

University of Groningen

Dual RAAS suppression

de Boer, Rudolf A.; Azizi, Michel; Danser, A. H. Jan; Nguyen, Genevieve; Nussberger, Juerg; Ruilope, Luis M.; Schmieder, Roland E.; Volpe, Massimo

Published in:
Journal of the Renin-Angiotensin-Aldosterone System

DOI:
[10.1177/1470320312455271](https://doi.org/10.1177/1470320312455271)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

de Boer, R. A., Azizi, M., Danser, A. H. J., Nguyen, G., Nussberger, J., Ruilope, L. M., Schmieder, R. E., & Volpe, M. (2012). Dual RAAS suppression: recent developments and implications in light of the ALTITUDE study. *Journal of the Renin-Angiotensin-Aldosterone System*, 13(3), 409-412.
<https://doi.org/10.1177/1470320312455271>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).


The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Dual RAAS suppression: recent developments and implications in light of the ALTITUDE study

Journal of the Renin-Angiotensin-Aldosterone System
© The Author(s) 2012
Reprints and permission:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1470320312455271
jra.sagepub.com


**Rudolf A de Boer,¹ Michel Azizi,² AH Jan Danser,³
Geneviève Nguyen,⁴ Jürg Nussberger,⁵ Luis M Ruilope,⁶
Roland E Schmieder⁷ and Massimo Volpe⁸**

¹University Medical Center Groningen, Department of Cardiology, University of Groningen, the Netherlands

²Université Paris-Descartes, Assistance Publique des Hôpitaux de Paris, Département d'Hypertension Artérielle, France

³Division of Pharmacology and Vascular Medicine, Department of Internal Medicine, Erasmus MC, the Netherlands

⁴Centre for Interdisciplinary Research in Biology (CIRB), France

⁵Division of Angiology and Hypertension, Centre Hospitalier Universitaire Vaudois, Switzerland

⁶Hypertension Unit, Hospital 12 de Octubre and Department of Public Health and Preventive Medicine, Universidad Autonoma, Spain

⁷University Hospital Erlangen, Nephrology and Hypertension, Germany

⁸Division of Cardiology, Department of Clinical and Molecular Medicine, University of Rome "Sapienza" and IRCCS Neuromed, Italy

Email: r.a.de.boer@umcg.nl

The Renin-Angiotensin-Aldosterone System (RAAS) Working Group¹ held its meeting in London during the scientific sessions of the European Society of Hypertension in April 2012. The aim of the meeting was to review the data from ALTITUDE and the recent premature halt of this trial. This report summarises the main discussion points from this meeting.

The ALiskiren Trial In Type 2 diabetes Using cardiovascular and renal Disease Endpoints (ALTITUDE) study was designed as a four-year, multicentre, randomised, placebo-controlled trial that evaluated the efficacy of aliskiren 300 mg daily versus placebo in high-risk patients suffering from type 2 diabetes mellitus and renal dysfunction whose blood pressure was normalized using one or more antihypertensive drugs (including RAAS inhibitors). Endpoints were cardiovascular and renal events. ALTITUDE was studying aliskiren on top of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II type 1 receptor blocker (ARB) therapy, since this therapy is considered state-of-the-art in eligible patients.

The Data Safety Monitoring Board recommended in an interim analysis that it is unlikely that patients benefit from aliskiren on top of standard therapy and advised halting the trial. This came into effect in December 2011.

First, the outcomes of ALTITUDE were reviewed. Importantly, only 69% of all endpoints have officially been adjudicated, so these data should be considered as preliminary.² Given these limitations, it nevertheless becomes clear that patients receiving aliskiren 300 mg daily experienced an increased incidence of serious adverse events over 18 to 24 months of follow-up. Specifically, aliskiren treatment was associated with increased risk of nonfatal stroke ($P < 0.05$), while there was a tendency toward more cardiovascular and total mortality, sudden death, nonfatal

myocardial infarction, and hyperkalaemia and end-stage renal disease. This was accompanied by more frequent side effects, including hypotension, syncope, renal impairment and drug discontinuation.

Second, a comparison was made versus preclinical studies investigating the blood pressure and renal effects of dual RAAS blockade, since these studies may provide insight into the physiological consequences of dual RAAS blockade with ACE inhibitor/ARB therapy and aliskiren. Studies in spontaneously hypertensive rats put on a low-sodium diet revealed that dual blockade rapidly caused a major decrease in blood pressure and severe renal failure which were accompanied by massive rises (up to several 100-fold) in plasma renin and renal renin levels, thereby decreasing the angiotensinogen concentration in plasma.³ These deleterious effects of dual RAAS blockade were prevented by a high-salt diet. It was concluded that the observations in the low-salt-treated rats mirrored, at least in part, those in patients enrolled in ALTITUDE (Figure 1).

Moreover, studies in human cardiac tissue, obtained from patients undergoing cardiac transplantation⁴ or severe heart failure patients at the time of left ventricular assist device (LVAD) implantation,⁵ both being treated with (high) RAAS blocker doses, also revealed that renin levels in the human heart may rise >100-fold, thereby decreasing cardiac angiotensinogen. Interestingly, following LVAD implantation, renin levels dropped 10-fold, and cardiac angiotensinogen levels rose again, thus paradoxically allowing a rise in cardiac angiotensin II levels⁵ (Figure 2). Therefore, it was put forward that a renin inhibitor like aliskiren, by diminishing cardiac renin activity, may also increase cardiac angiotensinogen and thus similarly increase cardiac angiotensin II, even when the majority of cardiac renin is blocked. This

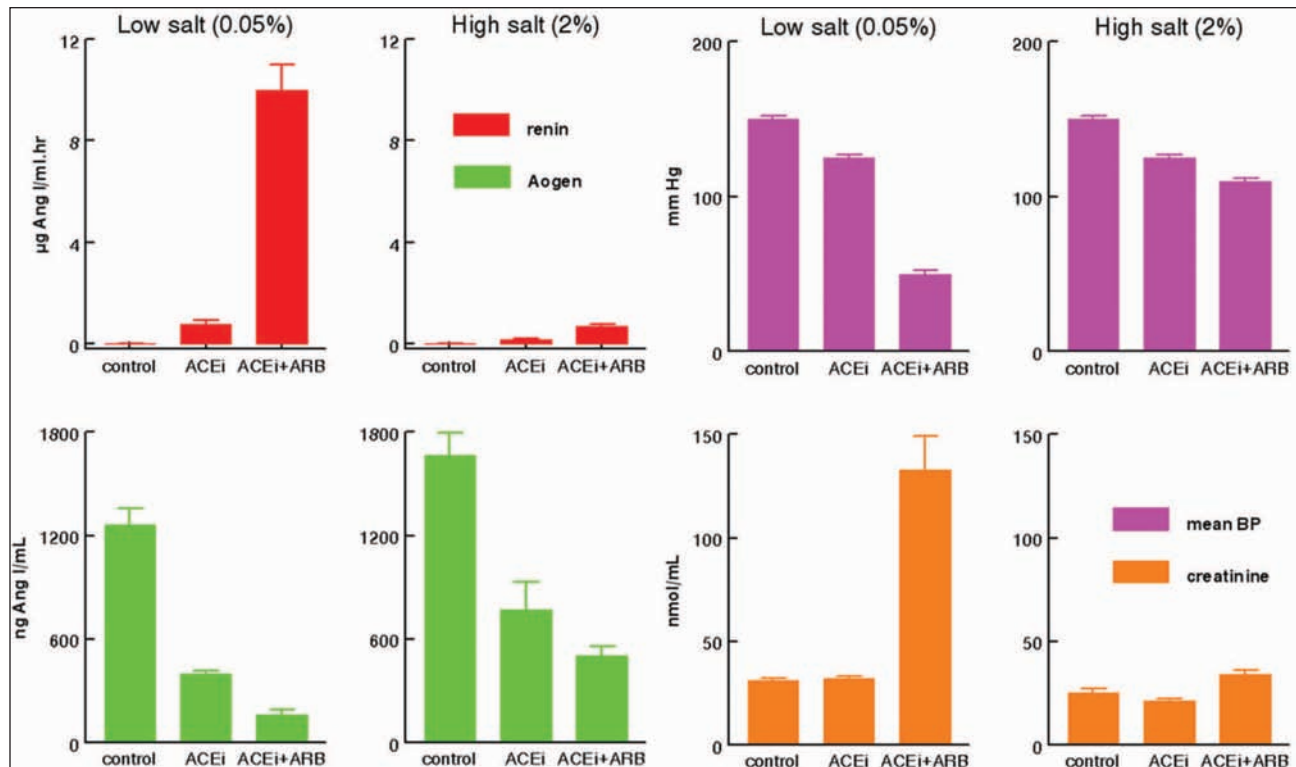


Figure 1. The consequences of RAAS blockade under low- and high-salt conditions. Studies in hypertensive rats on a low-sodium diet showed that dual RAAS blockade (combination of ACE inhibitor and ARB) causes extreme increases in plasma renin concentration, with associated decreases in plasma angiotensinogen (left panels). This is accompanied by severe hypotension with renal dysfunction (right panels). These effects are largely absent in rats fed a normal-high salt diet that have a neutral response to dual RAAS blockade. Adapted from².

might be an unexpected ‘side-effect’ of aliskiren on top of other RAAS blockers that could explain, at least in part, the disappointing results from ALTITUDE.

Subsequently, data on the use of aliskiren in real-life treatment of hypertension (data from the Agenzia Italiana del Farmaco, the Italian Medicines Agency) were discussed. This web-based registry comprises data of >11,000 patients suffering from hypertension who received aliskiren and who were followed for at least six months.⁶ As indicated by the agency, aliskiren could be added only when blood pressure could not be controlled with the current drug regimens. Left ventricular hypertrophy, diabetes and renal disease were additional reasons for prescribing aliskiren. The results, obtained in all patients prescribed with aliskiren between March 2009 and May 2011, showed that the vast majority reached target blood pressure after addition of aliskiren. This observation was even more striking, as it was observed that in ~30% of the patients other antihypertensive drugs (diuretics, calcium channel blockers, beta blockers and ACE inhibitors) were stopped after the addition of aliskiren. Prespecified subanalyses in patients with coronary artery disease and type 2 diabetes mellitus showed similar results. Overall, tolerability and safety profile of aliskiren were

favourable, and in this general hypertensive population only two serious adverse events (necessitating withdrawal of the drug) were reported. From these data it seems that aliskiren is a potent antihypertensive agent, and that addition of aliskiren apparently prompts physicians to reduce or even stop other antihypertensive agents.

In ALTITUDE, the median baseline systolic blood pressure was 135 mm Hg, and thus blood pressure was already very well controlled. Probably, many patients may have become hypotensive when aliskiren 300 mg daily was added to their regimen. Of note, the inclusion criteria did not specify entry blood pressure, since not controlling blood pressure but protective effects by aliskiren were the objective. Thus, patients with low blood pressure could enter the study, which may not have been ideal. Furthermore, different from this real-life registry, patients in ALTITUDE clearly had no dose reduction or drug withdrawal when aliskiren was added. This treatment regimen, inherent to the ALTITUDE study protocol, could explain the excess number of adverse events in these high-risk diabetic patients with renal dysfunction.

Finally, the implications of ALTITUDE for the use of aliskiren in heart failure were reviewed. Dual RAAS

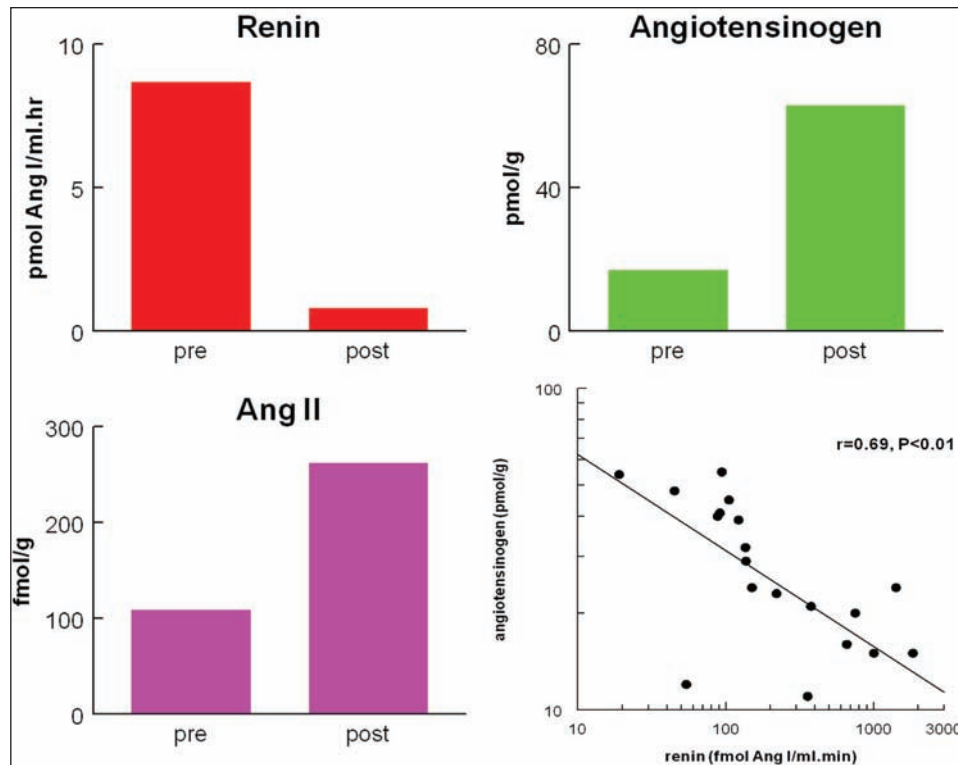


Figure 2. High tissue renin depletes tissue angiotensinogen. Studies were performed in cardiac tissue from patients treated with a left ventricular assist device (LVAD), pre- and post-implantation. Exceptionally high renin levels may deplete tissue angiotensinogen (upper panels). Upon recovery of the left ventricular function post-LVAD implantation, renin levels return to more physiological levels, and as a result tissue angiotensinogen stores recover with a paradoxical increase in angiotensin II (lower left panel). An inverse correlation between renin and angiotensinogen was observed (lower right panel). Adapted from^{3,4}.

blockade has been studied extensively in heart failure, in particular the combination of ACE inhibitors and ARBs.⁷ Although some studies hinted toward a reduction of heart failure hospitalisation, this was consistently associated with an increased incidence of renal dysfunction, hyperkalaemia, hypotension and drug discontinuation, which has offset the widespread use of this combination.⁸ As a consequence, the use of dual RAAS blockade is controversial.⁹ There are several lines of evidence to suggest that renin inhibition might be effective in heart failure.^{10,11} However, data on the use of aliskiren in heart failure are still limited. The Aliskiren Observation of Heart Failure Treatment (ALOFT) trial¹² reported good tolerability when aliskiren was added to standard therapy (including an ACE inhibitor), with beneficial effects on the surrogate efficacy outcome marker brain natriuretic peptide. The Aliskiren Study in Post-MI Patients to Reduce REmodeling (ASPIRE) study¹³ reported neutral effects of aliskiren on left ventricular remodelling in post-myocardial infarction heart failure when added on top of standard therapy. Yet, this was associated with more (serious) side effects, thus contraindicating its use in combination with other RAAS blockers in

post-myocardial infarction patients. Currently, two large studies testing aliskiren in heart failure are ongoing: the Aliskiren Trial of Minimizing OutcomeS for Patients with HEart failuRE (ATMOSPHERE) (chronic heart failure) and the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) (acute heart failure). In comparison with ALTITUDE, these trials differ considerably in patient characteristics and in an active run-in period, and they have a treatment arm with aliskiren alone, as reviewed recently.¹⁴ Furthermore, after ALTITUDE was stopped, recruitment for ATMOSPHERE and ASTRONAUT was temporarily halted, allowing a safety interim analysis. No major safety issues have come up, and to the best of our knowledge these trials are currently recruiting again.

Summary

The premature halting of ALTITUDE raises questions about the potential position of aliskiren (and other renin inhibitors) as an additional RAAS-inhibitor in the treatment of hypertension when present in diabetes together with renal and/or cardiovascular disease.

From reviewing data from ALTITUDE and from experimental data, it seems that aliskiren is a very potent antihypertensive agent, in particular when administered in combination with other RAAS inhibitors and in low-sodium states. Patients in ALTITUDE were treated with optimal medication, including high-dose ACE inhibitors or ARBs, while blood pressure and sodium were well balanced. From experimental and observational data, we know that such subjects are particularly prone to the side effects of excessive RAAS blockade.¹⁵

Furthermore, no standard dose reduction of other antihypertensive agents was suggested in ALTITUDE, something commonly practised in the 'real world'. The same data from aliskiren in the real world do not suggest an additional vulnerability in patients with type 2 diabetes mellitus or coronary artery disease. Finally, we have limited data in patients with heart disease and heart failure, where aliskiren could be of benefit.

Where do we stand with renin inhibition? From available data, it seems that dual RAAS blockade in diabetic patients with reduced renal function on optimal treatment including full-dose ACE inhibitors or ARBs, is likely to cause side effects, while additional efficacy is questionable. Under such conditions, the use of aliskiren as a single agent to block the RAAS seems much more promising. In this light, it is reassuring to note that several studies that are part of the aliskiren clinical development program will compare aliskiren as a single RAAS inhibitor with another RAAS inhibitor. These studies are extremely important as they will provide insights in the efficacy of aliskiren, its safety and its potential future position in cardiovascular disease treatment.

Funding

GN has received research grants from Novartis and Servier. JN has received research grants from Novartis. MV has received research support from Novartis. RAdB has received grants from Novartis, Abbott and BG Medicine. MA has received grants from Novartis, Sanofi, Servier and Actelion. AHJD has received research grants from Novartis and Vitae Pharmaceuticals.

Conflict of interest

RAdB has consulted for Novartis, Abbott and BG Medicine. MA has consulted for Novartis, Sanofi, Servier and Actelion. AHJD has consulted for Novartis and Vitae Pharmaceuticals. LMR has served as advisor/speaker for Novartis.

References

1. RAAS Working Group. Introducing the RAAS Working Group. *J RAAS* 2010; 12: 123.
2. U.S. Food and Drug Administration. FDA Drug Safety Communication: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna), <http://www.fda.gov/drugs/drugsafety/ucm300889.htm> (accessed 28 April 2012).
3. Richer-Giudicelli C, Domergue V, Gonzalez M-F, et al. Haemodynamic effects of dual blockade of the renin-angiotensin system in spontaneously hypertensive rats: influence of salt. *J Hypertens* 2004; 22: 619–627.
4. Danser AHJ, van Kesteren CAM, Bax WA, et al. Prorenin, renin, angiotensinogen, and angiotensin-converting enzyme in normal and failing human hearts. Evidence for renin binding. *Circulation* 1997; 96: 220–226.
5. Klotz S, Burkhoff D, Garrelts IM, et al. The impact of left ventricular assist device-induced left ventricular unloading on the myocardial renin-angiotensin-aldosterone system: therapeutic consequences? *Eur Heart J* 2009; 30: 805–812.
6. Volpe M, Tocci G, Bianchini F, et al. Use of aliskiren in a 'real-life' model of hypertension management: analysis of national Web-based drug-monitoring system in Italy. *J Hypertens* 2012; 30: 194–203.
7. Volpe M, Danser AHJ, Ménard J, et al. Inhibition of the renin-angiotensin-aldosterone system: is there room for dual blockade in the cardiorenal continuum? *J Hypertens* 2012; 30: 647–654.
8. Kuenzli A, Bucher HC, Anand I, et al. Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. *PLoS One* 2010; 5: e9946.
9. Messerli FH, Staessen JA and Zannad F. Of fads, fashion, surrogate endpoints and dual RAS blockade. *Eur Heart J* 2010; 31: 2205–2208.
10. Schrotten NF, Gaillard CA, van Veldhuisen DJ, et al. New roles for renin and prorenin in heart failure and cardiorenal crosstalk. *Heart Fail Rev* 2012; 17: 191–201.
11. Szymanski MK, Damman K, van Veldhuisen DJ, et al. Prognostic value of renin and prorenin in heart failure patients with decreased kidney function. *Am Heart J* 2011; 162: 487–493.
12. McMurray JJ, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008; 1: 17–24.
13. Solomon SD, Shin SH, Shah A, et al. Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction. *Eur Heart J* 2011; 32: 1227–1234.
14. McMurray JJ, Abraham WT, Dickstein K, et al. Aliskiren, ALTITUDE, and the implications for ATMOSPHERE. *Eur J Heart Fail* 2012; 14: 341–343.
15. Azizi M and Ménard J. Renin inhibitors and cardiovascular and renal protection: an endless quest? *Cardiovasc Drugs Ther.* Epub ahead of print 06 March 2012.