# NATIONAL PBM BULLETIN

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**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.[1] 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.[2] 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.[3-5] 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.[2]

### 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);[6-8] 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.[9,10] 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.[11]
- 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)[3,4]**
**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) [4]; pre-specified renal outcome (dialysis, renal transplantation, doubling serum creatinine, or death)[3]

| | Ramipril (N=8576) | Telmisartan (N=8542) | Combination (N=8502) | Telmisartan vs. Ramipril RR (95% CI) | Combination vs. Ramipril RR (95% CI) |
|---|---|---|---|---|---|
| **Outcome** | | | | | |
| 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) |
| **Reason for Discontinuation** | | | | | |
| 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)[5]**
**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) | Aliskrien vs. Placebo HR (95% CI) | P value |
|---|---|---|---|---|
| **Outcome** | | | | |
| 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 1.23) | 0.74 |
| Death from any cause | 376 (8.8%) | 358 (8.4%) | 1.06 (0.92 to 1.23) | 0.42 |
| **Adverse Events (AE)** | | | | |
| 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


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11. 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).*