# New Direct Renin Inhibitor as Monotherapy or in Combination with Hydrochlorothiazide Controls Blood Pressure

Aliskiren, the first orally active direct renin inhibitor, chronically suppresses the entire renin-angiotensin-aldosterone system (RAAS) by targeting the system at its point of activation, resulting in definitive 24-hour blood pressure control, said researchers at the 21st Annual Scientific Meeting and Exposition of the American Society of Hypertension.

Phase 3 data on aliskiren demonstrated antihypertensive efficacy when used as monotherapy and in combination with hydrochlorothiazide. Aliskiren inhibits the angiotensin cascade at its point of activation, said Jerry Mitchell, MD, PhD, chairman and CEO of the Texas Center for Drug Development, Houston, whereas angiotensin-converting enzyme inhibitors and angiotensin receptor blockers interrupt the RAAS further downstream. Aliskiren produces a decline in plasma renin activity (PRA), which is believed to be important in end-organ protection. Independent of other risk factors, PRA is a strong predictor of myocardial infarction.

Dr Mitchell presented data from 216 patients with mild-to-moderate hypertension who had 24-hour ambulatory blood pressure monitored over 8 weeks (ASH 2006. Abstract P209). As part of a larger study, patients had been randomized to placebo or 1 of 3 doses of aliskiren (150, 300, or 600 mg daily). "All 3 [aliskiren] treatment groups were highly statistically effective at lowering blood pressure," he said. Reductions in mean ambulatory systolic blood pressure were superior to placebo by 11.4 mm Hg (150 mg), 10.5 mm Hg (300 mg), and 11.7 mm Hg (600 mg) (all $P$ <.0001). Reductions in

24-hour ambulatory diastolic blood pressure were also significantly better with all doses of aliskiren compared with placebo ($P$ <.0001).

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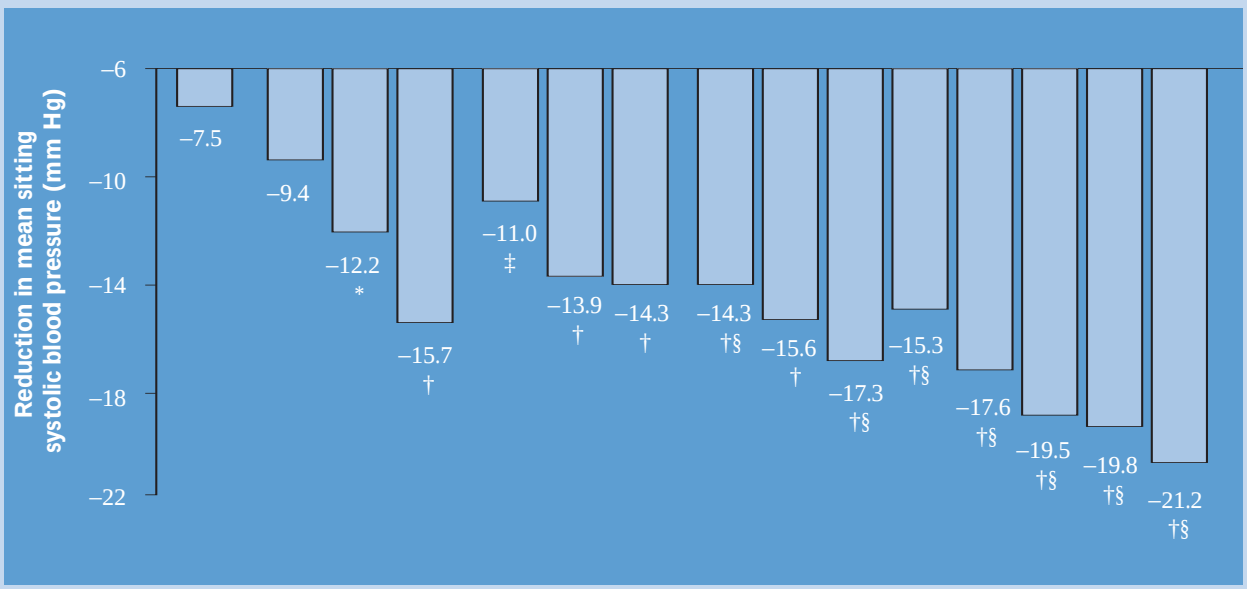
>
> *—Jerry Mitchell, MD, PhD*

"There was no morning surge in blood pressure [with aliskiren]," said Dr Mitchell. "The drug works throughout the 24-hour cycle. It is important that antihypertensive therapy provides smooth 24-hour blood pressure control, as variability and early morning surges are associated with inferior cardiovascular and renal outcomes and suboptimal end-organ protection."

In a trial presented by lead investigator Alberto Villamil, MD, from Fundapres, Las-Heras, Buenos Aires, Argentina, aliskiren in combination with hydrochlorothiazide achieved greater reductions in sitting blood pressure than either monotherapy. This study included 2776 patients who were randomized to placebo, aliskiren (75, 150, or 300 mg), hydrochlorothiazide (6.25, 12.5, or 25 mg), or combinations of the 2 drugs for 8 weeks (ASH 2006. Abstract P228). Aliskiren produced a dose-dependent reduction in blood pressure. A mean reduction of 21.2/14.3 mm Hg in sitting blood pressure was achieved with the aliskiren 300 mg/hydrochlorothiazide 25-mg combination ($P$ <.001 vs placebo) (Figure 1).

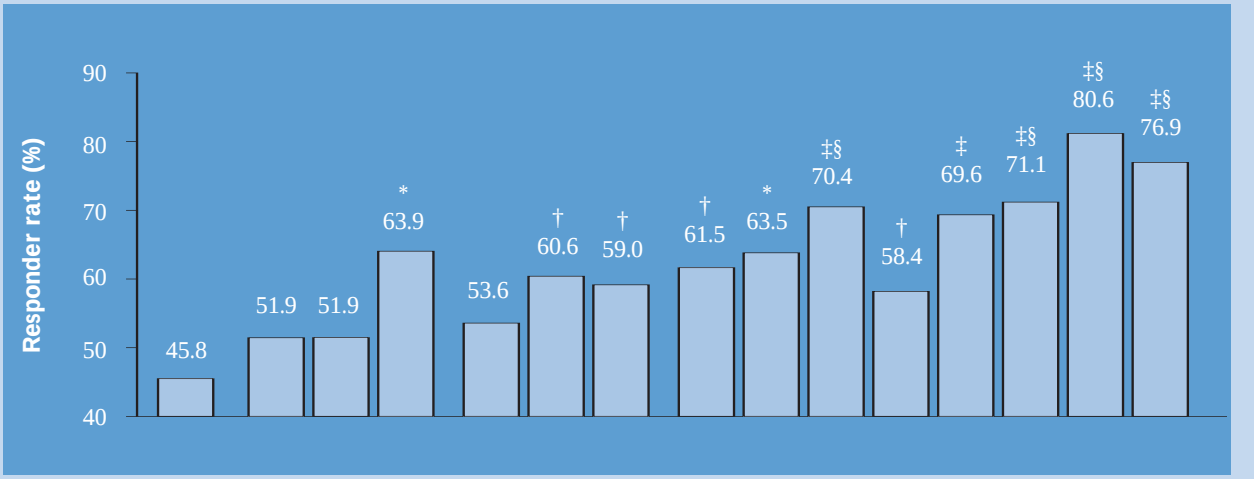
**Figure 1.** Change from Baseline in Mean Sitting Systolic Blood Pressure After 8 Weeks of Treatment




$P$ <.0001.
Overall significance of HCTZ effect not tested.
Pairwise comparisons: *$P$ <.001, †$P$ <.0001 vs placebo; ‡$P$ <.05, §$P$ <.05 vs each component monotherapy.
HCTZ indicates hydrochlorothiazide.

**Figure 2.** Responder Rates After 8 Weeks of Treatment

- **Responder rates were higher with aliskiren and HCTZ combination therapy than with component monotherapies.**




Pairwise comparisons: **P* <.001, †*P* <.05, ‡*P* <.0001 vs placebo; §*P* <.05 vs each component monotherapy.
HCTZ indicates hydrochlorothiazide.

Combination therapy increased the proportion of responders compared with either monotherapy. The responder rate, defined as a final achieved sitting diastolic blood pressure <90 mm Hg or at least a 10-mm Hg reduction in sitting diastolic blood pressure, was significantly higher with aliskiren 300 mg (64%) and all combinations (58%-81%) than with placebo (46%) (Figure 2).

The incidence of adverse events was similar between the aliskiren and placebo groups, headache and nasopharyngitis being the most common adverse events in both the placebo and treatment groups, said Dr Villamil. Discontinuation due to adverse events occurred in 0% to 4.4% of the aliskiren groups compared with 3.6% of the placebo group.

Reporting on a third study with aliskiren, James Herron, MD, Herron Medical Center, Ltd, Chicago, stated that after 8 weeks of treatment, an abrupt discontinuance did not result in rebound increases in blood pressure (ASH 2006. Abstract P193). Blood pressure lowering persisted for at least 2 weeks after withdrawal, a pharmacodynamic benefit most likely secondary to the 40-hour half-life of aliskiren. This sustained effect may prove to be of clinical benefit to those who occasionally miss doses.