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ADHT: Amlodipine Diabetic Hypertension Efficacy Response Evaluation Trial

Disclosures

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Diabetic patients have a better chance of controlling their blood pressure with a combination of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB), according to the results of the Amlodipine Diabetic Hypertension Efficacy Response Evaluation Trial (ADHT).[1] Adding a second drug, in this case the CCB amlodipine, to monotherapy with an ACE inhibitor or an ARB more than doubled the control rate in diabetic hypertensive patients in this study. The study "confirms that the use of combination therapy is critically important in the management of hypertension -- when you do it, you need to do it early and more aggressively," Dr. Neutel said.

Background

Diabetic patients with elevated blood pressure are at greater risk of cardiovascular disease than patients without diabetes, yet most diabetic patients treated for hypertension do not achieve blood pressure goals set out by current US guidelines.[2-4] Although tight blood pressure control in diabetic patients confers even more protection than glycemic control, < 20% of these patients achieve blood pressure levels of 130/80 mm Hg.

Another factor is "therapeutic inertia," with surveys showing too many physicians accepting inadequate control, even after treatment, in these patients. Aggressive blood pressure treatment is important in these patients, and addition of a second, complementary antihypertensive drug will always be more successful in lowering blood pressure than uptitrating the first drug. "We are dealing with multifactorial disease and we have to block more than one physiologic system," Dr. Neutel said.

Study Design

Either an ACE inhibitor or an ARB is recommended as first-line therapy in diabetic patients. ADHT was a multicenter, randomized, double-blind, double-dummy study to evaluate the safety and

efficacy of adding amlodipine therapy to existing monotherapy with either the ACE inhibitor quinapril or the ARB losartan. The aim of the study was to provide more information about what can be done to get diabetic patients to goal blood pressure levels.

Patients and Treatment

Patients eligible for the trial were male or female, aged 35-75 years, with type 2 diabetes and on stable treatment ≥ 2 months before entering the study, and with glycosylated hemoglobin (HbA1c) < 9%. Blood pressure had to meet at least 1 of 4 criteria:

- Systolic blood pressure (SBP) 140-170 mm Hg and/or diastolic blood pressure (DBP) 90-110 mm Hg and not taking any antihypertensive therapy;
- SBP 140-155 mm Hg and/or DBP 85-100 mm Hg and on a single antihypertensive agent;
- SBP 135-150 mm Hg and/or DBP 80-90 mm Hg and on an antihypertensive fixed-dose combination product (1 pill); or
- SBP 135-150 mm Hg and/or DBP 80-90 mm Hg and on 2 separate antihypertensive agents (2 pills) at doses equivalent to a fixed-dose product.

After a 7- to 14-day washout period, patients were randomized to receive either quinapril 20 mg or losartan 20 mg for 4 weeks (Table). If their SBP was > 130/80 mm Hg at that time, they were uptitrated to quinapril 40 mg or losartan 100 mg for another 4 weeks, after which, if their blood pressure was still uncontrolled, they were randomized in a double-blind fashion on each arm to amlodipine 5 mg or to placebo for 6 weeks. After this time, if blood pressure remained uncontrolled, the dose of amlodipine was uptitrated to 10 mg.

Table. Study Design/Regimen

	Visit 2: Randomization	Visit 3: Uptitration	Visit 4: Add-on Amlodipine	Visit 5: Add-on Uptitration
Arm 1	Quinapril 20 mg + placebo	Quinapril 40 mg + placebo	Add amlodipine 5 mg or placebo	Add amlodipine 10 mg or placebo
Arm 2	Losartan 50 mg + placebo	Losartan 100 mg + placebo	Add amlodipine 5 mg or placebo	Add amlodipine 10 mg or placebo
Duration	4 wks	4 wks	6 wks	6 wks

Of 739 patients entered into the study at 75 sites in the United States and elsewhere, 626 completed the monotherapy stage. On monotherapy, 20% of patients achieved goal blood pressure

of ≤ 130/80 mm Hg, and 331 went on to combination therapy. Another 83 patients had blood pressure on monotherapy ≥ 160/100 mm Hg and were either dropped from the study or given open-label amlodipine.

Primary and Secondary Endpoints

Combination treatment with quinapril or losartan plus amlodipine resulted in 27.49% of patients reaching goal blood pressure goal of ≤ 130/80 mm Hg compared with 12.50% on monotherapy (overall comparison of amlodipine vs placebo: OR [95% CI] 2.73 [1.61-4.64)], *P* = .0002). This result did not vary according to whether the first-line treatment was an ACE inhibitor or an ARB. Similar results were seen for the percentage of patients reaching SBP ≤ 130 mm Hg or DBP ≤ 80 mm Hg. The mean change in blood pressure after adding amlodipine in either group was a further mean reduction of 8.19 mm Hg in SBP and 5.4 mm Hg in DBP.

Safety

No serious treatment-related adverse effects were recorded with combination therapy, and the rate of other adverse events was low and did not differ from that seen with monotherapy. As an aside, Dr. Neutel commented that when drugs with complementary effects are used in combination, there tend to be fewer side effects than when they are used as monotherapy.

Implications

According to Dr. Neutel, the results of this study add to the evidence that diabetic hypertensive patients will require multiple medications to achieve their aggressive, guideline-recommended blood pressure goals. He admitted that, ultimately, diabetic hypertensive patients will probably need 3 to 4 drugs to get to goal blood pressure. More studies need to be done to identify which are the appropriate third and fourth drugs and which 4-drug combinations are going to be most efficacious in these patients. In this study, with patients already on 2 vasodilators, the third drug would almost certainly be a diuretic, Dr. Neutel added.

Patients must get to blood pressure goal, and "we know that if we get them to goal they are going to significantly reduce their cardiovascular disease," Dr. Neutel said. "This study is an important step up, to double the control rate, but it is not enough and we need to go further." He stressed that physicians have to be much more aggressive with combination therapy and not fall into clinical inertia with these patients.

ADHT was supported by Pfizer.

References

1. Kloner RA, Neutel JM, Roth EM; the Trial Investigators. Addition of amlodipine to the antihypertensive regimen of diabetic hypertensives initiated with quinapril or losartan monotherapy more than doubles blood pressure goal attainment: Results from the Amlodipine Diabetic Hypertension Efficacy Response Evaluation Trial (ADHT). Program and abstracts from the American Society of Hypertension 21st Annual Scientific Meeting and Exposition; May 16-20, 2006; New York, NY. Recent and Late Breaking Clinical Trials.
2. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-1252. Abstract
3. American Diabetes Association. Treatment of hypertension in patients with diabetes. Diabetes Care. 2003;26(Suppl 1):S80-S82. Abstract
4. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-S290.