Efficacy of Eplerenone Added to Renin-Angiotensin Blockade in Hypertensive Patients

Henry Krum, Hector Nolly, Diane Workman, Weizhong He, Barbara Roniker, Scott Krause, Kaffa Fakouhi

Abstract—The efficacy and tolerability of eplerenone, a selective aldosterone blocker, was assessed when added to existing antihypertensive therapy with an ACE inhibitor or an angiotensin II receptor blocker (ARB). Hypertensive patients (n=341) whose blood pressure (BP) was not controlled despite ACE inhibitor or ARB were randomized (double-blind) to receive 50 mg eplerenone (increasing to 100 mg if required) once daily or placebo for 8 weeks. Diastolic and systolic BP and adverse events were recorded. By study end (week 8), mean seated diastolic BP was significantly reduced from week 0 among patients receiving eplerenone/ARB (−12.7±0.81 mm Hg) compared with those receiving placebo/ARB (−9.3±0.83 mm Hg). The change in mean seated diastolic BP was −9.9±0.88 mm Hg in eplerenone/ACE inhibitor patients and −8.0±0.86 mm Hg in placebo/ACE inhibitor patients (P=NS). Systolic BP levels were also significantly lower at week 8 for eplerenone/ACE inhibitor (−13.4±1.35 mm Hg) and eplerenone/ARB (−16.0±1.37 mm Hg) patients, respectively, compared with placebo/ACE inhibitor (−7.5±1.31 mm Hg) and placebo/ARB patients (−9.2±1.41 mm Hg). Adverse events were generally nonsevere and not significantly different between eplerenone and placebo. This study demonstrated that in patients whose BP was not controlled with an ACE inhibitor or ARB, the addition of eplerenone over an 8-week period significantly lowered systolic BP in both groups and diastolic BP in ARB patients. Selective aldosterone blockade with eplerenone, therefore, may be useful add-on therapy in hypertensive patients inadequately controlled on ACE inhibitor or ARB alone. (Hypertension. 2002;40:117-123.)

Key Words: aldosterone ■ angiotensin-converting enzyme inhibitors ■ receptors, angiotensin ■ eplerenone
2 drugs with differing mechanisms of action, however, may provide additional antihypertensive efficacy with a lower incidence of adverse effects.\textsuperscript{8,17,18}

Because aldosterone production is not always adequately controlled with current inhibitors of the RAAS pathway, the combination of a selective aldosterone blocker with other antihypertensive drugs may be a rational treatment option. Eplerenone, the first available selective aldosterone blocker, has a low binding affinity for androgen and progesterone receptors, and has demonstrated antihypertensive efficacy in clinical trials.\textsuperscript{13,14,19–21} The present study was designed to examine the safety, tolerability, and antihypertensive efficacy of eplerenone when added to patients with mild to moderate hypertension not adequately controlled on an ACE inhibitor or ARB as monotherapy.

Methods

This was a multicenter, placebo run-in, double-blind, randomized, placebo-controlled, parallel-group study conducted at 45 sites in the United States, Australia, Canada, Argentina, Brazil, and Mexico. The study protocol was approved by institutional review boards at each study site. The studies were conducted in accordance with the Declaration of Helsinki and with use of good clinical practice. All patients provided written informed consent before participation.

Study Population

The eligible patient was a man or nonpregnant women between 18 and 85 years of age who was taking a fixed dose of an ACE inhibitor or an ARB (which could be a component of a multiple antihypertensive therapy regimen) and had a history of mild to moderate hypertension, or who was taking a fixed dose of one ACE inhibitor or one ARB alone and had current hypertension (defined as diastolic BP $\geq 95$ mm Hg and $<110$ mm Hg and systolic BP $<180$ mm Hg).

In addition, eligible patients had an ECG without arrhythmia, no clinically significant abnormal clinical laboratory values, and serum potassium level $\geq 3.0$ mEq/L and $\leq 5.0$ mEq/L. To qualify for randomization, all patients had to demonstrate between 80% and 120% medication compliance during the single-blind placebo lead-in period, and women of childbearing potential had to have a negative pregnancy test result.

Patients were not eligible for the study if they had any of the following: secondary, severe, or malignant hypertension; a history of myocardial infarction; coronary revascularization; unstable angina pectoris or arrhythmias requiring treatment during the previous 6 months; a history of class II through IV congestive heart failure or severe aortic or mitral valvular disease requiring medical treatment or causing hemodynamically significant disturbances; stroke or transient ischemic attack within the previous 6 months; concurrent use of other hypertensives, including diuretics, $\alpha$-blockers, $\beta$-blockers, or calcium channel blockers; insulin-dependent or uncontrolled diabetes mellitus; evidence of alcohol or drug abuse; known hypersensitivity to eplerenone. ACE inhibitors, or ARBs; a gastrointestinal disorder that may interfere with the pharmacokinetics of eplerenone, ACE inhibitors, or ARBs; a serious comorbid condition; or use of any other investigational medication 30 days before the study.

Study Design

The study was designed to assess the tolerability and efficacy of eplerenone (compared with placebo) when added to fixed-dose therapy with a single ACE inhibitor or ARB. The study consisted of 3 stages: a 1- to 2-week pretreatment screening period, a 2- to 4-week single-blind placebo run-in period, and an 8-week double-blind treatment period (Figure 1). Patients were stratified according to whether they were receiving treatment with an ACE inhibitor or ARB and were then allocated within each group to receive eplerenone or placebo in a 1:1 ratio according to a computer-generated randomization schedule.

The pretreatment screening period gave patients on multiple antihypertensive therapy regimens an opportunity to remain on monotherapy with an ACE inhibitor or ARB alone while withdrawing additional therapies. All eligible patients then entered the single-blind placebo run-in period on such monotherapy. If BP entry criteria were met at the end of this period (diastolic BP $\geq 95$ mm Hg and $<110$ mm Hg and systolic BP $<180$ mm Hg), patients then entered the 8-week double-blind treatment period, randomized to receive either eplerenone or placebo in addition to the background ACE inhibitor or ARB.

In addition to background ACE inhibitor or ARB monotherapy, patients initially received eplerenone 50 mg or placebo once daily for 2 weeks during the double-blind treatment period; they remained on this dose throughout the study if diastolic BP was controlled ($<90$ mm Hg). If BP was still uncontrolled at the end of week 2 or became uncontrolled by weeks 4 or 6, the study medication was increased to eplerenone 100 mg or placebo once daily. If BP remained uncontrolled at week 6 in patients who had received the increased dose at weeks 2 or 4, they were withdrawn from the study (Figure 1).

Study Assessments

BP, heart rate, and hematologic and biochemistry values were assessed at the initial screening. Subsequent to this, BP, heart rate, concomitant medications, adverse events, and serum potassium levels were assessed at weeks 0, 2, 4, 6, 8, and 9 after randomization. The visit on week 9 was a safety visit 1 week $\pm 3$ days after the last dose of double-blind medication and consequently was not used for analysis. Hematology and biochemistry evaluations and urinalysis were conducted at weeks 0, 8, and 9 after randomization, and plasma renin and serum aldosterone were determined at weeks 0 and 8 after randomization. A 12-lead ECG and physical examination were conducted at screening and week 9 after randomization.

BP was measured using a well-calibrated manual mercury sphygmomanometer. After 5 minutes of rest in the seated position at each clinic visit, 3 measurements of seated BP, separated by 3 to 5 minutes, were obtained for each patient. Measurements were taken consistently from the same arm using the same cuff size. The mean
of the second and third readings was used in all calculations and analyses.

Study Endpoints
The primary endpoints of the study were a comparison between mean change from baseline of trough cuff seated diastolic BP and systolic BP at week 8 in patients who received either eplerenone or placebo. These evaluations were made separately for those receiving background treatment with either an ACE inhibitor or ARB. Other endpoints were the incidence of adverse events; mean change from baseline in hematology, biochemistry, and urinalysis parameters; and mean change from baseline in plasma renin and serum aldosterone at week 8. The percentage of responders, defined as patients who had a diastolic BP <90 mm Hg or exhibited ≥10 mm Hg reduction from baseline, was also assessed.

Statistical Methods
A sample size of 60 patients per group was planned to provide a 90% power to detect a difference of at least 4.8 mm Hg in seated cuff–assessed diastolic BP at trough plasma levels between baseline and week 8. A SD of 8 mm Hg was assumed, and differences were detected with a 2-sided test at the 5% level. The intent-to-treat population included all patients who had at least 1 postbaseline assessment. Missing values were computed using a last-observation-carried-forward method. All randomized patients who took at least 1 dose of medication in the double-blind stage of the study were included in the safety analyses. All statistical analyses were conducted separately for the ACE inhibitor and ARB groups.

Treatment groups were compared for continuous variables, such as age, using a 1-way ANOVA model. Categorical variables such as sex and race were evaluated using Pearson χ² tests. Changes between baseline and week 8 in seated trough cuff-assessed diastolic and systolic BP, plasma renin, serum aldosterone, and in laboratory test results between groups, were evaluated using a 2-way ANCOVA, with baseline as the covariate and with treatment and center as cofactors. Within the treatment group, changes between baseline and endpoint were analyzed using a paired t test. Response rates were compared with the Cochran-Mantel-Haenszel test stratified by center. The results from small centers were pooled to prevent artificial effects of severe imbalances in patient counts among centers. Adverse events were coded and summarized by treatment groups and body system. Geometric means are shown for RAAS hormone data at baseline and week 8. Endpoint and treatment effect is presented as the mean percent change from baseline in RAAS hormone data. Data are presented as mean±SD, except where specifically stated otherwise.

Results
Patient Disposition and Baseline Characteristics
Of 341 patients who entered the study, 177 were receiving ACE inhibitors and 164 were taking an ARB (Table 1). Enalapril (34.5%), lisinopril (18.6%), quinapril (11.9%), and ramipril (11.3%) were the most commonly used ACE inhibitors (135 of the 177 patients taking these agents). ARBs used were losartan (29.3%), irbesartan (24.4%), telmisartan (17.1%), candesartan (16.5%), and valsartan (12.8%) in the whole group taking these agents. Doses of ACE inhibitor and ARB were similar in those randomized to eplerenone and placebo. There were no significant differences in baseline parameters among the 4 treatment groups in terms of gender, age, ethnicity, weight, BP, or heart rate (Table 1).

A total of 96 patients did not complete the study, including 59 in the ACE inhibitor group and 37 in the ARB group. Study withdrawal was owing to treatment failure in 66 patients (placebo/ACE inhibitor, 26; eplerenone/ACE inhibitor, 15; placebo/ARB, 17; and eplerenone/ARB, 8). Other reasons for withdrawal were for adverse events (5), lost to follow-up (4), protocol noncompliance (5), preexisting pro-
protocol violation (5), or other reasons (11). There was no difference between any of the treatment groups in the rate of withdrawal for any of these reasons.

**BP Changes**

Significant differences in change in systolic BP from week 0 were demonstrated between the eplerenone/ACE inhibitor group and the placebo/ACE inhibitor group at week 8 (eplerenone/ACE inhibitor $-13.4 \pm 1.35$ mm Hg versus placebo/ACE inhibitor $-7.5 \pm 1.31$ mm Hg) (Figure 2A). No difference in the change in diastolic BP was seen, however, between eplerenone/ACE inhibitor and placebo/ACE inhibitor at week 8, (eplerenone/ACE inhibitor $-9.9 \pm 0.88$ mm Hg versus placebo/ACE inhibitor $-8.0 \pm 0.86$ mm Hg) (Figure 2B).

The change in systolic BP levels for eplerenone/ARB patients was significantly greater than that for placebo/ARB patients at week 8 (eplerenone/ARB $-16.0 \pm 1.37$ mm Hg versus ARB/placebo $-9.2 \pm 1.41$ mm Hg) (Figure 2C). Change in diastolic BP from for eplerenone/ARB recipients was significantly greater than that for those receiving placebo/ARB at week 8 (eplerenone/ARB $-12.7 \pm 0.81$ mm Hg versus placebo/ARB $-9.3 \pm 0.83$ mm Hg) (Figure 2D).

At week 8, 87.8% of eplerenone/ARB patients and 73.8% of placebo/ARB patients were responders ($P=0.003$). No significant difference in response rate was observed between eplerenone/ACE inhibitor recipients and placebo/ACE inhibitor patients throughout the entire course of study.

Eplerenone had no significant effect on heart rate during the study, whether used in combination with an ACE inhibitor or an ARB. The mean change in heart rate from baseline ranged from $-1.0$ to $1.5$ bpm.

**Neurohormonal Parameters**

Whereas minor changes in neurohormonal levels from week 0 were observed in the placebo/ACE inhibitor and placebo/ARB groups, total plasma renin concentrations were increased by 71.7% in eplerenone/ACE inhibitor patients and by 67.3% in eplerenone/ARB patients (Table 2). Mean serum aldosterone concentrations increased from baseline by 85.3% in the eplerenone/ACE inhibitor group and 60.5% in the eplerenone/ARB group.

### Table 2. Geometric Mean and Mean Percent Change from Baseline in RAAS Hormones

<table>
<thead>
<tr>
<th>Neurohormonal Parameter</th>
<th>Placebo</th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td>Week 8</td>
<td>% Change</td>
<td>Base</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total plasma renin, mU/L</td>
<td>191.9</td>
<td>178.7</td>
<td>$-7.2$</td>
<td>169.7</td>
</tr>
<tr>
<td>Active plasma renin, mU/L</td>
<td>21.5</td>
<td>24.2</td>
<td>13.4</td>
<td>23.9</td>
</tr>
<tr>
<td>Serum aldosterone, ng/dL</td>
<td>6.9</td>
<td>6.7</td>
<td>$-2.3$</td>
<td>7.1</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total plasma renin, mU/L</td>
<td>186.7</td>
<td>176.2</td>
<td>$-5.8$</td>
<td>176.0</td>
</tr>
<tr>
<td>Active plasma renin, mU/L</td>
<td>23.2</td>
<td>24.2</td>
<td>4.5</td>
<td>24.6</td>
</tr>
<tr>
<td>Serum aldosterone, ng/dL</td>
<td>7.4</td>
<td>6.9</td>
<td>$-10.7$</td>
<td>7.8</td>
</tr>
</tbody>
</table>

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Figure 2. Mean change from baseline for systolic (A and C) and diastolic (B and D) BP with placebo (dotted line) or eplerenone (solid line) added to patients receiving background ACE inhibitor or ARB over the 8-week study period ($*P=0.05$ vs corresponding value for ACE inhibitor/placebo and ARB/placebo).
Safety and Tolerability

A total of 136 (40%) patients reported at least 1 adverse event (Table 3). These were generally mild to moderate, although 4 events, all in the ACE inhibitor group, were considered to be serious: aggravated hypertension with addition of placebo and syncope, inguinal hernia (leading to hospitalization), and myocardial infarction (leading to death) with addition of eplerenone. None of the 3 serious adverse events in the eplerenone/ACE inhibitor group withdrew, one because of impotence. Two patients in the placebo/ACE inhibitor group withdrew because of headache, diarrhea, and micturition frequency. There were no reports of gynecomastia, menstrual disturbances, or hypotension in any study patient.

One patient in the eplerenone/ARB group withdrew because of headache and moderate orchitis and one male patient in this group withdrew because of impotence. Two patients in the eplerenone/ACE inhibitor group withdrew, because of aggravated hypertension and the other because of myocardial infarction. Finally, 2 patients in the placebo/ACE inhibitor group withdrew because of headache, diarrhea, and micturition frequency. There were no reports of gynecomastia, menstrual disturbances, or hypotension in any study patient.

The mean changes from baseline in laboratory values are shown in Table 4. No statistically significant differences were observed between the placebo/ACE inhibitor and eplerenone/ACE inhibitor groups in any of the selected laboratory variables. In contrast, statistically significant, but clinically unimportant, differences were observed between the placebo/ARB and eplerenone/ARB groups for a number of variables; all of the changes remained within normal ranges for each treatment group. No patient had a serious adverse event or was prematurely discontinued from the study because of an adverse event of hyperkalemia. Only 1 patient in the eplerenone/ACE inhibitor cohort experienced an adverse event of mild hyperkalemia (5.5 mmol/L) after 17 days of treatment. However, the potassium level returned to normal (4.9 mmol/L) by the end of the study, without adjustment of study medication. The investigator considered the event to have an uncertain attribution to study medication. No other eplerenone patients had potassium values that met the laboratory criteria for an event of special interest.

Discussion

This study demonstrated that, compared with placebo/ARB, eplerenone 50 mg or 100 mg/ARB significantly lowered diastolic BP from baseline. The difference between eplerenone/ACE inhibitor and placebo/ACE inhibitor on diastolic BP did not reach statistical significance. The effect of eplerenone on systolic BP was even more notable than its effect on diastolic BP, with significant reductions from baseline compared with placebo in ARB and ACE inhibitor patients. The addition of eplerenone to ACE inhibitors or ARBs was associated with increased levels of total renin, active renin, and serum aldosterone, which supports previous findings that eplerenone blocks the actions of aldosterone at the level of receptor antagonism.

Eplerenone, when coadministered with either an ACE inhibitor or an ARB, appeared to be well tolerated compared with placebo, with no reports of gynecomastia, impotence, menstrual disorders, or hypotension during the 8-week treatment period. Serious adverse events were low and not significantly different between patients receiving eplerenone and placebo, additional to ACE inhibitor or ARB. Only 1 patient (eplerenone/ACE inhibitor cohort) experienced an adverse event of mild hyperkalemia after 17 days of treatment, but the potassium level returned to normal by the end of the study without adjustment of study medication. It must be emphasized, however, that this study was of only 8 weeks in duration. Clinically significant hyperkalemia generally occurs soon after commencement of aldosterone blockade, especially when added to ACE inhibitor or ARB. Thus, the low rate of this event occurring within the 8-week duration of the double-blind period of the present study suggests that the long-term event rate for this side effect may be low. In support of this, recent studies of up to 9 months in patients with hypertension record low clinically significant hyperkalemia rates either alone or in combination with an ACE inhibitor.20,21

Less clear is the timing of the occurrence of the endocrine side effects (gynecomastia, altered menses) frequently observed with agents such as spironolactone. Clearly, 8 weeks is
not a long enough period to make these assessments in the present study. Nevertheless, the absence of these adverse events in the present study is mirrored by the low incidence of these side effects in longer-term studies of hypertensive patients receiving eplerenone.20,21

There have been very few studies of additive effect of 2 neurohormonal antagonist drugs in patients with hypertension. In this context, the magnitude of background renin-angiotensin blockade is of considerable importance. In the present study, patients were receiving at least moderate doses of ACE inhibitor and ARB. These doses reflect usual clinical practice in the management of the hypertensive patient requiring multiple BP-lowering agents and, thus, are of practical relevance to the future prescribing of eplerenone in this setting. However, the mechanistic question of whether eplerenone significantly lowers BP in patients force-titrated to artificially high doses of background ACE inhibitor or ARB has not been addressed by the present study.

ACE inhibitors and ARBs target angiotensin production by the RAAS; however, they do not directly block the effects of aldosterone at the receptor level or its deleterious effects on the cardiovascular system.13 Thus, addition of eplerenone to either ACE inhibitors or ARBs may more completely inhibit the adverse effects of aldosterone on relevant organs such as heart and blood vessels. Specifically, aldosterone blockade may result in greater inhibition of sodium reabsorption and expansion of intravascular volume; reduction in cardiac hypertrophy, vascular inflammation, and fibrinoid necrosis of the small arteries and arterioles; and decreased aortic collagen accumulation.13 It must be emphasized, however, that these putative benefits are very much theoretical, as, until recently, antihypertensive therapies appeared to confer similar reductions in cardiovascular morbidity or mortality for an equal lowering of BP. This has however recently been disputed, with fewer cardiovascular endpoints observed with losartan than atenolol (despite similar reductions in BP) in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study.23 Nevertheless, in the context of the present study, 8 weeks of therapy only permits assessment of BP-lowering efficacy and short-term tolerability; the study is unable to address the clinical significance of the putative mechanistic benefits of added selective aldosterone blocker therapy, as described above. It is of interest, however, that recent studies in hypertensive patients support a strong additive effect of eplerenone when combined with the ACE inhibitor enalapril on surrogate markers of end-organ damage such as echocardiographic parameters of left ventricular hypertrophy and microalbuminuria in diabetics.20,21 Further data addressing this issue with eplerenone are awaited from the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS)24 in patients with left ventricular dysfunction and symptoms of chronic heart failure early post–myocardial infarction.

**Perspectives**

Many patients with hypertension are prescribed an ACE inhibitor or ARB, based on the known benefits of RAAS blockade. If BP is not adequately controlled on either of these agents as monotherapy, additional agent(s) will be required. There are many potential options for add-on therapy, the most commonly used being diuretics. As eplerenone selectively blocks aldosterone receptors, its use in combination with

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**TABLE 4. Mean Changes in Selected Laboratory Parameters at Study Completion**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ACE Inhibitor</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Eplerenone</td>
</tr>
<tr>
<td>Potassium, n</td>
<td>89</td>
<td>84</td>
</tr>
<tr>
<td>Baseline, mmol/L</td>
<td>4.36</td>
<td>4.32</td>
</tr>
<tr>
<td>Change to week 8, mmol/L (SE)</td>
<td>0.06 (0.04)</td>
<td>0.14 (0.04)</td>
</tr>
<tr>
<td>Sodium, n</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Baseline, mmol/L</td>
<td>141.8</td>
<td>142.3</td>
</tr>
<tr>
<td>Change to week 8, mmol/L (SE)</td>
<td>0.3 (0.3)</td>
<td>−0.6 (0.3)</td>
</tr>
<tr>
<td>Magnesium, n</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Baseline, mmol/L</td>
<td>0.847</td>
<td>0.853</td>
</tr>
<tr>
<td>Change to week 8, mmol/L (SE)</td>
<td>0.002 (0.008)</td>
<td>−0.003</td>
</tr>
<tr>
<td>Blood urea nitrogen, n</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Baseline, mmol/L</td>
<td>5.85</td>
<td>5.88</td>
</tr>
<tr>
<td>Change to week 8, mmol/L (SE)</td>
<td>−0.02 (0.14)</td>
<td>0.06 (0.15)</td>
</tr>
<tr>
<td>Creatinine, n</td>
<td>82</td>
<td>73</td>
</tr>
<tr>
<td>Baseline, μmol/L</td>
<td>71.6</td>
<td>71.4</td>
</tr>
<tr>
<td>Change to week 8, μmol/L (SE)</td>
<td>1.7 (1.2)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td>Uric acid, n</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Baseline, μmol/L</td>
<td>344.3</td>
<td>339.1</td>
</tr>
<tr>
<td>Change to week 8, μmol/L (SE)</td>
<td>2.3 (5.4)</td>
<td>11.3 (7.0)</td>
</tr>
</tbody>
</table>

*P<0.05 vs value for the corresponding placebo group.
ACE inhibitor or ARB therapy may confer additional benefits as described above. These effects have not been observed with diuretics. However, longer-term studies of surrogate and major clinical cardiovascular endpoints are required to formally test this hypothesis.

This study demonstrated that, in patients whose BP was not controlled with an ACE inhibitor or an ARB, the addition of eplerenone over an 8-week period significantly lowered systolic BP in both groups and diastolic BP in ARB patients. Eplerenone appeared to be well tolerated in relation to placebo over the 8 weeks of the study. Selective aldosterone receptor blockade with eplerenone may therefore be useful add-on therapy in hypertensive patients inadequately controlled on ACE inhibitor or ARB alone.

List of Study Investigators


References

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