



---

# NATIONAL PBM BULLETIN

February 12, 2013

---

DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)  
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),  
AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

## DUAL RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKADE IN DIABETIC NEPHROPATHY AND INCREASED ADVERSE EVENTS

### I. ISSUE

Recently, the VA Cooperative Study, “Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)” had medications terminated early per recommendations of the Data Monitoring Committee. The decision was based on a greater number of observed acute kidney injury events and hyperkalemia in the combination angiotensin receptor blocker (ARB), losartan, and angiotensin-converting enzyme inhibitor (ACEI), lisinopril, therapy group compared to patients receiving an ARB plus placebo. These outcomes, combined with additional evidence on the use of combination therapy with an ACEI and ARB in general, suggest VA consider implications in practice, especially for patients who are being prescribed combination therapy for a potential benefit on kidney outcomes.

### II. BACKGROUND

Whether combination therapy with an ACEI and ARB provides additional benefit over treatment with either of these classes of agents alone in patients with chronic kidney disease (CKD) has yet to be confirmed in long-term outcome trials.<sup>1</sup> Guidelines caution that the use of combination with an ACEI and ARB cannot be recommended at this time, referencing the increase in adverse events including impaired kidney function and hyperkalemia, despite a decrease in albuminuria, with combination therapy.<sup>2</sup> Refer to section IV for results from two trials that report no outcome benefit with dual blockade of the renin-angiotensin aldosterone system, with an increase in adverse events, compared to monotherapy.<sup>3-5</sup> Therefore, the safety of using combination therapy with agents that block the renin-angiotensin-aldosterone system needs to be taken into consideration given that the long-term outcome benefit has not been established.<sup>2</sup>

### III. PBM AND VA MedSAFE PROVIDER RECOMMENDATIONS

- Because of the potential for harm and the lack of proven long-term outcome benefits, combination therapy with an ACEI and ARB should not be initiated in patients with: diabetic nephropathy; diabetes and CKD; or nondiabetic kidney disease, if being used for kidney outcomes. Similarly, an ACEI or ARB should not be used concomitantly with aliskiren.
- For patients already taking an ACEI and an ARB for the potential benefit on kidney outcomes, providers should review treatment for potential discontinuation of either ACEI or ARB, as applicable. If combination therapy is continued, it should be documented that the patient has benefited from combination therapy and that there are no current safety concerns.
- For patients who are receiving combination ACEI and ARB for management of systolic heart failure, combination therapy with an ACEI and ARB may be considered in patients with persistent symptoms despite maximized standard therapy (if it is determined that the benefit outweighs the potential risk for adverse events);<sup>6-8</sup> however, use of combination with an aldosterone antagonist and conventional therapy for heart failure that includes an ACEI may be preferable to an ACEI and ARB.<sup>9,10</sup> Combination therapy in patients with heart failure/evidence of systolic dysfunction after acute MI is not routinely recommended due to an increased risk for adverse events without a survival benefit.<sup>11</sup>
- A brief assessment of combined therapy in fiscal year 2012 showed that a large number of patients in the VA system-wide were receiving a combination of an ACEI and ARB. Based on the aforementioned safety considerations, VISN PBM(s)/P&T Committee(s) should discuss these recommendations for considering discontinuation of either an ACEI or ARB in patients with chronic kidney disease who are receiving combination therapy with both agents, with facilities implementing them upon direction from their VISN Chief Medical Officer and VISN Pharmacist Executive. Additionally, VA Patient and Provider Letters are available on the PBM INTRAnet at: <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>.

#### IV. DATA SUMMARY

##### Summary Results from ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)<sup>3,4</sup>

**Patient population:** vascular disease (coronary, peripheral, or cerebrovascular) or high-risk DM (37.5%)

**Primary composite outcome:** death from cardiovascular (CV) causes, myocardial infarction (MI), stroke, or hospitalization for heart failure (HF)<sup>4</sup>; pre-specified renal outcome (dialysis, renal transplantation, doubling serum creatinine, or death)<sup>3</sup>

	Ramipril (N=8576)	Telmisartan (N=8542)	Combination (N=8502)	Telmisartan vs. Ramipril RR (95% CI)	Combination vs. Ramipril RR (95% CI)
<b>Outcome</b>					
Primary composite outcome	1412 (16.5%)	1423 (16.7%)	1386 (16.3%)	1.01 (0.94 to 1.09)	0.99 (0.92 to 1.07)
Death from any cause	1014 (11.8%)	989 (11.6%)	1065 (12.5%)	0.98 (0.90 to 1.07)	1.07 (0.98 to 1.16)
Renal outcome	1150 (13.5%)	1147 (13.4%)	1233 (14.5%)	1.00 (0.92 to 1.09)	1.09 (1.01 to 1.18)
<b>Reason for Discontinuation</b>					
Hypotensive symptoms	149 (1.7%)	229 (2.7%)	406 (4.8%)	1.54; P<0.001	2.75; P<0.001
Syncope	15 (0.2%)	19 (0.2%)	29 (0.3%)	1.27; P=0.49	1.95; P=0.03
Hyperkalemia (> 5.5 mmol/L)	283 (3.3%)	287 (3.4%)	480 (5.7%)	NS	P<0.001
Renal impairment*	871 (10.2%)	906 (10.6%)	1148 (13.5%)	1.04 (0.96 to 1.14)	1.33 (1.22 to 1.44)

\*Based on clinical investigator's report of study discontinuation due to event; P<0.001 combination vs. ramipril  
NS=not statistically significant

##### Summary Results from ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints)<sup>5</sup>

**Patient population:** type 2 diabetes and additional CV (94.5% hypertension; 42.3% known CV disease other than hypertension), or renal complications (98.0% CKD; 84.1% proteinuria)

**Primary composite outcome:** composite of death from CV causes or first occurrence of cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke; unplanned hospitalization for HF; end-stage renal disease (ESRD), death attributable to kidney failure, or the need for renal replacement therapy with no dialysis or transplantation available or initiated; or doubling of baseline serum creatinine to above the upper limit of normal and sustained for at least one month

	Aliskiren* (N=4274)	Placebo* (N=4287)	Aliskiren vs. Placebo HR (95% CI)	P value
<b>Outcome</b>				
Primary composite outcome	783 (18.3%)	732 (17.1%)	1.08 (0.98 to 1.20)	0.12
CV composite outcome	590 (13.8%)	539 (12.6%)	1.11 (0.99 to 1.25)	0.09
Renal composite outcome	257 (6.0%)	251 (5.9%)	1.03 (0.87 to 1.21)	0.74
Death from any cause	376 (8.8%)	358 (8.4%)	1.06 (0.92 to 1.23)	0.42
<b>Adverse Events</b>				
Discontinuation due to AE	563 (13.2%)	437 (10.2%)		<0.001
Hyperkalemia	1670 (39.1%)	1244 (29.0%)		<0.001
Hypotension	519 (12.1%)	357 (8.3%)		<0.001
Renal impairment	418 (9.8%)	371 (8.7%)		0.07

\*Receiving standard therapy that included an ACEI or ARB

#### V. REFERENCES

- Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Inter Suppl* 2012; 2:337-414.
- National Kidney Foundation. K/DOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60(5):850-86.
- Mann JFE, Schmieder RE, McQueen M, et al., on behalf of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) Investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. *Lancet* 2008;372:547-53.
- ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.
- Parving HH, Brenner BM, McMurray JJV, et al., for the ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012. DOI: 10.1056/NEJMoa1208799.
- Hunt SA, Abraham WT, Chin MH, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, International Society for Heart and Lung Transplantation. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. *J Am Coll Cardiol* published online Mar 26, 2009; doi:10.1016/j.jacc.2008.11.013
- McMurray JJV, Östergren J, Swedberg K, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
- Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013;346:f360 doi: 10.1136/bmj.f360
- Butler J, Ezekowitz JA, Collins SP et al. Update on aldosterone antagonist use in heart failure with reduced left ventricular ejection fraction Heart Failure Society of America Guidelines Committee. *J Cardiac Fail* 2012;18:265-81.
- Bangalore S, Kumar S, Messerli FH. When conventional heart failure therapy is not enough: angiotensin receptor blocker, direct renin inhibitor, or aldosterone antagonist? *Congest Heart Fail* 2012. Doi: 10.1111/chf.12011.
- Pfeffer MA, McMurray J, Leizorovicz A, et al., for The Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.

#### ACTIONS

- Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., primary care providers, nephrologists, endocrinologists, and cardiologists, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).