Aliskiren Monotherapy Results in the Greatest and the Least Blood Pressure Lowering in Patients With High- and Low-Baseline PRA Levels, Respectively

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Hypertensive patients with low-baseline plasma renin activity (PRA) are known to respond best to natriuretic drugs, and those with high PRA respond best to renin–angiotensin system (RAS) blockade. However, there has been recent speculation that blood pressure (BP)–lowering responses to the renin inhibitor, aliskiren, might also be blunted in some patients with medium-to-high baseline PRA. It has been suggested that treatment resistance in these patients may result from excessive reactive increases in renin secretion, such that aliskiren's blockade of PRA is overwhelmed. In order to test for evidence in support of this hypothesis, we conducted a reanalysis of original data from three published clinical trials of aliskiren. When aliskiren was administered as a monotherapy, or in combination with other blockers of the RAS, changes in PRA were closely correlated with baseline PRA. Patients with low-baseline PRA demonstrated small reductions or rises in PRA, rather than patients with medium-to-high baseline PRA. We confirmed that ambulatory BP-lowering responses to full dose aliskiren monotherapy were greatest and least among patients with high- and low-baseline PRA, respectively. However no such association was demonstrated during aliskiren combination therapy. With either monotherapy or combination therapy, no patient with a baseline PRA >0.65 ng/ml/h was observed to have a rise in both PRA and BP. We conclude, therefore, that there is only evidence for one type of resistance to aliskiren—as with all blockers of the RAS, lesser BP-lowering responses to aliskiren occur in those with the least renin to block.

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In a recently published article, Sealey and Laragh set out to investigate the causes of treatment failure of antirenin drugs, and in particular aliskiren, the first renin inhibitor to be licensed for use in hypertension in both the United States and Europe.[1] They suggested that there were two likely reasons for treatment failure with aliskiren—in addition to patients with low-baseline plasma renin activity (PRA) levels having a lesser response, they hypothesized that large reactive increases in renin secretion in some patients with medium-to-high baseline PRA could overwhelm aliskiren's blockade of PRA, and that this could lead to a paradoxical rise in blood pressure (BP). They tested this hypothesis through a reanalysis of published data from four clinical trials.[2–4] Their conclusions were as follows: "There are two reasons for treatment failure with aliskiren. Many hypertensive patients have large BP falls, but BP does not fall in most low-renin patients, or in medium-to-high renin patients whose PRA levels do not fall sufficiently."

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As investigators for three of the clinical trials used in these reanalyses, we have a number of concerns about the methodology used by Sealey and Laragh.

1. The data for this reanalysis were somewhat unusually acquired though enlargement of the published figures, calculation of the antilog of logarithmic data, and transcribing individual data points to an Excel file, a procedure that obviously has considerable potential for inaccuracies, especially when applied to sequential three-period studies of dual renin–angiotensin system (RAS) blockade, where aliskiren was administered in combination with either irbesartan or ramipril.[4]
2. The post hoc cutoffs chosen for BP responses and for low vs. medium–high baseline, PRA appears somewhat arbitrary and unusual. Rises or falls in systolic BP were considered "significant" if ≥10 mm Hg. This appears rather large, given that the average response to full dose monotherapy of any antihypertensive agent is of a similar magnitude, and the average response to a second antihypertensive agent is usually considerably less. Patients were defined as being "low-renin" if baseline PRA was ≤0.3 ng/ml/h—the more usual cutoff is ≤0.65 ng/ml/h. When this very low cutoff was applied, <20% of patients participating in these four clinical trials were classified as low-renin—comparisons of BP-lowering responses of "low-renin" and

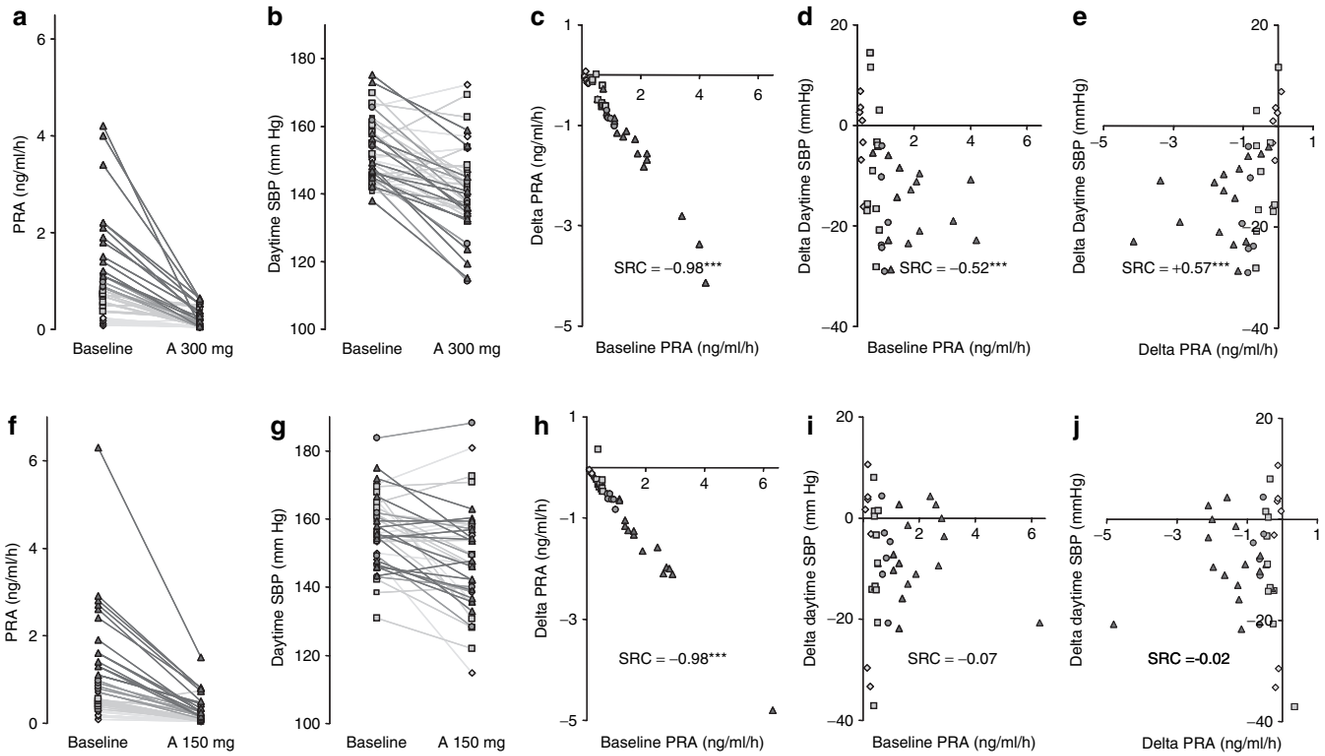
"medium-to-high-renin" patients were based on groups as small as 5 out of 37 patients treated with aliskiren 150 mg daily in the Stanton and colleagues 2003 study,[2] and 17 out of 107 patients treated with aliskiren 600 mg daily in the Nussberger and colleagues 2007 study.[3] Furthermore, probably due to the above described inaccuracies in data acquisition, it is clear that some misclassifications and omissions resulted in further erroneous group size shrinkage—the correct group numbers for the above comparisons were 7 out of 39, and 17 out of 113, respectively.

3. Lastly and importantly, although statistical analyses, in the form of independent samples *t*-tests, were applied to the question of whether BP responses differed between low-PRA patients and the medium-to-high-PRA patients, no statistical tests whatsoever were used in assessing whether there were associations between changes in PRA and changes in BP with treatment. Indeed, Sealey and Laragh were unable to evaluate whether reactive increases in renin secretion were an important cause of reduced BP-lowering responses to aliskiren—they even went so far as to admit that these analyses could not be performed as "the published data did not allow us to determine whether the patients who had a rise in PRA also had a rise in BP."[1]

We think that it would have been far more beneficial scientifically, apart from being correct procedure, if Sealey and Laragh had approached the investigators for the original data—we would have gladly shared our data with them, in our mutual interest of improving understanding into the optimal use of renin inhibitors in cardiovascular medicine. However, because this collaborative approach did not occur, we have now reexamined the original data from the three clinical trials, for which we were lead investigators.[2,4] Our objective, in performing these further analyses, was to test whether these trials provide robust evidence to support the principal conclusions of Sealey and Laragh's recent publication, namely that direct renin inhibitors, such as aliskiren, differ from other classes of RAS blockers, in that they demonstrate two types of treatment resistance or failure.

METHODS

Methods and study design of the three studies were described in detail in the original publications.[2,4] Hence only brief summaries are provided here within the figure legends. Mean daytime and night time, systolic and diastolic, ambulatory BP levels were the original primary endpoints for all three studies. Only the results for daytime systolic BP are illustrated and discussed here, as similar results were seen for daytime diastolic BP and for night time pressures. As neither baseline PRA levels nor delta PRA followed normal distributions, associations between baseline PRA, delta PRA, and ambulatory pressures were tested using Spearman's rank correlations. All analyses



[Q1] **Figure 1** | Plasma renin activity (PRA) and daytime ambulatory systolic blood pressure (BP) responses in patients, with mild-to-moderate essential hypertension, treated with aliskiren (A) monotherapy for 4 weeks. Effects of aliskiren 300 mg (**a**) on PRA and (**b**) on daytime systolic BP. Scatterplots illustrating the associations of (**c**) baseline PRA with baseline-to-end of study delta PRA, and of both (**d**) baseline PRA and (**e**) delta PRA with delta daytime systolic BP. (**f–j**) Analogous data and analyses for patients treated with aliskiren 150 mg. Data points for patients with baseline PRA ≤0.3 ng/ml/h are indicated by diamonds, ≤0.65 ng/ml/h squares, ≤1.0 ng/ml/h circles, and >1.0 ng/ml/h triangles. Spearman's rank correlation coefficients (SRC) and their significance (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$) are shown.

treated baseline PRA, delta PRA, and ambulatory pressures as continuous variables. However, in the interests of total transparency, in the figures, we also color coded data from patients according to baseline PRA—we used both the very low cutoff of Sealey and Laragh for distinguishing low vs. medium-high baseline PRA of ≤0.3 ng/ml/h, and a more standard cutoff of ≤0.65 ng/ml/h.

RESULTS

BP responses to aliskiren monotherapy

Figure 1 confirms that BP-lowering responses to high-dose aliskiren monotherapy (300 mg daily, **Figure 1d**) were greatest in those with the highest baseline PRA, and least in those with low-baseline PRA. There was no such relationship demonstrated with lower dose aliskiren monotherapy (150 mg daily, **Figure 1i**). BP responses to aliskiren 300 mg were also blunted in patients with little reduction or rises in PRA levels (**Figure 1e**). However as **Figure 1c,h** illustrates, delta PRA was tightly correlated with baseline PRA during treatment with both doses. As indicated by Spearman's rank correlation coefficients of −0.98, in excess of 95% of the variation in delta PRA was explained by baseline PRA. **Figure 1** clearly demonstrates that it is not medium-to-high renin patients that demonstrate small reductions or rises in PRA—it is those who start out with a low-baseline PRA.

BP responses to aliskiren in combination with an angiotensin-converting enzyme-inhibitor, or an angiotensin receptor blocker

The data illustrated in **Figure 2** are from two studies looking at the BP- and PRA-lowering responses when patients are treated with aliskiren in combination with an angiotensin-converting enzyme inhibitor, ramipril, or an angiotensin receptor blocker, irbesartan. With dual RAS blockade delta PRA was once again correlated with baseline PRA (**Figure 2c,h**), albeit a weaker association than that observed with aliskiren monotherapy. In contrast to the response to aliskiren monotherapy, baseline PRA did not predict BP-lowering responses to dual RAS blockade (**Figure 2d,i**). Also in contrast with the response to monotherapy, BP lowering with the irbesartan and aliskiren combination tended to be greatest in those that demonstrated a rise in PRA (**Figure 2j**), but this trend did not achieve standard statistical significance (Spearman's rank correlation −0.42, $P = 0.07$). In both studies, BP was lowered in the majority of patients—there were a few individuals in whom BP rose, but none of these demonstrated an increment in PRA (**Figure 2e,j**).

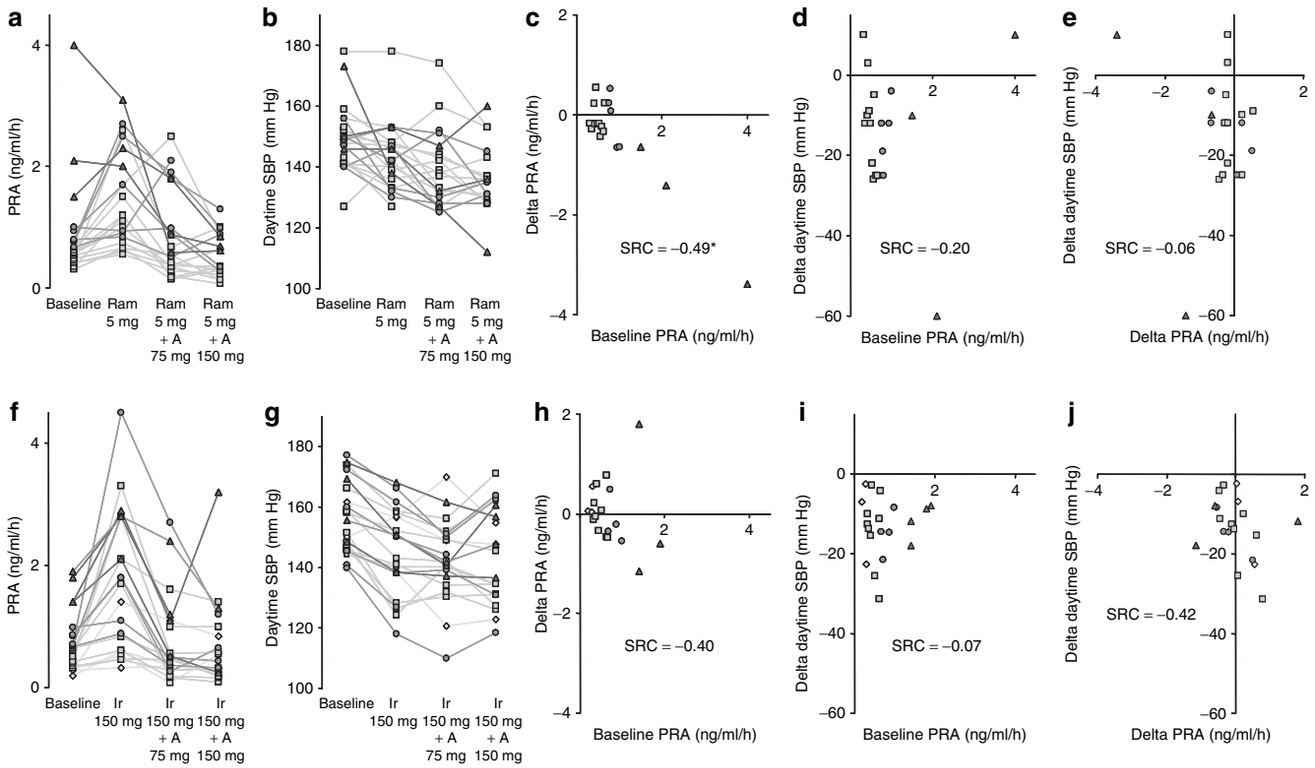


Figure 2 | Plasma renin activity (PRA) and daytime ambulatory systolic blood pressure (BP) responses in patients, with mild-to-moderate essential hypertension, initially treated with ramipril (R) 5 mg daily or irbesartan (Ir) 150 mg daily for 3 weeks. Aliskiren (A) 75 mg was added during the second 3-week period. The dose of aliskiren was increased to 150 mg daily for the final 3 weeks of both studies. Effects of ramipril (5 mg) alone or in the presence of aliskiren (75 and 150 mg) (**a**) on PRA and (**b**) on daytime systolic BP. Scatterplots illustrating the associations of (**c**) baseline PRA with baseline-to-end of study delta PRA, and of both (**d**) baseline PRA and (**e**) delta PRA with delta daytime systolic BP. (**f–j**) Analogous data and analyses for patients treated with irbesartan (150 mg) and aliskiren (75 mg and 150 mg) in combination. Data points for patients with baseline PRA ≤0.3 ng/ml/h are indicated by diamonds, ≤0.65 ng/ml/h squares, ≤1.0 ng/ml/h circles, and >1.0 ng/ml/h triangles. Spearman's rank correlation coefficients (SRC) and their significance (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$) are shown.

DISCUSSION

Our findings confirm that ambulatory BP-lowering responses to full dose aliskiren monotherapy are greatest and least among patients with high- and low-baseline PRA, respectively. Delta PRA was also correlated with BP responses. However baseline PRA and delta PRA were very tightly correlated with each other. Within individual variability in PRA with time, regression to the mean, and the fact that patients with a low-baseline PRA have little renin enzymatic activity to block are all likely to have contributed to this phenomena. The implications of the very close association between baseline PRA and delta PRA, is that patients with low-baseline PRA are the same patients that demonstrate small reductions or rises in PRA. Hence for monotherapy, these data only identified a single patient group who exhibit a lesser response to aliskiren, namely patients with "no renin to block." Furthermore these data suggest that neither measurement of on-treatment PRA, nor calculation of delta PRA, is of clinical utility, as no additional prediction of BP-lowering response is gained.

With dual RAS blockade, we found no statistically significant direct association between either baseline PRA or delta PRA with BP lowering. In fact BP lowering tended to be greater among those with an increment in PRA. We certainly acknowledge there are important limitations to these two clinical trials of dual RAS blockade; relatively low doses of aliskiren, ramipril, and irbesartan were used; and the trials were neither designed nor powered to comprehensively examine relationships between PRA- and BP-lowering responses. Nonetheless, they provide no evidence whatsoever in favor of Sealey and Laragh's hypothesis that treatment failure with aliskiren combination therapy is more likely, either where baseline PRA is low, or where an insufficient reduction or a reactive rise in PRA levels occurs in medium-to-high renin patients. It would be informative if similar analyses to those of this paper are conducted on studies such as that of Oparil and colleagues,[5] where aliskiren 300 mg daily was administered in combination with full dose valsartan (320 mg)—both PRA and ambulatory BP monitoring data are available from a large number of participants in this clinical trial.

The conclusions of Sealey and Laragh's article were that there are two reasons for "treatment failure with aliskiren" or "BP resistance to aliskiren": (i) no renin to block in low-renin patients or (ii) an insufficient reduction or even a reactive rise in PRA levels in medium-to-high renin patients. The first reason for a reduced response to aliskiren is shared by all blockers of the RAS,[6] and has previously been described and commented on for aliskiren within the original three publications.[2–4] When we sought evidence for the second reason, we found that patients with medium-to-high baseline PRA universally demonstrated a large decrement in PRA with aliskiren monotherapy. With dual RAS blockade regimens which included aliskiren, no patient was observed to have a rise in both PRA and BP. The short title for Sealey and Laragh's article is given as "Two Types of BP Resistance to Aliskiren". We think that, to date, only one type of BP resistance has been clearly demonstrated—as with all blockers of the RAS, lesser BP-lowering responses to aliskiren monotherapy appear to be more common in patients with low PRA at baseline.

Disclosure: A.V.S. has had research contracts with Novartis, Speedel Pharma, Servier, Pfizer, and Boehringer Ingelheim in the past 5 years. She has received honoraria for speaking engagements on behalf of Novartis, Speedel Pharma, Servier, and Pfizer, and has served on an advisory board for Novartis. P.D. has no conflicts of interest to disclose. E.T.O. has had research contracts with Speedel Pharma, Servier, Pfizer, and Boehringer Ingelheim in the past 5 years. He has received honoraria for speaking engagements and acted in an advisory capacity on behalf of a number of pharmaceutical companies.

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