Angiotensin II Receptor Antagonists (AIIRAs) Criteria for Use in Veteran Patients

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The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations. Refer to the PBM-MAP The Pharmacologic Management of Hypertension, Supplement to the VHA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care Setting and the PBM-MAP The Pharmacologic Management of Chronic Heart Failure at ***www.vapbm.org*** *or* ***http://vaww.pbm.med.va.gov*** *for recommendations on dosing, potential drug interactions, side effects and precautions of the AIIRAs and cost comparison with other agents.*

Due to the limited data on clinical outcomes comparing the AIIRAs (also referred to as ARBs) to the angiotensin-converting enzyme inhibitors (ACEIs) and the high cost, it is recommended that the AIIRAs be reserved for **patients with a specific indication for an ACEI AND a documented adverse drug reaction to at least one formulary ACEI (i.e., other than angioedema or hyperkalemia)**. For each indication listed below, please refer to the discussion section at the end of the document.

Recommendations for or against routine use of an AIIRA in patients with hypertension (HTN)

- **Cough:** The cough associated with an ACEI has been described as dry, nonproductive, persistent, beginning with a tickling sensation, and often worse at night. The onset is usually within the first week of ACEI therapy and continues throughout treatment, resolving within a few days to 4 weeks after the ACEI is discontinued. The cough is not usually dose-dependent, although in some instances it may be eliminated with a reduction in dose. Since therapy with an ACEI has proven valuable, it is important to consider alternative diagnoses (e.g, asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory tract infection, heart failure, gastroesophageal reflux disease) before a diagnosis of ACEI-induced cough is made. **If a patient develops cough on an ACEI and they do not have a specific indication for an ACEI, clinicians should consider an alternative antihypertensive therapy (e.g., diuretics, beta-blockers) unless contraindicated.** Use of an AIIRA may be considered in patients who have a specific indication for an ACEI (refer to recommendations below) and are unable to tolerate treatment with at least one formulary ACEI. Patients with a history of cough associated with an ACEI may experience improvement if switched to fosinopril. Patients should be reevaluated once prescribed an AIIRA since there is a slight chance that patients may develop a cough with these agents as well.
- **Angioedema:** An AIIRA should be used with extreme caution, if at all, in patients who have previously experienced angioedema on an ACEI.
- **Hyperkalemia:** It is unclear if treatment with an AIIRA is an appropriate alternative in patients who develop hyperkalemia with an ACEI since they may experience the same adverse effect with an AIIRA. An alternative class of antihypertensive agent is recommended or the addition of a diuretic may be considered to offset the hyperkalemia.

Recommendations for or against routine use of an AIIRA in patients with systolic heart failure (HF)

- **HF:** The lack of conclusive data that AIIRAs are superior to ACEIs in patients with HF precludes them as the drug of choice in HF, unless the patient is intolerant to an ACEI as described above.
- **Combination with an ACEI:** An AIIRA combined with an ACEI may have benefits in patients with HF who have failed treatment with a beta-adrenergic blocker (since the combination of all three classes of medications was found to be detrimental in patients with HF), however there is not enough data to support the long-term safety, effectiveness, survival, and quality of life for patients receiving combination therapy.
- **Recent myocardial infarction (MI):** Results of outcome trials are not available to provide enough evidence in favor of recommending an AIIRA in patients with a recent MI and evidence of HF.

Recommendations for or against routine use of an AIIRA in patients with renal disease

- **Renal insufficiency or type 1 or 2 diabetes mellitus (DM) with proteinuria or nephropathy:** Evidence is available as to the ability of an AIIRA to slow the progression of microalbuminuria to nephropathy in patients with type 2 DM. This was not evaluated in patients with type 1 DM. Data is also available in patients with type 2 DM where an AIIRA slowed the progression of nephropathy along with doubling of creatinine, end-stage renal disease, and/or death. In addition, there is evidence to suggest that a combination of an ACEI and AIIRA may be beneficial therapy in patients with type 2 DM and microalbuminuria. Long-term outcome trials comparing an ACEI to an AIIRA are needed to determine if these agents provide similar benefit in patients with DM and proteinuria or nephropathy. Treatment with an AIIRA may be an appropriate alternative in patients who are unable to tolerate an ACEI.

DISCUSSION

Hypertension:

According to JNC VI[1] and the VHA/DoD Clinical Practice Guidelines for the Diagnosis and Management of Hypertension in the Primary Care Setting (refer to www.vapbm.org or http://vaww.pbm.med.va.gov), diuretics and beta-blockers are the preferred agents for patients with uncomplicated HTN. Another class of agents may be considered in patients who have a contraindication to a diuretic and beta-blocker or who are inadequately controlled on these agents OR in patients who have an indication for an agent in another antihypertensive class. Angiotensin-converting enzyme inhibitors are considered preferred therapy in patients with HTN and one or more of the following compelling indications: heart failure, post-MI with systolic dysfunction, or type 1 DM with proteinuria. These agents may also be preferred in patients with renal insufficiency or type 2 DM with proteinuria, due to their potential favorable effects.

Clinical studies for these same indications are being conducted with the AIIRAs. To date, the data have not been as compelling as with the ACEIs. Of the specific indications for use of an ACEI as listed above, use of an AIIRA in patients with HF who are unable to tolerate an ACEI, may be beneficial. More data are required before a recommendation can be made regarding the other indications to use an ACEI. If the patient is not able to tolerate an ACEI and does not have an indication with long-term evidence as to its benefit, another antihypertensive class (other than the AIIRAs) is recommended according to the individual needs of the patient.

Cough: The incidence of cough is estimated to be anywhere from 0 to 39% in patients treated with an ACEI.[2] In SOLVD (evaluating patients with HF), cough was reported in 37% of patients treated with enalapril compared to 31% of patients randomized to placebo.[3] In V-HeFT II, 37% of HF patients on enalapril complained of cough compared to 29% receiving HYD/ISDN.[3] The incidence of cough associated with the AIIRAs is similar to placebo (2.6 to 3.4% vs. 1.5 to 3.3%).[2] In the ELITE Study, 3.8% of patients on an ACEI withdrew from the study due to complaints of cough compared to 0% of patients treated with an AIIRA.[5] Patients who experienced cough with an ACEI were found to have a significant decrease in frequency, severity, index, and characteristics of the cough when switched to fosinopril.[6-8] There is a slight chance that patients who are unable to tolerate treatment with an ACEI due to cough may develop a cough with an AIIRA.[9] If congestion is present, which is often noted in patients with HF, adjustment of the diuretic dose may relieve symptoms due to congestion, allowing the ACEI to be continued.

Angioedema: The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%. There have been a number of published case reports of angioedema in patients treated with an AIIRA. In approximately one third of these cases, the patients previously experienced angioedema with an ACEI.[10-19] Therefore, an AIIRA should be used with extreme caution, if at all, in patients who have previously experienced angioedema.[11, 19]

Hyperkalemia: It is unclear at this time if treatment with an AIIRA would be an appropriate alternative in patients who develop hyperkalemia on an ACEI. In SOLVD, hyperkalemia with potassium levels greater than 5.5 mmol/L was reported in 6.4% of patients on enalapril compared to 2.5% of patients on placebo.[3] In the ELITE Study, an increase in serum potassium of $\geq$ 0.5 mmol/L above baseline was observed in 22.7% patients receiving captopril compared to 18.8% of patients on losartan.[5] The proportion of patients with potassium levels $\geq$ 5.5 mmol/L did not differ significantly among the treatment groups in the RESOLVD Pilot Study.[20]

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[20] McKelvie RS, Yusuf S, Pericak D et al. for the RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study. Circulation 1999;100:1056-64.

Heart Failure:

According to the ACC/AHA guidelines[1] and the PBM-MAP The Pharmacologic Management of Chronic Heart Failure (refer to www.vapbm.org or http://vaww.pbm.med.va.gov), an AIIRA may be considered in patients with HF on standard therapy who are intolerant to an ACEI (e.g., due to cough or possibly angioedema).

The Val-HeFT (Valsartan Heart Failure Treatment) trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF on standard therapy (diuretics: 85%; ACEI: 93%; beta-adrenergic blockers: 35%; and digoxin 67%). Baseline left ventricular ejection fraction (LVEF) was 27%. Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily) or placebo. Mean follow-up was 23 months. The two primary endpoints were mortality and the combined endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). Overall mortality was similar, occurring in 19.7% of patients in the valsartan group and 19.4% of patients on placebo (P=0.80). The combined primary endpoint occurred in 28.8% and 32.1% of patients on valsartan and placebo, respectively (RR 0.87 CI 0.77-0.97, P=0.009; ARR 3.3%; NNT=30.3). This included a reduction in hospitalizations for HF (13.8% valsartan vs. 18.2% placebo; ARR 4.4%; NNT=22.7). However, death from any cause (as first event) was higher in patients on valsartan compared to patients receiving placebo (14.2% vs. 12.6%, respectively). According to a subgroup analysis, there was an increased risk of mortality (P=0.0009) and a trend toward an increased risk of combined morbidity and mortality (P=0.10) in patients receiving valsartan in conjunction with an ACEI and beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a significant reduction in mortality (P=0.012). Patients on valsartan but not on an ACEI (with or without a beta-adrenergic blocker) had a lower risk of death (RR 0.67, CI 0.42-1.06) and a lower risk of the combined endpoint (RR 0.56, CI 0.39-0.81).[2]

In the ELITE Study, the AIIRA losartan (titrated to 50mg qd) was compared to an ACEI, captopril (titrated to 50mg tid), in 722 patients with NYHA class II to IV HF and LVEF < 40%, for 48 weeks. Death and/or hospitalization for HF occurred in 9.4% of patients on losartan and 13.2% on captopril (32% risk reduction, P=0.075). These results were primarily due to a 46% decrease in all-cause mortality in patients on losartan compared to patients on captopril (P=0.035), primarily due to a reduction in sudden cardiac death. The two treatment groups did not differ in the frequency of hospital admission for HF. NYHA functional class improved significantly and similarly compared to baseline for both groups.[3] The favorable mortality rate in the losartan group was not hypothesized *a priori*. Therefore, replication of the results was attempted in ELITE II.

ELITE II enrolled 3,152 HF patients to evaluate the effects of losartan (50mg qd) compared to captopril (50mg tid) on overall mortality and cardiac events (sudden cardiac death or resuscitated cardiac arrest) after a mean follow-up of approximately 2 years. There was no significant difference in all-cause mortality between the treatment groups. Patients taking captopril experienced a lower incidence of events compared to losartan (event rate 15.9% vs. 17.2%, respectively), but the difference was not statistically significant (P=0.16). There was no difference between the groups in sudden death, HF mortality, MI, stroke, or noncardiovascular deaths.[4]

Combination ACEI and AIIRA: In addition to the data presented above from the Val-HeFT trial, the RESOLVD Pilot Study compared candesartan, enalapril, and the combination of the two agents in 768 patients with NYHA class II to IV HF with a LVEF < 40%. Patients were placed on either candesartan (4, 8, or 16mg), candesartan (4 or 8mg) plus enalapril (20mg), or enalapril (20mg) for 43 weeks. The primary endpoints were exercise tolerance, ventricular function, quality of life, neurohormone levels, and tolerability. There was no significant difference between the treatment groups in results of the six-minute walk test, NYHA functional class, or quality of life. There was a trend toward an increase in ejection fraction, although not significant, in the patients treated with candesartan and enalapril compared to patients on candesartan or enalapril. End-diastolic and end-systolic volumes increased less with combination therapy compared with patients on candesartan or enalapril alone.[5] Although not powered to evaluate morbidity and mortality, another analysis suggested that there might be an increase in HF hospitalizations in the patients receiving candesartan by 3-way group comparison.[6] Other short-term trials have demonstrated a beneficial effect of combination therapy on hemodynamic and neurohormonal parameters. However, the long-term benefits of combination therapy has not been established.[7]

Recent MI: Patients with a recent MI and evidence of HF experienced a significant decrease in all-cause mortality and risk of developing severe heart failure when treated with an ACEI compared to placebo.[8-10] Future results of clinical trials should provide data as to the potential benefit of the AIIRAs in patients with a recent MI.[11-12]

Results of these studies do not provide enough evidence to recommend for or against using the AIIRAs in the management of HF unless there is a lack of tolerance to an ACEI.

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Renal Disease:

Recommendations of JNC VI include use of an ACEI in treating HTN in patients with type 1 or type 2 DM with proteinuria[1] [the nondihydropyridine calcium channel blockers (NCCBs) may also be beneficial][1-4] and in patients with renal insufficiency. [1] Although designed differently than the trials evaluating the effect of an ACEI on renal function, the United Kingdom Prospective Diabetes Study (UKPDS) 39 compared treatment with an ACEI vs. a beta-blocker in type 2 DM patients with tightly controlled blood pressure (goal < 150/85 mm Hg) in preventing macrovascular and microvascular complications (primary endpoints). The primary endpoints and surrogate endpoint of albuminuria was not significantly different between groups.[5] However, according to a meta-analysis in patients with DM and nephropathy, ACEIs and NCCBs were more effective than beta-blockers and/or diuretics in reducing urinary albumin excretion (UAE).[6] Treatment with an ACEI in patients with DM has also resulted in a decrease in cardiovascular morbidity and mortality. [7]

Angiotensin-converting enzyme inhibitors have also proven to be beneficial in normotensive patients with type 1 or 2 DM with microalbuminuria[8-10] and in patients with type 1 DM and nephropathy.[11] When compared to other antihypertensive agents, ACEI are more effective in delaying the development of end-stage renal disease from causes other than DM. [2,12,13]

The results of recently published trials demonstrate that treatment with an AIIRA is effective in patients with type 2 DM with microalbuminuria or nephropathy.[14-17] Further investigation is needed comparing an ACEI to an AIIRA to determine if these agents provide similar benefit in patients with DM and microalbuminuria or nephropathy.

AIIRA trials in type 2 DM and microalbuminuria or diabetic nephropathy

Trial	Methods	Results	Comments
IRMA 2[14] R, DB, PC Supported by BMS and Sanofi-Synthelabo	590 pts w/HTN, type 2 DM, persistent microalbuminuria, sCr nmt 1.5mg/dl men/1.1mg/dl women (194 IRB 300mg, 195 IRB 500mg, 201 PL) Mean age: 58 years HbA_{1c}: IRB 300mg 7.1%, IRB 150mg 7.3%, PL 7.1% Pts on ACEI excluded F/U: 2yrs PEP: time to onset DN (persistent albuminuria in overnight specimens, with UAE rate >200μg/min and at least 30%> BL)	PEP developed in: IRB 300mg (5.2%; HR 0.3, CI 0.14-0.61; P<0.001 vs. PL); ARR: 9.7% IRB 150mg (9.7%; HR 0.61, CI 0.34-1.08; P=0.08 vs. PL); ARR:5.2% PL (14.9%) *NNT for PEP: 10.2 IRB 300mg; 19.3 IRB 150mg*	Secondary Endpoints <u>UAE rate</u> IRB 300mg ↓ 38% IRB 150mg ↓24% PL ↓2% (P<0.001 both IRB vs. PL; P<0.001 IRB 300mg vs. IRB 150mg) <u>↓ CrCl</u> Initial and sustained ↓ CrCl not stat sig between groups <u>Average trough BP</u> IRB 300mg 141/83 mm Hg IRB 150mg 143/83 mm Hg PL 144/83 mm Hg (P=0.004 vs. IRB)
IDNT[15] R, DB, PC Supported by BMS and Sanofi-Synthelabo	1715 pts w/ type 2 DM and DN (579 IRB 300mg, 567 AML 10mg, 569 PL controlled HTN) Mean age: 59 years HbA_{1c}: IRB 300mg 8.1%, AML 10mg 8.2%, PL 8.2% Pts on ACEI excluded F/U: mean 2.6yrs PEP: composite doubling baseline sCr, development of ESRD, or all-cause death	IRB ↓ PEP by 20% (RR 0.80, CI 0.66-0.97) vs. PL (P=0.02); ARR: 6.4% IRB ↓ PEP 23% (RR 0.77, CI 0.63-0.93) vs. AML (P=0.006); ARR:8.5% *NNT for PEP:15.7 IRB 300mg*	Secondary Endpoints <u>Doubling sCr</u> IRB ↓ 33% vs. PL (P=0.003) IRB ↓ 36% vs. AML (P<0.001) <u>ESRD</u> IRB ↓ 23% vs. PL and AML (P=0.07) <u>Death from any cause</u> IRB ↓ 8% vs. PL; AML ↓ 12% vs. PL Not stat sig between groups BP not stat sig IRB vs. AML
RENAAL[16] R, DB, PC Supported by Merck and Co.	1513 pts w/ type 2 DM and DN [751 LOS 50-100mg (71% 100mg/d), 762 PL) Mean age: 60 years HbA_{1c}: LOS 8.5%, PL 8.4% Pts on ACEI excluded F/U: mean 3.4yrs PEP: composite doubling baseline sCr, ESRD, or death	LOS ↓ PEP 16% (RR 0.84, CI 0.72-0.98) vs. PL (P=0.02); ARR:3.6% *NNT for PEP: 28.0 LOS 50-100mg*	Secondary Endpoints <u>CV morbidity and mortality</u> LOS ↓ 10% vs. PL (P=0.26) <u>UAC ratio</u> LOS ↓ 35% (P<0.001 overall treatment effect) <u>Rate of decline in renal function</u> LOS ↓ 18% vs. PL (P=0.01) <u>Doubling sCr</u> LOS ↓ 25% vs. PL (P=0.006) <u>ESRD</u> LOS ↓ 28% vs. PL (P=0.02) No effect on death rate vs. PL BP not stat sig LOS vs. PL

ACEI=angiotensin-converting enzyme inhibitor; AML=amlodipine; ARR=absolute risk reduction; BL= baseline; BMS=Bristol-Myers Squibb; BP=blood pressure; CI=95% confidence interval; CrCl=creatinine clearance; DN=diabetic nephropathy; ESRD=end-stage renal disease; F/U=follow-up; HTN=hypertension; HR=hazard ratio; IRB=irbesartan; LOS=losartan; nmt=no more than; NNT=number needed to treat; PC=placebo-controlled; PEP=primary endpoint; PL=placebo; RR=relative risk; sCr=serum creatinine; stat sig=statistically significant; UAC=urinary albumin:creatinine; UAE=urinary albumin excretion

A few studies have been conducted comparing an ACEI to an AIIRA. Losartan 50mg was compared to enalapril 20mg in 93 patients with HTN. There were similar reductions in blood pressure and a significant reduction in UAE with the two agents. The effect on UAE was more evident in the patients with baseline microalbuminuria.[18] Losartan was also compared to enalapril in a study of 16 patients with type 1 DM and nephropathy for 2 months. The blood pressure was decreased in both groups. There was not a statistically significant difference between losartan 100mg and enalapril 20mg in the reduction in UAE.[19] In another trial comparing losartan with enalapril in 92 patients with HTN and type 2 DM with early nephropathy, blood pressure and UAE significantly decreased in both treatment groups after one year.[20] In a study comparing valsartan with captopril in 122 patients with type 2 DM and microalbuminuria, valsartan demonstrated a similar reduction in UAE rate as captopril after one year of follow-up.[21] Long-term studies are needed to evaluate the effectiveness of combination therapy with and ACEI and AIIRA.[4]

The Candesartan and Lisinopril Microalbuminuira (CALM) study compared the effects of candesartan 16mg, lisinopril 20mg, or the combination on UAE and blood pressure in 197 patients with HTN, type 2 DM, and microalbuminuria. There was a statistically significant reduction in blood pressure in all treatment groups, with the greatest reduction in patients on combination therapy. Urinary albumin:creatinine ratio was reduced with candesartan (24%, 0% to 43%; P=0.05), lisinopril (39%, 20% to 54%; P<0.001), and combination therapy (50%, 36% to 61%; P<0.001).[22] Combination therapy decreased the urinary albumin:creatinine ratio 34% compared to patients on candesartan alone (P=0.04). The difference between combination therapy and lisinopril was not statistically significant. Combination with an ACEI and NCCB may also be considered in patients with inadequate response to an ACEI alone.[4,23] Every attempt should be made to control blood pressure in patients with HTN.

As with the ACEIs, similar precautions are recommended for the AIIRAs in patients with renal artery stenosis. As seen in ELITE, where the primary endpoint was the effect of treatment on serum Cr ($\geq$ 0.3mg/dL increase), there was no difference between treatment with an ACEI vs. an AIIRA in the rise in serum creatinine during continued treatment.[24] It is unknown if an AIIRA can be used as an alternative in patients where treatment with an ACEI is limited due to renal dysfunction or in a patient who develops renal dysfunction as a result of treatment with an ACEI.[25]

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