Aliskiren, a Novel Orally Effective Renin Inhibitor, Provides Dose-Dependent Antihypertensive Efficacy and Placebo-Like Tolerability in Hypertensive Patients

Alan H. Gradman, MD; Roland E. Schmieder, MD; Robert L. Lins, MD, PhD; Juerg Nussberger, MD; Yanntong Chiang, PhD; Martin P. Bedigian, MD

Background—Stopping the detrimental effects of the renin-angiotensin system at the most upstream point of the cascade offers theoretical advantages for cardiovascular protection. This study compares the antihypertensive efficacy and safety of the novel oral renin inhibitor aliskiren with placebo and an active comparator.

Methods and Results—The study was a randomized, multicenter, double-blind, placebo-controlled, active-comparator 8-week trial in patients with mild-to-moderate hypertension (mean sitting diastolic blood pressure [DBP] ≥95 and <110 mm Hg). After a 2-week, single-blind placebo run-in, 652 patients were randomized to receive double-blind treatment with once-daily oral doses of aliskiren (150, 300, or 600 mg), irbesartan 150 mg, or placebo. Aliskiren 150, 300, and 600 mg effectively lowered both trough mean sitting DBP and systolic blood pressure (SBP) (P<0.001 versus placebo for both variables). The least-squares mean reductions in trough DBP were 9.3±0.8, 11.8±0.8, and 11.5±0.8 mm Hg, respectively, versus 6.3±0.8 mm Hg for placebo, and the least-squares mean reductions in trough SBP were 11.4±1.3, 15.8±1.2, and 15.7±1.2 mm Hg, respectively, versus 5.3±1.2 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was comparable to that of irbesartan 150 mg (8.9±0.7 and 12.5±1.2 mm Hg, least-squares reduction in mean sitting DBP and SBP, respectively, for irbesartan). Aliskiren 300 and 600 mg lowered mean sitting DBP significantly more than irbesartan 150 mg (P<0.05). Aliskiren showed safety and tolerability comparable to those of placebo and irbesartan; the incidence of adverse events and number of patients discontinuing therapy were similar in all groups.

Conclusions—Once-daily oral treatment with aliskiren lowers blood pressure effectively, with a safety and tolerability profile comparable to that of irbesartan and placebo, in patients with mild-to-moderate hypertension. Aliskiren 150 mg is as effective as irbesartan 150 mg in lowering blood pressure. (Circulation. 2005;111:1012-1018.)

Key Words: angiotensin ■ blood pressure ■ hypertension ■ renin
Aliskiren, 2(S),4(S),5(S),7(S)-N-(2-carbanoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]octanamid hemifumarate, is the first in a new class of orally effective, nonpeptide, low-molecular-weight renin inhibitors for the treatment of hypertension.10,11 Designed through a combination of molecular modeling techniques and crystal structure elucidation, aliskiren is a potent and specific inhibitor of human renin in vitro (IC\textsubscript{50} \approx 0.6 nmol/L).10,12 Oral administration of aliskiren to sodium-depleted marmosets caused complete inhibition of renin and sustained reductions in arterial BP.12 In humans, once-daily oral doses of aliskiren of up to 640 mg were well tolerated and caused dose-dependent and sustained RAS inhibition in healthy volunteers.13 Moreover, a recent study in 226 patients with mild-to-moderate hypertension showed that aliskiren 300 mg daily lowered BP with efficacy and tolerability similar to those of the ARB losartan at twice the recommended daily dose.13

The present placebo-controlled trial investigates the antihypertensive efficacy and safety of high-dose aliskiren treatment. Aliskiren was administered to patients with mild-to-moderate hypertension as once-daily oral doses of 150, 300, or 600 mg over an 8-week double-blind treatment period. The effects of aliskiren were compared with those of placebo and with those of irbesartan, an ARB with a well-established safety and efficacy profile.14

Methods

Participants

Eligible patients were men and women, age 18 years or older, with mild-to-moderate essential hypertension (mean sitting DBP \( \geq 95 \) mm Hg and \( < 110 \) mm Hg). Exclusion criteria included severe hypertension (mean sitting diastolic BP [DBP] \( \geq 110 \) mm Hg or systolic BP [SBP] \( \geq 180 \) mm Hg), secondary hypertension, type 1 diabetes mellitus, type 2 diabetes mellitus with poor glucose control (HbA\textsubscript{1c} \> 8% at screening), a history of cardiovascular disease (including heart failure, myocardial infarction, unstable angina, or transient ischemic cerebral attack), a history of malignancy or other life-threatening disease, and any medical or surgical condition that might significantly alter the absorption, distribution, metabolism, or excretion of study drugs.

All subjects gave written informed consent. The study protocol was approved by local and central institutional review boards and by the appropriate local research ethics committees. The research was performed in accordance with the Declaration of Helsinki of the World Medical Association.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel-group study. After withdrawal of previous antihypertensive medication during a 2-week washout period, eligible patients entered a single-blind placebo run-in period of 2 to 4 weeks. Patients who met the study inclusion criteria at the end of the placebo run-in were randomized to receive double-blind treatment with aliskiren 150 mg, aliskiren 300 mg, aliskiren 600 mg, irbesartan 150 mg, or placebo once daily for 8 weeks. During the treatment period, patients were asked to take the study medication with water daily at approximately 8:00 AM, except on the day of a study visit. All study personnel and participants remained blinded to the treatment assignment for the duration of the study.

Randomization with a block size of 5 and stratified by region was performed by the interactive voice response system provider using a validated system that automates the random assignment of treatment groups to randomization numbers. The regions of pooled study centers were prespecified before the start of the study. Randomization data were kept strictly confidential until completion of the study and blinded data cleaning process. Access during the study was available only to authorized persons who maintained the randomization database and were not involved in the conduct of the study. The database lock procedure was followed to merge clinical data and treatment codes for analyses after the completion of the study and data cleaning.

Before initiation of the placebo run-in period, a screening assessment was performed on all patients. This included a complete medical history, physical examination, safety laboratory tests (blood hematology, blood chemistry, and urine analysis), and a standard 12-lead ECG. Premenopausal women also underwent a serum pregnancy test. These tests were repeated at randomization; patients were eligible for randomization if they met all inclusion criteria stated above and if the absolute difference between the mean sitting DBP values recorded at visit 1 and visit 2 was \( < 10 \) mm Hg. Follow-up visits took place at 2, 4, 6, and 8 weeks after randomization. During each follow-up visit, adverse events, concomitant medication, and compliance with study medication were recorded. Safety assessments were repeated at the conclusion of the double-blind treatment period. After the follow-up visit at week 8, post-dose withdrawal BP measurements were made in patients in the withdrawn per-protocol sample at week 8.5 (between 7:00 and 10:00 AM, 3 to 4 days after the week 8 visit).

Clinic BP and Heart Rate Measurements

Sitting clinic BP was measured from the arm in which the higher sitting DBP was found at visit 1 with a calibrated, validated standard sphygmomanometer. Three measurements of sitting BP were taken from each patient at each study visit, and the average of the 3 measurements was used for analysis.

Data Analysis and Statistical Methods

All data analyses were performed using SAS Software (SAS Institute Inc). Efficacy analyses were performed on the intent-to-treat sample (all randomized patients with baseline and at least 1 postbaseline measurement during the double-blind treatment period; n=649). All statistical tests used a nominal 5% significance level (2 sided).

Assuming a standard deviation of 8 mm Hg for the primary efficacy variable (change from baseline in trough mean sitting DBP), a sample size of 525 patients who completed the study (randomized sample, 620 patients, assuming a dropout rate of 15%) was targeted, with an equal randomization ratio between the 5 treatment groups. With 105 patients who completed the study per treatment group, the present study had 90% power to detect a treatment difference of 4 mm Hg (chosen on the basis of a recent phase II study)\textsuperscript{11} between at least 1 aliskiren dose and placebo, using Dunnett’s procedure to adjust for multiple comparisons.

Two-way ANCOVA was used for the primary analysis of the primary efficacy variable, with treatment and region (randomization strata) as factors and baseline as covariate. The null hypothesis was no treatment difference among the 3 aliskiren doses (150, 300, and 600 mg) and placebo; Dunnett’s procedure was used to adjust for multiple comparisons. Pairwise comparisons with 95% confidence intervals were also performed for (1) each aliskiren dose versus placebo, (2) each aliskiren dose versus irbesartan 150 mg, and (3) irbesartan 150 mg versus placebo.

Dose-Response Analysis

The dose-response profile for aliskiren treatment was assessed at the end point using a second-order regression analysis with dose as the predictor (including placebo as zero dose). A lack-of-fit test for the model was performed. A positive dose-response was considered evident if the first-order and/or second-order coefficient was statistically significantly different from zero and the fitted relationship between trough mean sitting DBP reduction and dose level was positive.
Responder Analysis
The percentage of patients achieving BP control (defined as trough mean sitting SBP <140 mm Hg and trough mean sitting DBP <90 mm Hg) was analyzed at study end point by means of a logistic regression model with treatment and region as factors and baseline mean sitting DBP as covariate.

Trough-to-Peak Ratio
The trough-to-peak (T:P) ratio is commonly used as an index of the duration of action of antihypertensive agents, and previous guidelines for the treatment of hypertension have recommended the use of drugs with a T:P ratio >0.5. Steady-state T:P ratios were assessed in a subset of 325 patients at 2 hours after dosing at the study end point. T:P ratios for each active treatment group were calculated from least-squares mean (LSM) estimates of the change from baseline in mean sitting DBP, measured at hour 0 ("trough," immediately before dosing), and at 2, 4, or 6 hours after dosing ("peak"), as follows: \[ \frac{[\text{LSM}_{\text{A,T}} - \text{LSM}_{\text{A,P}}]}{[\text{LSM}_{\text{P,T}} - \text{LSM}_{\text{P,B}}]} \]
where LSM_{A,T} and LSM_{A,P} represent "trough" least-squares mean estimates at hour 0 for the active treatment and placebo, respectively, and LSM_{P,T} and LSM_{P,B} represent "peak" least-squares mean estimates at 2, 4, or 6 hours after dosing for the active treatment and placebo, respectively.

Withdrawal Effect
The percentage of patients showing a withdrawal effect after discontinuation of study drug was assessed in the withdrawn period; only patients with BP values at baseline, week 8, and week 8.5 were included (n=435). Withdrawal effect was defined as a higher trough mean sitting DBP or SBP at week 8.5 compared with the respective measurement at week 0 and was analyzed by use of a logistic regression model with treatment and region as factors.

Safety and Tolerability Assessments
The safety sample included all randomized patients who received at least 1 dose of study treatment and had at least 1 postbaseline safety measurement. For all adverse events, the duration, severity, relationship to the study drug, and outcome were recorded.

Results

Study Participants
Of the 793 recruited patients, 652 satisfied all inclusion criteria and were randomized to receive study treatment. Three patients without postbaseline BP readings were excluded from the intent-to-treat analyses for efficacy assessment. All randomized patients were included in the safety assessment. A total of 66 patients discontinued study treatment before the end of the trial; the proportion of patients discontinuing study treatment was similar across all 5 treatment groups. Major reasons for discontinuation of study treatment were unsatisfactory therapeutic effect (21 patients), adverse events (18 patients), withdrawal of patient consent (12 patients), protocol violation (7 patients), and loss to follow-up (6 patients). Baseline characteristics for the safety sample showed that the 5 treatment groups were well balanced (Table 1).

Effect of Study Treatments on Mean Sitting DBP and SBP
Once-daily oral treatment with each of the 3 doses of aliskiren, 150, 300, or 600 mg, significantly (P<0.001) decreased trough mean sitting DBP compared with placebo (Table 2). All doses of aliskiren also significantly (P<0.001) lowered trough mean sitting SBP compared with placebo (Table 2). Placebo-corrected changes in trough mean sitting DBP (Figure 1) and SBP (Figure 2) are presented. The effects of aliskiren on mean sitting DBP and SBP showed significant dose-dependence (P<0.001 by dose-response analysis), but only up to the 300-mg dose of aliskiren; no additional reduction in DBP or SBP was obtained with aliskiren 600 mg.

Irbesartan 150 mg also significantly (P<0.05) decreased both mean sitting DBP and SBP compared with placebo (Table 2). The antihypertensive effect of aliskiren 150 mg was comparable to that of irbesartan 150 mg (Figures 1 and 2). Aliskiren 300 mg and 600 mg lowered mean sitting DBP significantly (P<0.05) more than irbesartan 150 mg (Figure 3).
TABLE 2. Effect of Study Treatment on Blood Pressure in Mild-to-Moderate Hypertensive Patients (ITT Sample)

<table>
<thead>
<tr>
<th>Mean Value (SE)</th>
<th>Mean Value (SE)</th>
<th>Mean Value (SE)</th>
<th>Mean Value (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough sitting</td>
<td>Placebo (n=130)</td>
<td>Placebo (n=130)</td>
<td>Placebo (n=130)</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Aliskiren 150 mg (n=127)</td>
<td>Placebo (n=130)</td>
<td>Aliskiren 300 mg (n=130)</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>Aliskiren 150 mg (n=127)</td>
<td>Placebo (n=130)</td>
<td>Aliskiren 300 mg (n=130)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; SBP, systolic blood pressure. Least-squares mean, CI, and P values were obtained from an ANCOVA model containing treatment, region, baseline, and treatment by baseline. Baseline was defined as the value at week 0. Nominal P values and treatment comparisons were evaluated at the average baseline level.

Responders Analysis

Trough mean sitting DBP and SBP values at baseline and study end point and the proportion of patients who had their BP controlled by treatment (defined as mean sitting DBP <140 mm Hg and mean sitting SBP <90 mm Hg) in each treatment group are presented in Table 3. The percentage of patients achieving BP control in each of the aliskiren treatment groups and in the irbesartan 150 mg group was significantly (P<0.05) higher compared with the placebo group. In addition, the proportion of patients achieving BP control with aliskiren at doses of 300 or 600 mg was significantly higher (P<0.05) compared with irbesartan 150 mg.

Trough-to-Peak Ratio

T:P ratios for mean sitting DBP at end point are presented in Table 4. T:P ratios for aliskiren and irbesartan were markedly higher when the peak effect was determined at 2 hours compared with T:P ratios calculated at 4 and 6 hours; the true peak for BP lowering with aliskiren and irbesartan is therefore probably at approximately 6 hours after dosing. The \( t_{\text{max}} \) of aliskiren in healthy subjects is 1.8±2.1 hours (mean±SD; J. Nussberger, MD, unpublished data, 2001), and the \( t_{\text{max}} \) of irbesartan in healthy subjects is 1.5 hours; these values therefore predict higher T:P ratios observed at 2 hours, because BP reductions are a downstream effect of RAS blockade. The T:P ratio determined at 6 hours after dosing for

Figure 1. Effect of study treatment on trough mean sitting DBP in patients with mild-to-moderate hypertension. Bars indicate placebo-corrected change in trough mean sitting DBP from baseline to study end point after treatment with aliskiren 150, 300, or 600 mg (filled bars) or irbesartan 150 mg (striped bars). Data are presented as least-squares mean±SEM. *P<0.05 vs irbesartan 150 mg.

Figure 2. Effect of study treatment on trough mean sitting SBP in patients with mild-to-moderate hypertension. Bars indicate placebo-corrected change in trough mean sitting SBP from baseline to study end point after treatment with aliskiren 150, 300, or 600 mg (filled bars) or irbesartan 150 mg (striped bars). Data are presented as least-squares mean±SEM.
aliskiren, 150 mg, was similar to that observed for irbesartan 150 mg. By contrast, aliskiren 300 or 600 mg showed markedly higher T:P ratios compared with irbesartan 150 mg.

Withdrawal Effect

In the withdrawal period, a higher mean sitting DBP or SBP was observed at week 8.5 compared with week 0 in 35.6%, 15.1%, and 22.2% of patients receiving aliskiren 150, 300, and 600 mg, respectively, and in 35.8% of patients receiving placebo and 30.8% of patients receiving irbesartan 150 mg. The results indicate no evidence of a withdrawal effect.

Safety and Tolerability

Aliskiren treatment was well tolerated at all doses administered in the study (Table 5). The incidence of adverse events and the number of study discontinuations as a result of adverse effects during aliskiren treatment were relatively low and were similar to results obtained in patients treated either with placebo or with irbesartan 150 mg (Table 5). The most common adverse effects reported were headache, dizziness, and diarrhea. Headache was reported by a total of 28 patients during the course of the study; the proportion of patients reporting headache was 2.4%, 6.2%, and 4.6% with aliskiren 150 mg, 300 mg, and 600 mg, respectively, compared with 5.3% of patients treated with placebo and 3.0% of patients treated with irbesartan 150 mg. Dizziness was reported by a total of 19 patients and diarrhea by 16 patients across the 5 treatment groups during the course of the study.

Four patients (2 in the placebo group and 2 in the irbesartan group) had serious adverse events during the double-blind treatment period. One patient receiving placebo reported infective arthritis and gout, and a second placebo-treated patient suffered left ventricular failure. One patient treated with irbesartan experienced type I bipolar disorder, and a second irbesartan-treated patient reported intervertebral disc protrusion, which resulted in hospitalization. No serious adverse events occurred in the aliskiren treatment groups. There were no deaths during the course of the study.

### TABLE 3. Blood Pressure Levels and Percentage of Patients With Controlled BP at End Point in the ITT Sample

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trough Mean Sitting DBP, mm Hg</th>
<th>Trough Mean Sitting SBP, mm Hg</th>
<th>No. of Patients With Controlled BP, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline End Point</td>
<td>Baseline End Point</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>98.9 ± 3.3 92.3 ± 9.6</td>
<td>152.3 ± 12.1 147.3 ± 17.6</td>
<td>27/130 (20.8)</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>98.8 ± 3.4 89.4 ± 8.7</td>
<td>151.3 ± 11.1 140.4 ± 14.2</td>
<td>48/127 (37.8)*</td>
</tr>
<tr>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>98.8 ± 3.4 86.8 ± 9.4</td>
<td>152.1 ± 10.2 136.6 ± 13.9</td>
<td>65/130 (50.0)*</td>
</tr>
<tr>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>99.1 ± 3.7 87.5 ± 9.6</td>
<td>152.6 ± 11.5 137.0 ± 16.2</td>
<td>59/129 (45.7)*</td>
</tr>
<tr>
<td>600 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>99.4 ± 4.0 90.3 ± 9.2</td>
<td>152.8 ± 11.2 140.3 ± 16.3</td>
<td>45/133 (33.8)*</td>
</tr>
<tr>
<td>150 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DBP indicates diastolic blood pressure; SBP, systolic blood pressure. BP control was defined as trough mean sitting DBP < 90 mm Hg and trough mean sitting SBP < 140 mm Hg at end point. Data are presented as the mean ± SD unless otherwise stated. P values were determined by a logistic regression model with treatment and region as factors and baseline mean sitting DBP as a covariate. *P < 0.05 vs placebo; †P < 0.05 vs irbesartan 150 mg.
Clinical laboratory values remained normal in the majority of patients throughout the study. One patient receiving aliskiren 600 mg discontinued study treatment because of an abnormal laboratory value (elevated SGOT and bilirubin) and elevated DBP.

**Discussion**

The results of the present study clearly demonstrate that once-daily oral treatment with the novel renin inhibitor aliskiren lowers BP effectively in patients with mild-to-moderate hypertension. Aliskiren 150 mg provided an antihypertensive efficacy similar to that of the AT1-receptor blocker irbesartan 150 mg, and higher doses of aliskiren lowered mean sitting DBP significantly more effectively than irbesartan 150 mg. Moreover, aliskiren treatment showed safety and tolerability similar to those with placebo, with an incidence of adverse events comparable to that observed in the placebo and irbesartan groups.

The present study extends previous investigations of the safety and efficacy of aliskiren in patients with hypertension by evaluating the effects of aliskiren compared with a placebo group and by investigating the effects of aliskiren at a daily dose of 600 mg. Once-daily treatment with aliskiren 150, 300, or 600 mg lowered SBP and DBP significantly compared with placebo in the present study, and statistical analysis confirmed that the antihypertensive effect of aliskiren was dose-dependent up to the 300-mg dose, consistent with previous findings. The antihypertensive effect of aliskiren 150 mg and the percentage of patients responding successfully to treatment were similar compared with the AT1-receptor blocker irbesartan used at the 150-mg starting dose recommended for the treatment of hypertension. Taken together with previous evidence that aliskiren 300 mg provides similar BP lowering compared with double the recommended antihypertensive starting dose of losartan, these results indicate that monotherapy with aliskiren 150 mg is an effective treatment for hypertension. Importantly, aliskiren 300 mg lowered mean sitting DBP significantly more effectively and brought more patients to target BP levels compared with aliskiren 150 mg. These results indicate that uptitration of the dose of aliskiren could be used for additional BP lowering in patients who do not achieve BP control with aliskiren 150 mg.

Once-daily treatment with aliskiren 300 mg or 600 mg was more effective than irbesartan 150 mg in BP reduction and achieving BP control. The present study is the first to investigate the antihypertensive efficacy of aliskiren 600 mg, and it suggests that the dose-response curve for aliskiren in patients with mild-to-moderate hypertension reaches a plateau at 300 mg, with no significant further DBP or SBP reductions observed at 600 mg.

In the present study, comparison of T:P ratios with peak measurements at 2, 4, and 6 hours confirmed that the peak effect of aliskiren and irbesartan was probably observed at...
approximately the 6-hour time point. The T:P ratio for aliskiren was greater than 0.5 at all doses tested, and ratios for aliskiren 300 mg (0.74) and 600 mg (0.78) were markedly higher than those obtained with irbesartan 150 mg (0.50). The high T:P ratio of aliskiren in hypertensive patients is consistent with the long plasma half-life (approximately 24 hours) observed after oral administration of the drug to healthy subjects.13 Ambulatory BP measurements also indicate a sustained antihypertensive effect of aliskiren over the 24-hour period after dosing.11 These results confirm that aliskiren provides effective, sustained BP lowering in a once-daily oral dose regimen, an important factor for improving patient compliance with antihypertensive therapy.17

Aliskiren treatment showed a good safety and tolerability profile in the present study, consistent with previous studies in humans.11–13 Across all doses tested, aliskiren treatment was associated with a relatively low incidence of adverse events, similar to that observed in the placebo and irbesartan groups. Moreover, no withdrawal effect was observed with any dose of aliskiren treatment. As with all AT1-receptor blockers, irbesartan has a proven placebo-like safety profile,14 and our finding that aliskiren showed comparable safety and tolerability to the AT1-receptor blocker is consistent with a previous comparison of aliskiren and losartan.11 The placebo-like tolerability of aliskiren is of major clinical importance, because concern over potential adverse effects is an important factor in patient non-compliance with antihypertensive therapy.18

Recent clinical outcome trials have provided convincing evidence for the benefits of RAS blockade in a range of indications including chronic heart failure, post–myocardial infarction management, and diabetic nephropathy.19–22 RAS blockade may improve cardiovascular outcomes independently of effects on BP by preventing target-organ damage caused by RAS activation.3 Given the success of ACE inhibitors and AT1-receptor blockers in reducing morbidity and mortality across a broad range of disease states, it seems reasonable to speculate that renin inhibitors such as aliskiren may provide such benefits. Whether these benefits are equal to, greater than, or less than those seen with existing RAS inhibitors will require long-term end-point assessment studies. Aliskiren nevertheless offers the prospect of highly effective RAS inhibition for the treatment of hypertension and related cardiovascular diseases using a new pharmacological approach.

Acknowledgment
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Disclosure
Drs Bedigan and Chiang are employees of Novartis Pharmaceuticals and are therefore eligible for Novartis stock and stock options. Dr Nussberger has acted as a consultant to Speedel Pharma AG and to Novartis Pharma AG, Basel, Switzerland.

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