Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients

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Received 22 November 2011; revised 1 February 2012; accepted 16 February 2012; online publish-ahead-of-print 26 March 2012

Aims

Aliskiren is a new oral non-peptide renin inhibitor. Its effects on vascular function in human hypertension are unknown. We assessed whether aliskiren may improve peripheral endothelial function and arterial stiffness in essential hypertensive patients (EH), when compared with the angiotensin-converting enzyme-inhibitor ramipril.

Methods and results

Fifty EH received treatment with aliskiren (150–300 mg/daily) or ramipril (5–10 mg/daily) for 12 weeks, according to a randomized, open with blind endpoints, parallel group design. We studied the forearm blood flow (strain gauge plethysmography) response to intrabrachial acetylcholine, repeated under the nitric oxide synthase inhibitor N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA) (4 μmol/min), or the antioxidant ascorbic acid (8 mg/100 mL/min). Carotid-to-femoral pulse wave velocity (PWV), central blood pressure and augmentation index (AIx) were obtained by applanation tonometry. Brachial blood pressure was similarly normalized by aliskiren (from 149/94 to 136/86 mmHg) and ramipril (from 148/92 to 135/85 mmHg), as well as central blood pressure. Aliskiren increased (P<0.001) the vasodilation to acetylcholine and restored the inhibitory effect of L-NMMA on acetylcholine. Ascorbic acid, which at baseline potentiated the response to acetylcholine, no longer improved endothelium-dependent relaxation after aliskiren treatment. In contrast, ramipril failed to affect the response to acetylcholine, the lacking inhibitory effect of L-NMMA, or the potentiating effect of ascorbic acid. Pulse wave velocity was significantly (P<0.05) and similarly reduced by both drugs. Aliskiren induced a significantly (P<0.05) greater AIx reduction than ramipril.

Conclusion

Aliskiren increased nitric oxide availability in the forearm resistance arterioles of EH, an effect probably determined by an antioxidant activity, which can also contribute to improved peripheral wave reflection.

Keywords

Acetylcholine • Endothelium • Hypertension • Microcirculation • Arterial stiffness

Introduction

In essential hypertension vascular alterations, including arterial stiffness and endothelial dysfunction, are important determinants of cardiovascular events. ESH/ESC Guidelines include increased arterial stiffness among the established measures of target organ damage for the stratification of cardiovascular risk.\textsuperscript{1} In addition, endothelial dysfunction is accepted as a promoter of atherosclerosis\textsuperscript{2} and cardiovascular disease.\textsuperscript{3} Thus, the possibility to reverse these alterations is considered an adjunctive advantage for antihypertensive pharmacological treatment.

The activation of the renin–angiotensin system (RAS) is one of the main pathogenetic mechanisms inducing vascular structural and functional changes.\textsuperscript{4} Angiotensin II exerts direct vasoconstriction and the promotion of vascular fibrosis via several mechanisms, including the inhibition of nitric oxide synthase (NOS) activity.\textsuperscript{5} Moreover, angiotensin II increases reactive oxygen species (ROS) production via membrane-bound NAD(P)\textsuperscript{+} oxidase.\textsuperscript{6} Aldosterone

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can directly impair endothelial function and determine structural changes inside the arterial wall. Finally, locally activated renin, as well as pro-renin, may trigger reactions, which determine endothelial dysfunction.\(^7\)

Although angiotensin-converting enzyme (ACE)-inhibitors and AT-1 receptor antagonists are generally effective in reversing vascular alterations in essential hypertension, available evidence clearly indicates that these drug classes do not improve endothelium-dependent vasodilation in the peripheral resistance arteries.\(^8\)–\(^12\) It is conceivable that these negative results might be explained by the non-complete RAS blockade exerted by both ACE-inhibitors and AT-1 receptor antagonists in such vascular district.

Aliskiren is a non-peptide renin inhibitor, which blocks the RAS at the first and rate-limiting step, reducing renin activity and the circulating levels of angiotensin I, angiotensin II, and aldosterone.\(^13\) Thus, at least theoretically, aliskiren should provide a better inhibition of the RAS and vascular protection when compared with both ACE-inhibitors and AT-1 receptor antagonists. At the present time, no information is available on the effect of aliskiren on vascular function in human hypertension. Therefore, the aim of the present research project was to evaluate whether treatment with aliskiren can improve vascular function and structure in patients with essential hypertension. More in details, this study evaluated the effect of aliskiren on endothelium-dependent vasodilation, nitric oxide (NO) availability and oxidative stress in the forearm resistance arterioles. Aortic stiffness and peripheral wave reflection were also assessed. To avoid the confounding effect of blood pressure (BP) reduction and to investigate any possible difference with other drug classes blocking the RAS, aliskiren was compared with the ACE-inhibitor ramipril.

### Methods

#### Patients

The study population included 25 normotensive control subjects and 50 matched patients with essential hypertension. Subjects with smoking history (more than five cigarettes per day), hypercholesterolaemia (total cholesterol >6.2 mmol/l), diabetes mellitus, cardiac and/or cerebral ischaemic vascular disease, or impaired renal function were excluded. Subjects were defined as normal according to the absence of family history of essential hypertension and to BP values. Essential hypertensive patients were recruited among the newly diagnosed cases in our out-patient clinic and enrolled if they reported the presence of positive family history of essential hypertension, whenever sitting BP (after 10 min of rest) measured by an automatic device (OMRON-950 CP) three times at 1-week intervals, was consistently >140/90 mmHg. Secondary forms of hypertension were excluded by routine diagnostic procedures. Patients were either never-treated \((n = 31)\) or reported a history of discontinued or ineffective pharmacological antihypertensive treatment \((n = 19)\). Among the latter subgroup, no patient had previously been prescribed an ACE-inhibitors or AT-1 receptor antagonists for at least 6 months prior to enrolment in the study. Moreover, to avoid possible drop-outs because of lack of BP normalization by aliskiren or ramipril treatment, hypertensive patients were tested for response to the ACE-inhibitor 4 weeks before enrolment into the study. Blood pressure response to a single dose of ramipril (10 mg) was evaluated and only those patients who showed more than a 10% systolic BP decrease induced by drug administration were finally enrolled. Following this procedure, we screened 68 essential hypertensive patients to select 50 patients who proved to be responders to ramipril treatment.

The protocol was approved by the local Ethical Committee (EUDRACT code: 2009-016738-28) and all participants gave their written consent to the study.

#### Experimental procedure

All measurements were performed after an overnight fast, with subjects in supine position in a quiet air-conditioned room. Blood pressure was measured three times at 3-min intervals at the dominant arm and calculated as mean value of the last two measurements.

#### Evaluation of endothelial function in resistance arterioles

Endothelial function at the level of the peripheral resistance arterioles was assessed by the utilization of the perfused forearm technique. Briefly, the brachial artery was cannulared for drug infusion at systematically ineffective rates and for intra-arterial BP and heart rate monitoring. The forearm blood flow (FBF) was measured in both forearms by strain-gauge venous plethysmography. Details on this methodology in our laboratory have already been published.\(^14\)

The endothelium-dependent relaxation and the contribution of NO were assessed by a dose–response curve to intra-arterial acetylcholine (Ach), repeated under infusion of the NOS inhibitor N\(^\circ\)-monomethyl-L-arginine (L-NMMA, 4 \(\mu\)mol/min). To avoid L-NMMA-induced basal flow modification, the NO-clamp (which allows assessment of endothelial agonists in the presence of NOS blockade without changes in basal flow) was applied, as previously published.\(^14\) Thus, after 10 min of L-NMMA infusion, sodium nitroprusside (SNP) was co-infused (0.2 and 0.4 \(\mu\)g/100 mL tissue/min for 5 min in hypertensive patients and controls, respectively) to neutralize the L-NMMA-induced vasoconstriction and restore baseline FBF.

The role of ROS generation on endothelial function was investigated by repeating Ach under infusion of the antioxidant ascorbic acid (8 mg/100 mL forearm tissue/min) and, finally, in the presence of simultaneous infusion of L-NMMA and ascorbic acid. N\(^\circ\)-monomethyl-L-arginine and ascorbic acid were started 10 min before Ach and continued throughout. A 30 min washout was allowed between each dose–response curve, prolonged to 60 min when L-NMMA was infused.

Endothelium-independent vasodilation was assessed with a dose–response curve to intra-arterial SNP (1, 2, and 4 \(\mu\)g/100 mL forearm tissue/min, 5 min each dose).

#### Arterial stiffness and wave reflection

Arterial tonometry was performed according to the international recommendations, as previously described.\(^15\) A hand held probe was placed on the selected artery 10–15 subsequent images were recorded. Radial pressure waveform was transformed into aortic pressure waveform by pulse wave analysis (SphygmoCor, AtCor Medical) using a validated transfer function. Three successive measurements were recorded. Augmented pressure was calculated as the difference between the second systolic peak and the first systolic peak, and augmentation index (AIx) was calculated as the ratio between augmented pressure and pulse pressure. Augmentation index values have been normalized at a heart rate of 75 b.p.m. Time to reflection and central BP were also obtained. Central pulse wave velocity (PWV) was assessed with the same device, recording waveforms at the femoral and carotid site, sequentially. Simultaneously recorded ECG was used to calculate wave transit time. Path length was measured
subtracting the distance between the sternal notch and the carotid site of recording from that between the sternal notch and the femoral site.16

**Humoral parameters of renin–angiotensin system and markers of oxidative stress**

Blood samples were collected at baseline in all individuals, and after 12 weeks of treatment in hypertensive patients. Plasma renin activity, plasma, and urine aldosterone were assayed by radioimmunoassay (DiaSorin: Saluggia, Italy). Active renin was measured by the radioimmunometric assay using a kit from IRMA Pasteur (ERIA Diagnostic, Pasteur, Marnes La Coquette, France). Angiotensin II was determined by radioimmunoassay after extraction of the peptide from plasma by Sep-Pak C18, as previously described.17

Measurements of malondialdehyde (MDA) and lipoxydides (LOOH) (colorimetric assay)18,19 were performed as indices of oxidative stress. Moreover, antioxidant capacity was measured as plasma ferric reducing ability of plasma (FRAP, colorimetric assay).20

**Experimental design**

Following the baseline vascular reactivity tests, essential hypertensive patients received aliskiren (150 mg/daily) or ramipril (5 mg/daily) treatment, according to a randomized, open with blind endpoints, parallel group design (n = 25 each group). After 4 weeks of treatment, patients were given aliskiren at 300 mg o.d. or ramipril at 10 mg o.d. Additional clinic visits were scheduled every 2 weeks for the total duration of the study. At the end of treatments, vascular reactivity tests were repeated (Figure 1).

The primary endpoint was the effect of aliskiren on Ach and the inhibitory effect of l-NMMA on response to the endothelial agonist in the forearm resistance arterioles. The secondary endpoints included the effect of aliskiren on Alx and PWV.

**Data analysis**

Evaluation of FBF, Aix, and PWV parameters were performed by observers (G.L., G.C., R.M.B., respectively) who had no knowledge of the drug taken by the patients. Statistical analysis was performed using NCSS 2004 (NCSS, Kaysville, UT, USA). The results were expressed as mean ± SD. Differences between hypertensive patients and normotensive subjects were compared by two-sided unpaired Student’s t-test or χ², as appropriate. Differences in clinical characteristics, humoral parameters and arterial stiffness were analysed by two-way ANOVA, considering as factors time and treatment. With respect to endothelial function, data were analysed in terms of changes in FBF, and FBF changes were taken as evidence of local vasodilation. Responses to Ach and SNP and changes in clinical parameters were analysed by ANOVA for repeated measures, followed by the Bonferroni post hoc test. Differences were considered statistically significant at a value of P < 0.05. The sample size was calculated in order to detect a difference in means after treatments of 50% change in FBF.
induced by Ach, 0.5 m/s for PWV, and 3% in Alx, with a power of 0.8 and a type I error probability of 0.05.

**Results**

Baseline clinical and humoral characteristics for all participants are summarized in Table 1. Hypertensive patients showed higher levels of active renin, angiotensin II, MDA and LOOH, and lower FRAP (Table 2).

**Baseline endothelium-dependent relaxation in the forearm resistance arterioles**

In essential hypertensive patients, the response to Ach was blunted (P < 0.001) compared with normotensive controls (Figure 2). In contrast, response to SNP was similar in normotensive subjects (FBF from 3.4 ± 0.4 to 16.8 ± 2.9 mL/100 mL/min; +394 ± 31%) and hypertensive patients (FBF from 3.4 ± 0.3 to 17.2 ± 2.9 mL/100 mL/min; +413 ± 36%).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of normotensive control subjects and essential hypertensive patients before and after 3-month treatment with aliskiren or ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Aliskiren-treated group (n = 25)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.9 ± 8.1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>18/7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9 ± 2.7</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>148.8 ± 9.9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>93.5 ± 8.4</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>67.2 ± 9.7</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>195.1 ± 23.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.5 ± 8.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>122.3 ± 58.1</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>128.1 ± 28.3</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>92.5 ± 9.5</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>97.9 ± 12.1</td>
</tr>
</tbody>
</table>

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

Values are mean ± SD.

*P < 0.05 vs. baseline.

**Table 2 Systemic Renin–Angiotensin–Aldosterone values and oxidative stress plasma markers of essential hypertensive patients before and after 3-month treatment with aliskiren or ramipril**

<table>
<thead>
<tr>
<th></th>
<th><strong>Aliskiren-treated group (n = 25)</strong></th>
<th><strong>Ramipril-treated group (n = 25)</strong></th>
<th><strong>Normotensive subjects (n = 25)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Baseline</strong></td>
<td><strong>12 weeks</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Active renin (pg/mL)</td>
<td>10.1 ± 1.6</td>
<td>30.3 ± 3.6,<strong>,</strong></td>
<td>10.4 ± 1.7</td>
</tr>
<tr>
<td>PRA (ng Ang I/mL/h)</td>
<td>1.0 ± 0.4</td>
<td>0.3 ± 0.2*</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>Plasma Ang II (pg/mL)</td>
<td>14.2 ± 2.6</td>
<td>8.8 ± 3.5,<strong>,</strong></td>
<td>16.3 ± 4.3</td>
</tr>
<tr>
<td>Plasma Aldosterone (pg/mL)</td>
<td>23.4 ± 7.1</td>
<td>13.4 ± 2.7,<strong>,</strong></td>
<td>24.2 ± 9.3</td>
</tr>
<tr>
<td>Urinary Aldosterone (µg/24 h)</td>
<td>21.8 ± 8.6</td>
<td>12.8 ± 4.1,<strong>,</strong></td>
<td>22.7 ± 9.3</td>
</tr>
<tr>
<td>FRAP (mmol/L)</td>
<td>360 ± 44</td>
<td>646 ± 83,<strong>,</strong></td>
<td>355 ± 49</td>
</tr>
<tr>
<td>LOOH (µmol/L)</td>
<td>5.1 ± 1.3</td>
<td>1.6 ± 1.1,<strong>,</strong></td>
<td>4.7 ± 1.2</td>
</tr>
<tr>
<td>MDA (µmol/L)</td>
<td>5.5 ± 1.0</td>
<td>2.5 ± 1.1,<strong>,</strong></td>
<td>5.1 ± 1.1</td>
</tr>
</tbody>
</table>

PRA, plasma renin activity; Ang, angiotensin; FRAP, ferric reducing ability of plasma; LOOH, lipoperoxide; MDA, malondialdehyde.

Values are mean ± SD.

*P < 0.05 vs. baseline.

**P < 0.05 vs. ramipril counterpart.

***P < 0.05 vs. hypertensive patients at baseline.
In normotensive subjects, L-NMMA blunted the vasodilating effect of Ach (Figure 2) and ascorbic acid did not affect the response to Ach (FBF, from 3.3 ± 0.2 to 25.5 ± 3.6 mL/100 mL/min: +672 ± 42%). In hypertensive patients, L-NMMA did not change Ach-induced vasodilation (Figure 2), while ascorbic acid potentiated the relaxation to Ach (P < 0.01 vs. Ach alone) and restored the inhibitory effect of L-NMMA on Ach (Figure 2).

**Baseline arterial stiffness and wave reflection**

Aortic PWV was higher (P < 0.05) in hypertensive patients when compared with controls (Table 3, Figure 3). Augmentation index and central systolic BP and pulse pressure were also higher (P < 0.05) in hypertensive patients when compared with controls (Table 3, Figure 3). Timing of the reflected wave tended to be longer in the normotensive subjects, but the difference did not reach statistical significance (Table 3).

**Effect of treatment in hypertensive patients**

Aliskiren and ramipril similarly decreased BP values after 12 weeks of treatment, while body weight, lipid profile, and glucose plasma levels were unchanged throughout the treatment period (Table 1).

**Endothelium-dependent vasodilation in the forearm resistance arterioles**

At baseline, in the aliskiren subgroup, response to Ach (+444 ± 40%) was unaffected by L-NMMA (+420 ± 54%) and potentiated by ascorbic acid (+554 ± 34%, P < 0.01) which also restored the inhibition of L-NMMA on Ach (+351 ± 41%, P < 0.01). Similarly, in the ramipril subgroup, the vasodilation to Ach (+412 ± 54%, Figure 4) was resistant to L-NMMA (+406 ± 42%) and potentiated by ascorbic acid (ascorbic acid + Ach: +542 ± 39%, P < 0.01; ascorbic acid + L-NMMA and Ach: +343 ± 31%, P < 0.01). The two groups were likewise similar in their response to SNP (aliskiren: +413 ± 36%; ramipril: +382 ± 24%).

Aliskiren administration increased (P < 0.01) vasodilation to Ach (+543 ± 51%, Figure 4), but not to SNP (+419 ± 24%). After aliskiren treatment, L-NMMA blunted the response to Ach (+336 ± 34%, Figure 5). In contrast, ascorbic acid no longer affected the response to Ach (+533 ± 61%) or the inhibitory effect of L-NMMA on Ach (+318 ± 36%; Figure 5). Univariate analysis showed an inverse correlation between the improved inhibitory effect of L-NMMA on relaxation to Ach and the plasma LOOH changes after aliskiren treatment (r = −0.583; P = 0.022).

Ramipril treatment did not change the vasodilation to Ach (+368 ± 41%, Figure 4) or SNP (+400 ± 47%), and it failed to
affect either the lacking effect of L-NMMA or the potentiating effect of ascorbic acid on Ach (Figure 5).

Throughout the study contralateral FBF did not significantly change (data not shown).

**Arterial stiffness and wave reflection**

Central BP values were similarly reduced by aliskiren and ramipril after 12 weeks of treatment (Table 3). Carotid-femoral PWV was also similarly reduced by both drugs (Table 3, Figure 2) to levels comparable with those of normotensive subjects. Timing of the reflected wave was not significantly modified by any kind of treatment (Table 3). Both drugs significantly reduced AIx, but aliskiren determined a significantly greater reduction in this value in comparison with ramipril (Table 3, Figure 2).

**Effect of treatment on humoral components of renin-angiotensin system and markers of oxidative stress**

At baseline, plasma values of active renin, PRA, angiotensin II, and aldosterone were similar between aliskiren and ramipril subgroups (Table 2). Aliskiren increased plasma active renin values and dramatically reduced PRA, angiotensin II, plasma, and urinary aldosterone (Table 2). In contrast, ramipril significantly raised plasma levels of active renin as well as PRA values, and decreased angiotensin II and plasma and urinary aldosterone (Table 2). Aliskiren increased plasma FRAP and reduced LOOH and MDA values. In contrast, ramipril failed to affect FRAP or LOOH levels, while only slighting but significantly reduced MDA values (Table 2).
Discussion

This study showed that treatment with aliskiren, but not with ramipril, improved endothelium-dependent vasodilation and NO availability in the peripheral resistance arterioles of hypertensive patients. This effect was also associated with a greater reduction in peripheral wave reflection. In agreement with previous observations, our essential hypertensive patients showed an attenuated endothelium-dependent vasodilation, a lacking inhibitory effect of L-NMMA on Ach together with a potentiating effect exerted by ascorbic acid, thus confirming the presence of an impaired endothelial NO availability secondary to oxidant excess.

Twelve-week treatment with aliskiren selectively increased the endothelium-dependent vasodilation and restored the inhibitory effect of L-NMMA on vasodilation to Ach, thus implying a restoration of NO availability. In these conditions, ascorbic acid no longer affected the relaxing response to Ach or the blunting activity exerted by L-NMMA. The present results represent the first demonstration in essential hypertensive patients of the ability of aliskiren to restore endothelial NO availability in the peripheral resistance arterioles. Our findings agree with experimental animal studies reporting a beneficial effect by this renin inhibitor on endothelial function, either in peripheral conduit arteries or in the coronary circulation.

In contrast, ramipril failed to improve endothelium-dependent vasodilation or NO availability, confirming previous negative evidence obtained in the forearm resistance arterioles of essential hypertensive patients, where ACE-inhibitors can selectively increase only vasodilation to bradykinin. However, this effect is resistant to L-NMMA and sensitive to ouabain, an inhibitor of Na⁺/K⁺/ATPase, indicating that vasodilating response was probably mediated by hyperpolarization with no efficacy on NO availability. On the contrary, several evidence indicates that ACE-inhibitors can ameliorate endothelial function in the peripheral conduit arteries. The discrepancy of the effect of ACE-inhibitors on conduit or resistance arteries underlines the concept that endothelium is a paracrine organ, whose function/dysfunction can vary depending on which vascular district is explored or which stimulus is employed.

Large-artery stiffness and peripheral wave reflection has been recently shown to be independent predictors of cardiovascular disease. Thus, the improvement of these parameter could be considered an adjunctive goal for optimal risk reduction in
hypertension. While the effect of ramipril was already demonstrated, our aliskiren and ramipril similarly reduced brachial and central BP.

Increased AIx in hypertensive patients was significantly reduced by both treatments. The effect of aliskiren was significantly greater than that exerted by ramipril. Pulse wave velocity influences AIx by increasing the velocity of both forward and reflected wave. Since the two drugs reduced similarly PWV, this factor does not explain the different behaviour. Another important factor influencing timing and amplitude of the reflected wave, and therefore AIx, is the site of reflection, which is determined by impedance mismatch sites and by the vaso motor state of micro-circulation. Since aliskiren determined a greater effect than ramipril on NO-dependent vasodilatation in the resistance arterioles, this mechanism might account for the greater effect of aliskiren on AIx. The results on wave reflection are clinically relevant, since a recent meta-analysis of 5648 subjects followed up for a mean of 45 months, showed that a 10% absolute increase in central AIx was associated with an increased relative risk of cardiovascular events (+32%), independently of age, risk-factors including brachial BP and heart rate. It has been suggested that antihypertensive drugs have differential effects on central BP, despite similar effects on brachial BP, and this may explain the superiority of ACE-inhibitors in recent outcome trials. In the present study, aliskiren and ramipril similarly reduced brachial and central BP. While the effect of ramipril was already demonstrated, our results indicate for the first time that aliskiren lowers central BP to a similar extent than that obtained by the ACE-inhibitor.

The beneficial effect of aliskiren on endothelial function is not caused by a mere BP pressure reduction, given the lack of improvement achieved by ramipril, despite comparable BP reduction. Moreover, other cardiovascular risk factors that could impair endothelial function, including the lipid or the glucose profile, were similar in the two subgroups showing no change during the treatment period. Therefore, the protective effect by aliskiren on endothelial responses is likely to be related to specific properties of this compound. Aliskiren prevented the facilitating effect of the antioxidant ascorbic acid on vasodilatation to Ach and it decreased plasma values of LOOH and MDA, concomitantly increasing plasma FRAP. A significant inverse correlation between the restored inhibitory effect of L-NMMA and the plasma LOOH level changes in patients who received aliskiren emerged. Taken together, these findings suggest that the beneficial activity of aliskiren treatment on endothelial function is related to an antioxidant activity, which in turn leads to an amelioration of NO activity. Aliskiren provides a better RAS blockade when compared with ramipril, determining a greater reduction in plasma angiotensin II and plasma and urinary aldosterone values. Since both angiotensin II and aldosterone are well-recognized sources of oxidative stress, it is conceivable that the antioxidant effect of aliskiren, not shown by ramipril, might be determined by a superior capacity of inhibiting these substances.

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Another possible mechanism contributing to explain the effect of aliskiren on peripheral endothelial function is the ability of this compound to up-regulate eNOS phosphorylation, a crucial step for eNOS activation and function. A limitation of the present study concerns that only patients’ responders to ACE-inhibitors were investigated. Therefore, these results cannot be extrapolated to the general population of hypertensive patients.

In conclusions, the present results demonstrate that RAS blockade secondary to renin inhibition or ACE inhibition is not equivalent, at least in terms of vascular function, in essential hypertension. While the effect on conduit artery compliance and central BP is equivalent, aliskiren was superior to ramipril in terms of restoration of NO availability in the peripheral circulation, an effect likely related to antioxidant activity. Of note, this effect might lead to a reduction in aortic AIx, an integrated parameter for global wave reflection.

Since both endothelial function and AIx are independent predictor of the cardiovascular outcome, these results might suggest a superiority of aliskiren when compared with ramipril to prevent clinical events. However, only prospective studies based on hard endpoints can really demonstrate whether renin-inhibition offers a greater efficacy than ACE inhibition for cardiovascular protection.

Conflict of interest: none declared.

References


