In NAVIGATOR, 9,306 patients who had impaired glucose tolerance and either known cardiovascular disease or CV risk factors were assessed at 806 medical centers in 40 countries during January 2002–January 2004. They were randomly assigned to take 60 mg of the insulin secretagogue nateglinide before meals three times daily, a placebo, or in a 2-by-2 factorial design, oral valsartan or placebo.

All the study subjects also were required to participate in a lifestyle modification program aimed at achieving a 5% weight loss, reduced dietary fats, and increased physical activity.

Nateglinide, which lowers postprandial glucose, was studied to determine whether it would slow progression to diabetes by restoring a more physiologic insulin response to meals. But during a mean follow-up of about 6 years, progression to diabetes occurred in 36% of the nateglinide group and 34% of the placebo group, a nonsignificant difference, said Dr. Rury R. Holman of Oxford (England) University's Centre for Diabetes, Endocrinology, and Metabolism, and his associates said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMoa1001122]).

Similarly, a composite cardiovascular outcome event occurred in 14% of the nateglinide group and 15% of the placebo group. There also were no differences between the two groups in any of the individual components of the composite CV outcome, including mortality rates.

The valsartan results, reported in a separate article, showed that the ARB had no effect on combined CV outcomes. Furthermore, it reduced the incidence of diabetes by 14% relative to placebo. This "would translate into 38 fewer cases of diabetes per 1,000 patients treated for 5 years," said Dr. Robert M. Califf of the Duke Translational Medicine Institute in Durham, N.C., and his NAVIGATOR colleagues.

It is possible that valsartan did not improve CV outcomes as it should have because most risk factors were already well controlled, since study subjects were allowed to take nonstudy medications such as ACE inhibitors, they said (N. Engl. J. Med. 2010 March 14 [doi:10.1056/NEJMoa1001121]).

In his editorial comment, Dr. Nathan agreed that "the high rates of loss to follow-up (13%), use of off-study ACE inhibitors or ARBs among participants assigned to placebo (24%), and nonadherence to valsartan (34% by study end) could explain the absence of an effect on cardiovascular disease."

Overall, the NAVIGATOR results "do not support the contention that reducing postprandial hyperglycemia has a specific role in preventing diabetes or reducing cardiovascular disease. Other than increasing the rate of hypoglycemia by a factor of two, nateglinide had little effect," Dr. Nathan commented.

The study was sponsored and designed by Novartis Pharma, manufacturer of both drugs. Novartis also collected, managed, and analyzed the data. In addition to support from Novartis, the NAVIGATOR researchers reported receiving financial support from Sanofi-Aventis and Merck. Dr. Nathan reported no financial conflicts of interest. ■

MY TAKE

RAS Inhibition, Lifestyle Modification Affirmed

The NAVIGATOR trial was an ambitious effort to assess the ability of nateglinide and valsartan to prevent the onset of diabetes and adverse cardiovascular outcomes. Given our growing diabetes epidemic, meaningfully positive findings for either outcome with either intervention would have been welcome.

Unfortunately, both treatments were disappointing with regard to each of the coprimary end points. Furthermore, nateglinide was also linked to greater weight gain and increase in waist circumference, likely foreboding a higher rate of future diabetes.

Although valsartan did not prevent CV events or any of its other component events, it was associated with a significantly lower incidence of new onset diabetes, compared with placebo.

Similar reductions have been noted with other inhibitors of the renin-angiotensin system, but these are far less impressive than those seen with successful life-style modifications or metformin, which reduced the onset of type II diabetes in similar patients in the Diabetes Prevention Program by 58% and 31%, respectively (N. Engl. J. Med. 2002;346:393-403).

It now appears that the goal of diabetes prevention is best addressed by changing behavior, and with the hope that improvements in cardiovascular (CV) outcomes will follow.

Until then, it seems reasonable to use an inhibitor of the RAS system as part of the antihypertensive regimen that most prediabetic and diabetic patients will need.

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Dual-Acting Investigational Drug Shows Promise

BY JENNIE SMITH

The experimental drug LCZ696, which inhibits both the angiotensin II receptor and neprilysin, has been shown to reduce blood pressure more effectively than the established angiotensin receptor blocker valsartan—and without apparent risk of angioedema, in a phase II trial.

LCZ696 is a single molecule, developed by Novartis, that contains properties of both valsartan (Novartis, Diovan) and AHU377, an experimental neprilysin inhibitor also developed by Novartis. In a randomized, double-blind, phase II trial sponsored the manufacturer, all three agents were compared for efficacy, and the dual-acting molecule did better than either comparator (Lancet 2010 March 16 [DOI:10.1016/S0140-6736(09)61966-8]).

"There is synergistic effect when the two are put together," Dr. Luis Miguel Ruilope of the Hospital 12 de Octubre in Madrid, the lead investigator of the study, said in an interview.

Dr. Ruilope and colleagues enrolled 1,328 patients, with a mean age 53, all with mild to moderate essential hypertension (mean sitting diastolic blood pressure of 90-109 mm Hg after antihypertensive washout, or 95-109 mm Hg for untreated patients).

Enrollees were divided into eight paired groups of between 156 and 173 patients each. Six of the groups were randomized to receive oral LCZ696 100 mg, 200 mg, 200 mg daily switched after 5 weeks to 400 mg daily, or a comparable-strength regimen of valsartan (80 mg, 160 mg, or 320 mg daily). A seventh group received 200 mg of AHU377 daily, the neprilysin inhibitor, and was paired with an eighth group that received placebo. A total of 91% of patients completed the 8-week treatment period.

The primary outcome was the lowering of mean sitting diastolic BP during the 8-week treatment period The investigators found greater reductions in mean sitting diastolic BP from baselines in all groups taking LCZ696 over those taking valsartan—of the three paired dose groups, the LCZ696 arm saw a mean drop –2.17/–4.20 mm Hg.

The difference in reduction was not significant at the lowest dose but became marked at the higher doses, and the contrast widened with the dose increases.

The neprilysin inhibitor AHU377, tested only at the 200-mg dose, performed better than placebo but not as well as LCZ696 at any dose, with a change from baseline in mean sitting blood pressure of -4.20/-2.99 mm Hg

Adverse effects across all study groups were minimal, even at the highest doses. Though patients with previous angioedema were not allowed to enroll, there were no reports of angioedema in any of the study categories.

Dr. Bernard Waeber and Dr. François Feihl of the Université de Lausanne in Switzerland, noted the "great potential" of LCZ696 in an accompanying editorial (DOI:10. 1016/S0140-6736[10]60363-7).

The absence of angioedema during the trial is especially encouraging, they wrote, since a previous hypertension drug candidate with somewhat similar dual activity, omapatrilat (Bristol-Myers Squibb), had shown great promise in reducing BP, but could not be marketed because of a high association with angioedema.

Dr. Ruilope and two of his co-authors have financial relationships with Novartis; two more authors are employees of Novartis, and one declared no conflicts of interest.

Dr. Waeber and Dr. Feihl declared no conflicts of interest. ■