Angiotensin II Receptor Antagonist Criteria for Use in Veteran Patients

VHA Pharmacy Benefits Management-Strategic Healthcare Group and Medical Advisory Panel

*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 should utilize this guidance and interpret it in the clinical context of the individual patient. Refer to the PBM-MAP The Pharmacologic Management of Chronic Heart Failure and the VHA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care at **www.oqp.med.va.gov**, **www.pbm.va.gov** or **http://vaww.pbm.med.va.gov** for recommendations on dosing, potential drug interactions, side effects and precautions of the angiotensin II receptor antagonists and cost comparison with other agents.*

Recommendations for Patients with Heart Failure (HF)	**#1**
Patients with systolic HF should be maximized on therapy with agents such as an angiotensin-converting enzyme inhibitor (ACEI), beta-adrenergic blocker, diuretic, and aldosterone antagonist, as indicated. **Criteria for Angiotensin II Receptor Antagonist:** ☐ Patient with systolic HF[a] (or HF/evidence of systolic dysfunction after acute myocardial infarction) who is intolerant to an ACEI[b] ☐ Combination therapy with an ACEI (at optimal dose) and an angiotensin II receptor antagonist may be considered in patients with systolic HF[a] however, due to conflicting data as to whether combination therapy of an AIIRA and ACEI, with or without a beta-adrenergic blocker, is of overall benefit in patients with systolic HF[a] (refer to Discussion section), it is recommended that cardiology consultation or suitable alternative mechanism be established to evaluate the appropriateness of combination therapy based on the patient's clinical status and concomitant medications (note: combination therapy in patients with HF/evidence of systolic dysfunction after acute myocardial infarction is not routinely recommended; refer to Discussion section)	**Met Either Criteria?** ☐ yes ☐ no *If yes, patient is eligible for angiotensin II receptor antagonist*
Recommendations for Patients with Diabetes Mellitus (DM) and Kidney Disease	**#2**
Standard therapy for patients with DM and kidney disease includes treatment with an ACEI. As treatment with an angiotensin II receptor antagonist has been shown to reduce the combined endpoint of increasing sCr, end-stage renal diseases (ESRD), and death in patients with type 2 DM and nephropathy with hypertension (HTN) and/or on antihypertensive medications, an angiotensin II receptor antagonist may be considered as another treatment option in this patient population. Combination therapy with an ACEI and angiotensin II receptor antagonist in patients with nondiabetic kidney disease with persistent proteinuria may be considered, although national treatment guidelines recommend the benefits be confirmed in other trials with a larger patient population (refer to Discussion section). **Criteria for Angiotensin II Receptor Antagonist:** ☐ Patient with type 2 DM and nephropathy[c] with HTN (or receiving antihypertensive medication) ☐ National treatment guidelines have also recommended an angiotensin II receptor antagonist in patients with DM and kidney disease or nondiabetic kidney disease with proteinuria who are intolerant to an ACEI[b]. Use of an angiotensin II receptor antagonist should be considered in patients who are intolerant to an ACEI[b] in this situation, although long-term survival data are not available ☐ Combination therapy with an ACEI and angiotensin II receptor antagonist may be considered in patients with diabetic kidney disease with persistent proteinuria (> 1gm/day) despite being appropriately titrated to an optimal dose of an ACEI (note: combination with an ACEI and nondihydropyridine calcium channel blocker may also be considered; if an angiotensin II receptor antagonist is prescribed in combination with an ACEI, the angiotensin II receptor antagonist should be discontinued if the patient does not respond, or experiences an adverse event such as hyperkalemia, as the long-term benefits and/or safety of this combination have not been established)	**Met Either Criteria?** ☐ yes ☐ no *If yes, patient is eligible for angiotensin II receptor antagonist*
Recommendations for Patients with HTN	**#3**
As per national treatment guidelines, thiazide-type diuretics are the preferred agents for patients with uncomplicated HTN; other agents reported to have benefits in reducing morbidity or mortality should be considered in patients who have a contraindication to or are inadequately controlled [e.g., ACEI, beta-adrenergic blocker, or long-acting calcium channel blocker (CCB)]. These agents in turn can be used together or in combination with other selected agents to achieve goal blood pressure. An angiotensin II receptor antagonist may be used as adjunct treatment or as specified below (also refer to Discussion section). In addition, angiotensin II receptor antagonists are appropriate in patients who have a compelling indication for an ACEI, but are intolerant to an ACEI (refer to Discussion section). **Criteria for Angiotensin II Receptor Antagonist:** ☐ In a patient treated with an ACEI in combination therapy with at least one other antihypertensive agent (e.g., thiazide-type diuretics, beta-adrenergic blockers, long-acting CCBs, etc), where the blood pressure is at or near goal, but is intolerant to the ACEI[b] ☐ In a patient with an indication for an ACEI, per VHA/DoD guidelines, but is intolerant to an ACEI[b]	**Met Either Criteria?** ☐ yes ☐ no *If yes, patient is eligible for angiotensin II receptor antagonist*

[a] **Systolic HF = LVEF ≤ 40% and New York Heart Association (NYHA) functional class II-IV**

[b] Intolerant to an ACEI = Unable to tolerate an ACEI due to cough or other non life-threatening reason. It is unknown if an angiotensin II receptor antagonist can be safely used as an alternative in patients who develop renal dysfunction, hyperkalemia, or angioedema with an ACEI; or where treatment with an ACEI is limited due to renal dysfunction, as these adverse events have also occurred with the use of an angiotensin II receptor antagonist (refer to Discussion section)

[c] Type 2 DM and nephropathy refers to patients with nephropathy (proteinuria > 0.5g/24h) due to type 2 DM

Approved by Physician: _____ **Date/Time:** _____

Discussion

Summary of recommendations for use of an angiotensin II receptor antagonist in patients with systolic heart failure (HF) with or without recent myocardial infarction (MI)

Heart Failure:

- The absence of data that angiotensin II receptor antagonists are superior to ACEIs (angiotensin-converting enzyme inhibitors) in patients with systolic HF precludes them as the drug of choice in HF. There is good evidence that an angiotensin II receptor antagonist is beneficial in reducing CV (cardiovascular) mortality and HF hospitalizations when used in patients who are intolerant to an ACEI and are therefore recommended in this setting.
- There are conflicting data as to whether combination of an angiotensin II receptor antagonist with an ACEI, with or without a beta-adrenergic blocker, is of overall benefit. One trial reported results that the addition of an angiotensin II receptor antagonist to treatment with an ACEI (93%) and beta-adrenergic blocker (35%) reduced the primary endpoint of combined morbidity and mortality in patients with HF, but showed an increase in mortality compared to placebo in the subgroup of those patients who received an angiotensin II receptor antagonist, ACEI, and beta-adrenergic blocker. Results from another trial demonstrated a reduction in combined CV mortality and HF hospitalizations when an angiotensin II receptor antagonist was added to therapy with an ACEI (100%) and a beta-adrenergic blocker (55%), without an increase in mortality in the subgroup of patients receiving all three medication classes. The difference in all-cause mortality or combined CV mortality and HF hospitalizations was not statistically significant with an angiotensin II receptor antagonist in the subgroup of patients on an ACEI (without beta-adrenergic blocker therapy), whereas the other trial did demonstrate a statistically significant reduction in combined morbidity and mortality with an angiotensin II receptor antagonist and ACEI (without a beta-adrenergic blocker), but not a difference in mortality. Data from a meta-analysis showed that all-cause mortality with the combination of an angiotensin II receptor antagonist and ACEI in patients with HF was not statistically significantly different compared to an ACEI alone, but was beneficial in decreasing HF hospitalizations. These data as well as where an aldosterone antagonist fits into the patient's therapy should be considered before prescribing an angiotensin II receptor antagonist in combination with an ACEI. In addition, patients should be closely monitored if combination therapy with an ACEI, angiotensin II receptor antagonist, and aldosterone antagonist is deemed appropriate, as the safety and efficacy of this combination has not been established.

HF with Acute MI:

- Results of outcome trials are not available to provide enough evidence in favor of recommending an angiotensin II receptor antagonist over an ACEI in patients with acute MI and HF/evidence of systolic dysfunction. An angiotensin II receptor antagonist should be used in this patient population who are ACEI intolerant.
- The combination of an angiotensin II receptor antagonist with an ACEI did not demonstrate a statistically significant improvement in all-cause mortality of CV endpoints compared to an angiotensin II receptor antagonist alone and resulted in an increase in adverse events and is therefore not routinely recommended in this patient population.

Heart Failure Discussion:

According to the ACC/AHA guidelines[1] and the PBM-MAP The Pharmacologic Management of Chronic Heart Failure (refer to http://www.pbm.va.gov/guidelines/28766chronicheartfailure.pdf), an angiotensin II receptor antagonist may be considered in patients with HF on standard therapy (e.g., diuretic, beta-adrenergic blocker, and usually digoxin) that are intolerant to an ACEI due to cough or possibly, angioedema. The combination of hydralazine and isosorbide dinitrate (HYD/ISDN) may be considered as an alternative to an ACEI in patients who are on standard therapy and are unable to tolerate an ACEI due to hypotension, renal insufficiency, or possibly, angioedema.

Combination of an angiotensin II receptor antagonist and an ACEI may be considered to decrease HF hospitalizations, however, there is conflicting data as to the effect of this combination on all-cause mortality. In addition, patients with recent NYHA (New York Heart Association) class IV HF and current class III or IV symptoms and left ventricular ejection fraction (LVEF) $\leq$ 35%, should be considered as a candidate for an aldosterone antagonist (provided the patient has preserved renal function and normal potassium levels), as low dose spironolactone was shown to improve symptoms, decrease hospitalizations for worsening HF, and decrease mortality in this patient population.[2]

In earlier trials such as ELITE (Evaluation of Losartan in Elderly Study),[3] the angiotensin II receptor antagonist losartan (titrated to 50mg once daily) 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), largely due to a reduction in sudden cardiac death. The two treatment groups did not differ in the frequency of hospital admissions for HF. NYHA functional class improved significantly and similarly compared to baseline for both groups. 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[4] enrolled 3,152 HF patients (mean LVEF 31%) to evaluate the effects of losartan 50mg once daily compared to captopril 50mg tid (diuretics: 78%; beta-adrenergic blockers: 22%; and digoxin 50%) 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. There is some speculation that the dose of losartan may have been suboptimal in these trials.[5]

The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study[6] 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 candesartan (4, 8, or 16mg/day), candesartan (4 or 8mg/day) plus enalapril (20mg/day), or enalapril (20mg/day) 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. 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.[7]

It wasn't until more recent studies, as described below, that recommendations for the use of an angiotensin II receptor antagonist in patients with HF could be based on more conclusive evidence (refer to Table 1 for detailed results).

The Val-HeFT (Valsartan Heart Failure Treatment)[8] trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF (baseline LVEF 27%) on standard therapy (diuretics: 85%; ACEI: 93%; beta-adrenergic blockers: 35%; and digoxin 67%). Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily; 84% achieved target dose; mean 254mg/day) or placebo. Mean follow-up was 1.9 years. 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 in the two groups. There was a 13% relative risk reduction in the combined primary endpoint in patients on valsartan compared to placebo. 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=0.009) 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. In the subgroup of patients who were on an ACEI without a beta-adrenergic blocker, there was a statistically significant reduction in the combined endpoint of morbidity and mortality (P=0.002) but the difference in all-cause mortality was not statistically significant. 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; 95% CI 0.42-1.06) and a lower risk of the combined endpoint (RR 0.56; 95% CI 0.39-0.81).[8] Another publication of the subanalysis of the 366 patients in Val-HeFT who were not on an ACEI reported a 33% decrease in all-cause mortality (P=0.017) and a 53% decrease in combined morbidity and mortality (P<0.001) in those treated with an AIIRA compared to placebo.[9] Valsartan is FDA approved for the treatment of NYHA class II-IV HF in patients who are intolerant to an ACEI.

The CHARM-Added trial[10] randomized 2548 patients with LVEF $\leq$ 40% (mean LVEF 28%; NYHA class: II 24%; III 73%; IV 3%) to candesartan (61% achieved target dose at 6 months; mean dose 24mg/day) in addition to standard therapy for HF (diuretics: 90%; ACEIs: 100%; beta-adrenergic blockers: 55%; digoxin: 58%; spironolactone: 17%) for 3.4 years. The combined primary endpoint of CV mortality or HF hospitalization was statistically significantly reduced by 15% compared to placebo. The difference in all-cause mortality was not statistically significant. In the subgroup of patients on therapy with candesartan in combination with an ACEI and beta-adrenergic blocker, there was a significant risk reduction in the primary endpoint of CV death or HF hospitalization compared to patients on placebo. The difference in all-cause mortality was not statistically significant. These results differ from the subgroup analysis of patients enrolled in Val-HeFT as described above.

The CHARM-Alternative trial[11] randomized 2028 patients with LVEF $\leq$ 40% (mean LVEF 30%; NYHA class: II 48%; III 48%; IV 4%), on standard therapy for HF (diuretics: 85%; beta-adrenergic blockers: 55%; digoxin: 45%; spironolactone: 25%) with a history of ACEI intolerance (ACEI: 0%), to candesartan (59% achieved target dose at 6 months; mean dose 23mg/day) or placebo for 2.8 years. Cough was reported in 70% of patients as the reason for ACEI intolerance. The combined primary endpoint of CV mortality or HF hospitalization was reduced by 23% in patients on candesartan compared to placebo. There was not a statistically significant reduction in all-cause mortality. Candesartan received FDA approval for the treatment of NYHA class II-IV HF and LVEF $\leq$ 40% to reduce the risk of death from cardiovascular causes and to reduce HF hospitalizations. Candesartan is also FDA approved for use in combination with an ACEI.

The CHARM-Preserved trial[12] enrolled 3023 patients with HF and LVEF > 40%. The reduction in the primary endpoint of CV mortality or HF hospitalizations did not reach statistical significance (P=0.118).

The CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) Overall program[13] combined the results of the three CHARM trials above and reported results of treatment with candesartan or placebo over 3 years in 7599 patients with symptomatic HF (NYHA class: II 45%; III 52%; IV 3%) on standard therapy (diuretics: 83%; ACEI: 0-100% depending on the protocol; beta-adrenergic blockers: 55%; digoxin: 43%; spironolactone: 17%). Patients were randomized to candesartan 4mg once daily and titrated to a target dose of 32mg once daily (63% achieved target dose at 6 months; mean dose 24mg/day). The primary outcome of all-cause mortality was reduced with candesartan, although the result did not achieve statistical significance. There was a 12% reduction in mortality in a subgroup analysis of patients with LVEF $\leq$ 40% that was statistically significant (P=0.018). The secondary endpoint of combined CV death or HF hospitalization was significantly reduced by 16% compared to placebo. Results of CHARM-Alternative[11] confirm the recommendation from Val-HeFT[8] to use an angiotensin II receptor antagonist in patients who are intolerant of an ACEI. The results of CHARM-Added[10] support the recommendation that the combination of an angiotensin II receptor antagonist with an ACEI and beta-adrenergic blocker may reduce

cardiovascular death and HF hospitalizations. The effect of combination therapy with an angiotensin II receptor antagonist, ACEI, and beta-adrenergic blocker on all-cause mortality requires further study. A meta-analysis of 38,080 patients reported that use of an angiotensin II receptor antagonist in patients with HF reduced all-cause mortality [OR (odds ratio) 0.83; 95% CI 0.69-1.00] compared to placebo, although this was influenced largely by data from CHARM-Alternative, and the reduction was not statistically significant when results from this trial were excluded from the analysis. There was a statistically significant reduction in HF hospitalizations (OR 0.64; 95% CI 0.53-0.78) with an angiotensin II receptor antagonist compared to placebo. When data with an angiotensin II receptor antagonist was compared to results with an ACEI, there was not a statistically significant difference in all-cause mortality or HF hospitalizations. The analysis also compared data with an angiotensin II receptor antagonist in combination with an ACEI vs. an ACEI alone and reported that there was not a statistically significant difference in all-cause mortality between the two treatment groups, but there was a statistically significant reduction in HF hospitalizations (OR 0.77; 95% CI 0.69-0.87).[14] These results are similar to a previous meta-analysis of 12,469 patients where there was a trend toward improved mortality and hospitalizations with an angiotensin II receptor antagonist compared to placebo in patients not on an ACEI, and the combination of an angiotensin II receptor antagonist and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone.[15]

Table 1. Results of CHARM and Val-HeFT Trials in Patients with HF[a]

CHARM-Overall						
Outcomes	**Candesartan (N=3803)**	**Placebo (N=3796)**	**Unadjusted HR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (3.1 years)**
All-cause mortality[b]	886 (23%)	945 (25%)	0.91 (0.83-1.00)	0.055	-	-
CV mortality or HF hospitalization	1150 (30.2%)	1310 (34.5%)	0.84 (0.77-0.91)	<0.0001	4.3%	23
CV mortality	693 (18.2%)	796 (20.3%)	0.88 (0.79-0.97)	0.012	2.8%	36
HF hospitalization	757/3801 (19.9%)	918 (24.21%)	0.79 (0.72-0.87)	<0.0001	4.3%	23
CHARM-Alternative						
Outcomes	**Candesartan (N=1013)**	**Placebo (N=1015)**	**Unadjusted HR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (2.8 years)**
All-cause mortality	265 (26.2%)	296 (29.2%)	0.87 (0.74-1.03)	0.11	-	-
CV mortality or HF hospitalization[b]	334 (33.0%)	406 (40.0%)	0.77 (0.67-0.89)	<0.0001	7%	14
CV mortality	219 (21.6%)	252 (24.8%)	0.85 (0.71-1.02)	0.072	-	-
HF hospitalization	207 (20.4%)	286 (28.2%)	0.68 (0.57-0.81)	<0.001	7.7%	13
CHARM-Added						
Outcomes	**Candesartan (N=1276)**	**Placebo (N=1272)**	**Unadjusted HR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (3.4 years)**
All-cause mortality	377 (30.0%)	412 (32.0%)	0.89 (0.77-1.02)	0.086	-	-
CV mortality or HF hospitalization[b]	483 (37.9%)	538 (42.3%)	0.85 (0.75-0.96)	0.011	4.4%	23
CV mortality	302 (23.7%)	347 (27.3%)	0.84 (0.72-0.98)	0.029	3.6%	28
HF hospitalization	309 (24.2%)	356 (28.0%)	0.83 (0.71-0.96)	0.014	3.8%	27
Val-HeFT						
Outcomes	**Valsartan (N=2511)**	**Placebo (N=2499)**	**RR (97.5% CI)**	**P value**	**ARR[c]**	**NNT[c] (1.9 years)**
All-cause mortality[b]	495 (19.7%)	484 (19.4%)	1.02 (0.88-1.18)[d]	0.80	-	-
All-cause mortality and morbidity[b]	723 (28.8%)	801(32.1%)	0.87 (0.77-0.97)	0.009	3.3%	31
HF hospitalization	348 (13.8%)	454 (18.2%)	0.725	<0.001	4.4%	23

[a] CV=cardiovascular; HF=heart failure; HR=hazard ratio; RR=relative risk
[b] Primary endpoint
[c] Calculated value (ARR=absolute risk reduction; NNT=number needed to treat)
[d] 98% Confidence Interval

HF with Acute MI Discussion:

The recommendation to use an angiotensin II receptor antagonist in patients with an acute MI and HF/evidence of systolic dysfunction who are intolerant to an ACEI is based on the following data.

VALIANT (The Valsartan in Acute Myocardial Infarction Trial) [16] evaluated the effects of the angiotensin II receptor antagonist valsartan (target dose of 160 mg twice daily), the ACEI captopril (target dose of 50 mg three times daily) and the combination of valsartan and captopril (target dose of 80 mg twice daily and 50 mg three times daily, respectively) over a 2 year period on all-cause mortality in 14,808 high-risk (i.e., signs and symptoms of acute HF, or left ventricular systolic dysfunction) patients within 0.5 to 10 days of an acute MI. The study reported a similar mortality rate with valsartan as with captopril. The combination of captopril plus valsartan resulted in an increased incidence of adverse events, without improving survival. Similar results were seen for the composite secondary endpoint of fatal and nonfatal cardiovascular events (Refer to Table 2). In addition, approximately 70% of patients enrolled were receiving concomitant therapy with a beta-adrenergic blocker and according to subgroup analysis, there was not an increase in mortality in patients receiving an angiotensin II receptor antagonist and ACEI in addition to a beta-adrenergic blocker. The trial was designed to assess equivalency of an angiotensin II receptor antagonist compared to an ACEI and according to the results, valsartan can be considered as effective as captopril in reducing all-cause mortality and fatal and non-fatal cardiovascular events in this patient population.

According to results of OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan),[17] a trial with losartan (target dose 50mg once daily) compared to captopril (target dose 50mg three times daily) in 5477 high-risk (i.e., signs and symptoms of HF or Q-wave MI) patients with acute MI, the primary endpoint of all-cause mortality was higher (18.2%) in patients on losartan compared to 16.4% of patients on captopril, with a trend toward statistical significance (RR 1.13; 95% CI 0.99-1.28; P=0.069) after a mean follow-up of 2.7 years. There was also not a statistically significant difference between treatment groups in the secondary endpoints. Due to the study design, superiority or non-inferiority of losartan relative to captopril was not shown. As with ELITE II, the target dose of losartan was thought to be suboptimal in this study.[5]

A meta-analysis reported that there was not a difference in all-cause mortality or HF hospitalizations with an angiotensin II receptor antagonist compared with an ACEI in patients with high risk acute MI. This conclusion was based on results of VALIANT and OPTIMAAL, although the data were not pooled due to heterogeneity.[14]

Table 2. Results of VALIANT in Patients with HF and Acute MI[a]

	VALIANT				
Outcomes	**Valsartan (N=4909)**	**Captopril (N=4909)**	**Valsartan + Captopril (N=4885)**	**HR (vs. captopril) (97.5% CI)**	**P value**
All-cause mortality[b]	979 (19.9%)	958 (19.5%)	941 (19.3%)	1.00 (0.90-1.11) 0.98 (0.89-1.09) (combination)	0.98 0.73
Combined CV death, recurrent MI, HF hospitalization	1529 (31.1%)	1567 (31.9%)	1518 (31.1%)	0.95 (0.88-1.03) 0.97 (0.89-1.05) (combination)	0.20 0.37

[a] CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction
[b] Primary endpoint

Summary of recommendations for use of an angiotensin II receptor antagonist in patients with diabetes mellitus (DM) and kidney disease

Type 2 Diabetic Nephropathy

- Data are available that treatment with an angiotensin II receptor antagonist in patients with type 2 DM with nephropathy [plus HTN (hypertension) or on additional antihypertensive medications], reduced the composite endpoints of doubling serum creatinine, ESRD (end-stage renal disease), or death. The ADA (American Diabetes Association), NKF (National Kidney Foundation), and VHA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care also recommend an angiotensin II receptor antagonist in this patient population.

DM and Kidney Disease

- National treatment guidelines have also recommended an angiotensin II receptor antagonist in patients with DM and kidney disease or nondiabetic kidney disease who are intolerant to an ACEI (refer to Discussion below), although long-term outcomes are not available. In addition, the NKF Work Group stated that combination of an ACEI and nondihydropyridine CCB, or ACEI and angiotensin II receptor antagonist, would be reasonable to reduce proteinuria in patients with DM and HTN, although the VA/DoD Clinical Practice Guidelines for the Diagnosis and Management of Hypertension in the Primary Care Setting concludes that it is unknown if the combination of an ACEI and an angiotensin II receptor antagonist provides an advantage over combination with other antihypertensive classes. The NKF stated that the benefit of combination ACEI and angiotensin II receptor antagonist in slowing the progression of nondiabetic kidney disease required further study in a larger patient population.

Diabetes Mellitus and Kidney Disease Discussion:

In patients with DM and HTN, the ADA recommends initial therapy with an ACEI, diuretic, or beta-blocker, due to their consistent beneficial effects of reducing CV events in patients with uncomplicated HTN, although any antihypertensive medication may be used. The ADA also recommends that an angiotensin II receptor antagonist can be used if a patient does not tolerate an ACEI.[18] The JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) states that diuretics, ACEIs, beta-blockers, CCBs, and angiotensin II receptor antagonists have all demonstrated benefit in patients with DM and HTN.[19] The VHA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care (refer to http://www.oqp.med.va.gov/cpg/HTN04/HTN_base.htm) recommend a thiazide-type diuretic or an ACEI as initial therapy in patients with HTN and DM; a beta-blocker, CCB (calcium channel blocker), or angiotensin II receptor antagonist may be considered as additional or alternative therapy.

For specific recommendations in patients with DM, the ADA states that an ACEI is recommended in patients with type 1 DM, with or without HTN, with microalbuminuria or macroalbuminuria.[18] The ACEIs have been reported to be beneficial in patients with type 1 DM with macroalbuminuria to reduce the combined risk of death, dialysis, or transplantation,[20] and in type 1 DM with microalbuminuria to decrease the progression of kidney disease.[21-23] The long-term effects of the angiotensin II receptor antagonists have not been adequately studied in patients with type 1 DM. The ADA recommends an ACEI or AIIRA in patients with type 2 DM, HTN, and microalbuminuria to delay progression to macroalbuminuria.[18] Treatment with an ACEI in trials of patients with type 2 DM that also included a percentage of patients with microalbuminuria, have demonstrated a reduction in CV endpoints.[24-28] Both the ACEIs and the angiotensin II receptor antagonists have resulted in a decrease in the progression of kidney disease in patients with type 2 DM and microalbuminuria.[29-31] As per the results from IDNT and RENAAL in patients with type 2 DM and macroalbuminuria, the ADA states that an angiotensin II receptor antagonist should be strongly considered in this patient population.[18] An ACEI has been shown to decrease surrogate endpoints in patients with type 2 DM and macroalbuminuria, but not long-term outcomes, as the ACEIs have not been as extensively studied in this patient population.[32] According to the ADA, for patients with type 1 or type 2 DM and microalbuminuria or macroalbuminuria, if either an ACEI or angiotensin II receptor antagonist are not tolerated, the other class should be used.[33]

The NKF K/DOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommend an ACEI or angiotensin II receptor antagonist in patients with type 1 or 2 DM and microalbuminuria based on surrogate endpoints. The evidence for this recommendation was graded as strong, due to the benefit seen with these classes in patients with diabetic nephropathy and due to the long duration of follow-up necessary to determine the long-term benefit in patients with microalbuminuria. For patients with type 1 DM and macroalbuminuria, ACEIs are recommended. An angiotensin II receptor antagonist is recommended for patients with type 2 DM and macroalbuminuria. According to the opinion of the NKF Work Group, an ACEI or angiotensin II receptor antagonist may be used to delay the progression of kidney disease in patients with type 2 DM and macroalbuminuria, and an angiotensin II receptor antagonist may be used in patients with type 1 DM and macroalbuminuria who are unable to tolerate an ACEI.[34] It is recommended that an ACEI be used in patients with nondiabetic kidney disease.[34, 35] The NKF strongly recommends treatment with an angiotensin II receptor antagonist in patients with nondiabetic kidney disease if a patient is unable to take an ACEI, this based on short-term studies of surrogate endpoints, therefore grading the evidence as weak. The NKF graded the evidence for combination ACEI and angiotensin II receptor antagonist in slowing the progression of nondiabetic kidney disease as weak, requiring further study. The NKF Work Group stated that combination of an ACEI and angiotensin II receptor antagonist or an ACEI and nondihydropyridine CCB would be reasonable to reduce proteinuria in patients with HTN.[34]

Criteria for Use: Angiotensin II Receptor Antagonists

The recommendation to use an angiotensin II receptor antagonist in patients with type 2 DM and nephropathy are based on the results of two long-term outcome trials in this patient population. The IDNT (Irbesartan Type 2 Diabetic Nephropathy)[36] and RENAAL (Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan)[37] trials both evaluated the effect of an angiotensin II receptor antagonist on the primary endpoint of composite all-cause mortality, doubling of sCr, and ESRD. In IDNT, 1715 patients with HTN, type 2 DM and nephropathy were randomized to irbesartan 300mg once daily, amlodipine 10mg once daily, or placebo for a mean follow-up of 2.6 years.[36] In RENAAL, 1513 patients with type 2 DM and nephropathy (with over 90% % on antihypertensive medications) were randomized to losartan 50-100mg once daily (71% received a dosage of 100 mg once daily) or placebo for a mean follow-up of 3.4 years.[37] Both trials demonstrated a reduction in the primary endpoint with an angiotensin II receptor antagonist compared to placebo[36, 37] and, in IDNT, this endpoint was also significantly reduced compared to amlodipine.[36] The secondary endpoints evaluating cardiac events were not statistically significantly different with an angiotensin II receptor antagonist compared to placebo.[36, 37] Data from IDNT and RENAAL are included in Table 3.

Table 3. Results of IDNT and RENAAL Trials in Patients with HTN and DN[a]

IDNT						
Outcomes	**Irbesartan (N=579)**	**Placebo (N=569)**	**Unadjusted RR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (2.6 years)**
Composite all-cause mortality, ESRD, doubling sCr[b]	189 (32.6%)	222 (39%)	0.80 (0.66-0.97)	0.02	6.4%	16
Doubling sCr	98 (16.9%)	135 (23.7%)	0.67 (0.52-0.87)	0.003	6.8%	15
ESRD	82 (14.2%)	101 (17.8%)	0.77 (0.57-1.03)	0.07	-	-
All-cause mortality	87 (15.1%)	93 (16.3%)	0.92 (0.69-1.23)	0.57	-	-
RENAAL						
Outcomes	**Losartan (N=751)**	**Placebo (N=762)**	**Adjusted RR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (3.4 years)**
Composite all-cause mortality, ESRD, doubling sCr[b]	327 (43.5%)	359 (47.1%)	0.84 (0.72-0.98)	0.02	3.6%	-[d]
Doubling sCr	162 (21.6%)	198 (26.0%)	0.75 (0.61-0.92)	0.006	4.4%	23
ESRD	147 (19.6%)	194 (25.5%)	0.72 (0.58-0.89)	0.002	5.9%	17
All-cause mortality	158 (21.0%)	155 (20.3%)	1.02 (0.81-1.27)	0.88	-	-

[a] ESRD=end-stage renal disease; RR=relative risk; sCr=serum creatinine
[b] Primary endpoint
[c] Calculated value (ARR=absolute risk reduction; NNT=number needed to treat)
[d] NNT not calculable based on crude rates of events

There have also been studies comparing an ACEI to an angiotensin II receptor antagonist, or evaluating their combination, on surrogate endpoints of kidney function. The CALM (Candesartan and Lisinopril Microalbuminuira) study compared the effects of candesartan 16mg, lisinopril 20mg, or the combination on UAE (urinary albumin excretion) and blood pressure in 197 patients with HTN, type 2 DM, and microalbuminuria for 24 weeks. 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). 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.[38] In the COOPERATE trial, 263 Japanese patients with nondiabetic renal disease were randomized to losartan 100mg, trandolapril 3mg, or the combination. The combined primary endpoint of doubling serum creatinine concentration or ESRD occurred in 11% of patients on combination therapy and 23% of patients on losartan (HR 0.40; 95% CI 0.17-0.69; P=0.016), and 23% of patients on trandolapril (HR 0.38; 95% CI 0.18-0.63; P=0.018).[39] There have also been short-term trials in patients with type 1 or 2 DM and nephropathy, with a greater reduction in albuminuria seen with the combination of an angiotensin II receptor antagonist and an ACEI, compared to treatment with an ACEI alone.[40-43] This benefit has also been seen with the combination of an ACEI and NCCB compared to treatment with either agent alone in a long-term trial of patients with type 2 DM and nephropathy.[44] When an angiotensin II receptor antagonist has been compared to an ACEI in trials including patients with type 1 or 2 DM, and microalbuminuria or macroalbuminuria, there has been a similar reduction in surrogate endpoints of kidney function between the two treatment groups.[45-49]

A meta-analysis of data with the ACEIs and the angiotensin II receptor antagonist s in patients with diabetic nephropathy showed that there was a statistically significant reduction in all-cause mortality with the ACEIs vs. placebo (RR 0.79; 95% CI 0.63-0.99; P=0.04). The difference in all-cause mortality with the angiotensin II receptor antagonist s was not statistically significant compared to placebo (RR 0.99; 95% CI 0.85-1.17; P=0.95). The reduction in doubling of sCr and ESRD were not statistically significant (P=0.08 and P=0.07, respectively) with the ACEIs compared to placebo or no treatment. With the angiotensin II receptor antagonist s, the reduction in doubling of sCr (P=0.004), ESRD (P=0.001), microalbuminuria to macroalbuminuria (P=0.001), and microalbuminuria to normoalbuminuria (P=0.02) were

statistically significant compared to placebo or no treatment. The reduction in microalbuminuria to macroalbuminuria (P=0.0007), and microalbuminuria to normoalbuminuria (P=0.0001) were statistically significant with the ACEIs vs. placebo or no treatment. In the three trials comparing an ACEI to an angiotensin II receptor antagonist, there was not a statistically significant difference in renal outcomes (i.e., progression from microalbuminuria to macroalbuminuria; regression from microalbuminuria to normoalbuminuria). The meta-analysis concluded that ACEIs should be used as first-line treatment in patients with diabetic nephropathy due their survival benefit, that which has yet to be demonstrated with the angiotensin II receptor antagonist s.[50]

Summary of recommendations for use of an angiotensin II receptor antagonist in patients with HTN

Hypertension

- Per national treatment guidelines, thiazide-type diuretics are the preferred agents for patients with uncomplicated HTN; another class of agents (e.g., ACEI, beta-adrenergic blocker, or long-acting CCB) reported to have benefits in reducing morbidity or mortality should be considered in patients who have a contraindication to or are inadequately controlled on a thiazide-type diuretic. These agents may be used together or in combination with other selected agents to achieve goal blood pressure. An angiotensin II receptor antagonist may be used as adjunct treatment in a patient where an ACEI is being utilized in combination therapy with at least one other antihypertensive agent (e.g., thiazide-type diuretics, beta-adrenergic blockers, long-acting CCBs, etc), where the blood pressure is at or near goal, but is intolerant to the ACEI ; or when multiple combination therapy does not reach target blood pressure (preferably after documented ACEI intolerance).

- In a patient who has an indication for an ACEI, per VHA/DoD guidelines, but is intolerant to an ACEI, an angiotensin II receptor antagonist may be used to achieve blood pressure control.

Hypertension Discussion:

According to JNC 7[21] and the VHA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care (refer to http://www.oqp.med.va.gov/cpg/HTN04/HTN_base.htm), a thiazide-type diuretic is the preferred therapy for patients with uncomplicated HTN. Another class of agents (e.g., ACEI, beta-adrenergic blockers, CCBs) may be considered in patients who are inadequately controlled, have a contraindication to a thiazide-type diuretic, or in patients who have an indication for an agent in another antihypertensive class. 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 angiotensin II receptor antagonists) may be considered according to the individual needs of the patient; or an angiotensin II receptor antagonist may be considered (refer to section on Additional Considerations); or if an angiotensin II receptor antagonist is required as additional antihypertensive therapy in a patient who is inadequately controlled or cannot tolerate treatment with first or second line therapy as described above.

Recommendations for the use of a thiazide-type diuretic are based on the results of placebo-controlled trials, comparison trials, and meta-analyses. Results of over 40,000 patients with HTN and one other risk factor for CHD (coronary heart disease) enrolled in ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[51] reported that there was not a statistically significant difference in the primary endpoint of combined coronary heart disease or nonfatal MI between treatment with a thiazide diuretic, an ACEI, or a dihydropyridine CCB. There was a statistically significant increase in the relative risk of combined CV disease (10%), stroke (15%), and HF (19%) with an ACEI and an increase in the relative risk of HF (38%) with a dihydropyridine CCB, each compared to a thiazide diuretic. National treatment guideline recommendations for a thiazide-type diuretic as initial and combination therapy also took into consideration the somewhat different results that were seen in an open-label blinded endpoint trial of diuretic-based therapy compared to ACEI-based therapy in the ANBP-2 (Second Australian National Blood Pressure) study. In this trial of over 6,000 patients with HTN (8% CHD; 5% stroke; mean age 72 years; 100% white), treatment with an ACEI-based regimen reduced the primary endpoint of all CV events or death from any cause (HR 0.89; 95% CI 0.79 to 1.00; P=0.05); this difference was statistically significant for males but not females.[52] There has not been a long-term outcome trial comparing a thiazide diuretic with an angiotensin II receptor antagonist in patients with HTN.

Three major clinical trials have been published evaluating treatment with an angiotensin II receptor antagonist in patients with HTN. Results of LIFE (Losartan Intervention for Endpoint reduction in hypertension study)[53] reported that treatment with losartan reduced the composite endpoint of CV death, MI, and stroke compared to atenolol, in 9193 patients with HTN and left ventricular hypertrophy (LVH). When the components of the primary endpoint were analyzed separately, only the difference in fatal and non-fatal stroke achieved statistical significance (refer to Table 4). In a prespecified subgroup of 1195 patients with concomitant DM, the primary endpoint of composite CV death, MI, and stroke were statistically significantly reduced (ARR 5.3%) with losartan compared to atenolol.[54]

Details of the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial[55] are also presented in Table 4. This trial compared treatment with valsartan to amlodipine in 15,245 patients with HTN at high risk for cardiac events. After a mean follow-up of 4.2 years, there was no statistically significant difference in the primary endpoint of combined cardiac mortality and morbidity, nor in any of the pre-specified secondary outcome measures except for a 23% reduction in new onset type 2 DM with valsartan compared to amlodipine in patients without DM at baseline (P<0.0001). There was a statistically significant 19% increase in fatal and non-fatal MI with valsartan compared to amlodipine (P=0.02). When evaluating blood pressure control, there was a statistically significantly lower blood pressure (4.0/2.1 mm Hg at 1 month; 1.5/1.3 mm Hg at 1 year) in the amlodipine group compared to valsartan (P<0.001).

Criteria for Use: Angiotensin II Receptor Antagonists

In SCOPE (The Study on Cognition and Prognosis in the Elderly),[56] 4964 patients with HTN were randomized to treatment with candesartan 8mg to 16mg once daily or placebo (open-label antihypertensive therapy added according to protocol with 84% of patients in the placebo group and 75% in the candesartan group receiving additional antihypertensive therapy). After a mean duration of 3.7 years, the primary endpoint of first major CV event (CV death, non-fatal MI or non-fatal stroke) was not significantly different between the two treatment groups. Only the risk of non-fatal stroke (of the pre-specified secondary endpoints) was statistically significantly reduced by 27.8% with candesartan compared to the placebo group (P=0.04). There was also a statistically significant greater mean reduction in blood pressure of 3.2/1.6 mm Hg with candesartan compared to the control group (P<0.001).

Table 4. Results of LIFE and VALUE Trials in Patients with HTN[a]

LIFE						
Outcomes	**Losartan (N=4605)**	**Atenolol (N=4588)**	**Adjusted HR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (4.8 years)**
Composite CV mortality, MI stroke[b]	508 (11%)	588 (13%)	0.87 (0.77-0.98)	0.021	1.79%	56
CV mortality	204 (4%)	234 (5%)	0.89 (0.73-1.07)	0.206	-	-
Fatal or non-fatal stroke	232 (5%)	309 (7%)	0.75 (0.63-0.89)	0.001	1.7%	59
MI	198 (4%)	188 (4%)	1.07 (0.88-1.31)	0.491	-	-
Total mortality	383 (8%)	431 (9%)	0.90 (0.78-1.03)	0.128	-	-
VALUE						
Outcomes	**Valsartan (N=7649)**	**Amlodipine (N=7596)**	**HR (95% CI)**	**P value**	**ARR[c]**	**NNH[c] (4.2 years)**
Composite cardiac mortality and morbidity[b]	810 (10.6%)	789 (10.4%)	1.04 (0.94-1.15)	0.49	-	-
MI	369 (4.8%)	313 (4.1%)	1.19 (1.02-1.38)	0.02	-	142
HF	354 (4.6%)	400 (5.3%)	0.89 (0.77-1.03)	0.12	-	-
Stroke	322 (4.2%)	281 (3.7%)	1.15 (0.98-1.35)	0.08	-	-
All-cause mortality	841 (11.0%)	818 (10.8%)	1.04 (0.94-1.14)	0.45	-	-

[a] CV=cardiovascular; HF=heart failure; HR=hazard ratio; MI=myocardial infarction
[b] Primary endpoint
[c] Calculated value (ARR=absolute risk reduction; NNH=number needed to harm; NNT=number needed to treat)

Although the results from one of these trials showed that an angiotensin II receptor antagonist may be preferable to a beta-adrenergic blocker in patients with HTN and LVH, or placebo in another trial in patients with HTN in decreasing the risk of stroke, or no difference compared to treatment with a dihydropyridine CCB except for decrease in new onset DM and increased risk of MI; results of comparison trials between an angiotensin II receptor antagonist and a thiazide-type diuretic or an ACEI in patients with HTN are not available. Results of three meta-analysis with the various antihypertensive classes including data with the angiotensin II receptor antagonists, showed that none of the antihypertensive classes were superior to a thiazide-type diuretic for all CV related outcomes and death;[57] there was a reduction in stroke, HF, and major CV events with an angiotensin II receptor antagonist compared to controls;[58] and that greater reduction in blood pressure accounted for the difference in benefit of the angiotensin II receptor antagonists on stroke compared to control therapy.[59]

Additional Considerations

ACEI Induced Cough

- 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-adrenergic blockers, CCBs) unless contraindicated. Use of an AIIRA may be considered in patients who have a specific indication for an ACEI (e.g., systolic HF, evidence of HF with recent MI) where an angiotensin II receptor antagonist has either been reported to be equivalent to an ACEI or demonstrated a reduction in long-term outcomes of morbidity and mortality in a similar patient population **AND** where the patient is unable to tolerate an ACEI due to cough. Patients with a history of cough associated with an ACEI may experience improvement if switched to fosinopril. Patients should be reevaluated once prescribed an angiotensin II receptor antagonist since there is a slight chance that patients may develop a cough with these agents as well.

ACEI Induced Cough Discussion:

The incidence of cough with an ACEI is estimated to be anywhere from 0.5 to 39%.[60] 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 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. In SOLVD (evaluating patients with HF), cough was reported in 37% of patients treated with enalapril compared to 31% of patients randomized to placebo.[61] In V-HeFT II, 37% of HF patients on enalapril complained of cough compared to 29% receiving HYD/ISDN (Hydralazine and isosorbide dinitrate).[62] 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.[63-65]

On the other hand, the incidence of cough associated with the angiotensin II receptor antagonists is similar to placebo (1.6%).[60] 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 angiotensin II receptor antagonist.[3] In the CHARM-Alternative trial, over 70% of patients randomized to candesartan experienced previous intolerance to an ACEI due to cough. In this trial, cough was the reason for discontinuation in 0.2% of patients on candesartan compared to 0.4% patients on placebo.[11] A number of trials evaluating an angiotensin II receptor antagonist in patients with previous ACEI induced cough showed that patients treated with an angiotensin II receptor antagonist complained of cough similar to that seen with placebo (15.6%-36.7% angiotensin II receptor antagonist, 9.7%-31.4% placebo), but statistically significantly less than seen when an ACEI was included (60-97%).[66-73] 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 angiotensin II receptor antagonist.[73]

Angioedema

- An angiotensin II receptor antagonist should be used with caution in patients who have previously experienced angioedema on an ACEI.

Angioedema Discussion:

The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%. The exact mechanism is unknown; in ACEIs, it is thought to be related to bradykinin accumulation. Angioedema has been reported with the angiotensin II receptor antagonists but to a much lesser degree than ACEIs. In the CHARM-Alternative trial with candesartan in patients with HF and a history of ACEI intolerance, 3 of 1013 patients randomized to candesartan experienced angioedema. One of these patients required discontinuation of the drug (0.1%). All 3 cases occurred out of the 39 patients who previously experienced angioedema or anaphylaxis on an ACEI (7.7%). None of the 1015 patients who received placebo experienced angioedema.[11] There have been a number of published case reports of angioedema in patients treated with an angiotensin II receptor antagonist.[60, 74-86] In approximately one third of these cases, the patients previously experienced angioedema with an ACEI. Therefore, an angiotensin II receptor antagonist should be used with caution in patients who have previously experienced angioedema.[74, 82, 83, 85]

Hyperkalemia

- It is unclear if treatment with an angiotensin II receptor antagonist is an appropriate alternative in patients who develop hyperkalemia with an ACEI since they may experience the same adverse effect with an angiotensin II receptor antagonist. An alternative class of antihypertensive agent is recommended or the addition of a diuretic may be considered to offset the hyperkalemia. If use of a diuretic is contraindicated or is not effective, an angiotensin II receptor antagonist may be considered instead of an ACEI, under close monitoring, in patients with moderate renal insufficiency who develop hyperkalemia on an ACEI and who have a strong indication for an ACEI.

Hyperkalemia Discussion:

The angiotensin II receptor antagonists, like the ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to decreased potassium excretion. It is unclear at this time if treatment with an angiotensin II receptor antagonist 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.[61] 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.[3] 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.[5] In the CHARM-Overall programme, hyperkalemia resulted in discontinuation of study drug in 2.2% of patients on candesartan compared to 0.6% patients on placebo (P<0.0001). In the overall analysis, 41% of patients received concomitant treatment with an ACEI and approximately 17% were on spironolactone.[10] The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on lisinopril compared to valsartan with mild renal insufficiency. In patients with moderate renal insufficiency with a GFR (glomerular filtration rate) $\leq$ 60mL/min/1.73 m^2, there was a significant increase of 0.28 mEq/L (P=0.04) above baseline (4.6 mEq/L) with lisinopril. The increase of 0.12 mEq/L seen with valsartan in this subgroup was not significant (P=0.1).[87]

Renal Failure

- It is unknown if an angiotensin II receptor antagonist 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. As with the ACEIs, similar precautions are recommended for the angiotensin II receptor antagonists in patients with renal artery stenosis.

Renal Failure Discussion:

In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system, treatment with the angiotensin II receptor antagonists and ACEIs have been associated with acute renal failure. These drugs are capable of reducing intraglomerular filtration pressure by causing dilation of the efferent renal arterioles. As with the ACEIs, similar precautions are recommended for the angiotensin II receptor antagonists in patients with renal artery stenosis. 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 angiotensin II receptor antagonist in the rise in serum creatinine during continued treatment.[3] It is unknown if an angiotensin II receptor antagonist 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.[88]

References:

[1]Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. American College of Cardiology Web site. Available at:http://www.acc.org/clinical/guidelines/failure/hf_index.htm
[2] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
[3] Pitt B, Segal R, Martinez FA, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure: Evaluation of Losartan in Elderly Study (ELITE). Lancet 1997;349:747-52.
[4] Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial: the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582-7.
[5] Lapointe N, Pourdjabbar A, Rouleau JL. The OPTIMAAL study, not so optimal: the lessons of LIFE, RENAAL and IDNT. Can J Cardiol 2003;19:994-6.
[6] 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.
[7] Greenberg BH. Role of angiotensin receptor blockers in heart failure not yet RESOLVD. Circulation 1999;100:1032-4.
[8] Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
[9] Maggioni AP, Anand I, Gottlieb SO, et al on behalf of the Val-HeFT investigators. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2002;40:1414-21.
[10] Pfeffer MA, Swedberg K, Granger CB, et al. for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759-66.
[11] Granger CB, McMurray JJV, Yusuf S, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.
[12] 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.
[13] Yusuf S, Pfeffer MA, Swedberg K, et al. for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
[14] Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med 2004;141:693-704.
[15] Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. J Am Coll Cardiol 2002;39:463-70.
[16] 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.
[17] Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Lancet 2002;360:752-60.
[18] American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003; 26(Suppl 1):S80-2.
[19] Chobanian AV, Bakris GL, Black HR, et al. for the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. JAMA. 2003;289:2560-2572.
[20] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, for The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-62.
[21] Viberti G, Morgensen CE, Groop LC, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin dependent diabetes mellitus and microalbuminuria. JAMA 1994;271:275-9.
[22] Laffel LM, McGill JR, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria: North American Microalbuminuria Study Group. Am J Med 1995;99:497-504.
[23] The ACE Inhibitors in Diabetic Nephropathy Trialists Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001;134:370-9.
[24] Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9.
[25] Niskanen L, Hedner T, Hansson L, et al. for the CAPPP study group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. Diabetes 2001;24:2091-6.
[26] UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-20.
[27] Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.
[28] Tatti P, Pahor M, Byington RP et al. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.
[29] Ravid M, Savin H, Jutrin I, et al. Long term stabilizing effect of angiotensin-converting enzyme inhibitors on plasma creatinine and proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577-81.
[30] Ravid M, Lang R, Rachmani R, Lishner M. Long term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. Ann Intern Med 1996;156:286-89.
[31] Parving H, Lehnert H, Bröchner-Mortensen J, et al. for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.
[32] Bakris GL, Weir M. ACE inhibitors and protection against kidney disease progression in type 2 diabetes: What's the evidence. J Clin Hypertens 2002;4:420-3.
[33] American Diabetes Association. Diabetic nephropathy. Diabetes Care 2003; 26(Suppl 1):S94-8.
[34] National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis 2004;43(suppl 1):S1-S290.
[35] Jafar TH, Schmid CH, Landa M, et al. for the ACEI Inhibition in Progressive Renal Disease Study Group. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. Ann Intern Med 2001;135:73-87.

[36] Lewis EJ, Hunsicker LG, Clarke WR, et al. for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60.
[37] Brenner BM, Cooper ME, De Zeeuw D, et al. for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
[38] Mogensen CE, Neldam S, Tikkanen I, et al. for the CALM study group. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000;321:1440-4.
[39] Nakao N, Yoshimura A, Morita H, et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. Lancet 2003;361:117-24.
[40] Jacobsen P, Andersen S, Rossing K, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. Kidney Int 2003;63:1874-80.
[41] Jacobsen P, Andersen S, Jensen BR, Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. J Am Soc Nephrol 2003;14:992-9.
[42] Jacobsen P, Andersen S, Rossing K, Hansen BV, Parving HH. Dual blockade of the renin-angiotensin system in type 1 patients with diabetic nephropathy. Nephrol Dial Transplant 2002;17:1019-24.
[43] Rossing K, Christensen PK, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system in diabetic nephropathy: a randomized double-blind crossover study. Diabetes Care 2002;25:95-100.
[44] Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACEI inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 1998;54:1283-9.
[45] Nielsen S, Dollerup J, Nielsen B, Jensen Æ, Mogensen CE. Losartan reduces albuminuria in patients with essential hypertension. An enalapril controlled 3 months study. Nephrol Dial Transplant 1997;12(Suppl 2):19-23.
[46] Anderson S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000;57:601-6.
[47] Lacourciere Y, Belanger A, Godin C, et al. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetes with early nephropathy. Kidney Int 2000;58:762-9.
[48] Muirhead N, Feagan BF, Mahon J, et al. The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. Curr Ther Res 1999;60:650-60.
[49] Barnett AH, Bain SC, Bouter P, et al. for the Diabetics Exposed to Telmisartan and Enalapril Study Group. N Engl J Med 2004;351:1952-61.
[50] Strippolo GFM, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ, doi:10.1136/bmk.38237.585000.7C (published 30 September 2004).
[51] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981-97.
[52] Wing LMH, Reid CM, Ryan P, et al. for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the eldery. N Engl J Med 2003;348:583-92.
[53] Dahlöf B, Devereux RB, Kjeldsen SE, et al. for the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995-1003.
[54] Lindholm LH, Ibsen H, Dahlöf B, et al. for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:1004-10.
[55] Julius S, Kjeldsen SE, Weber M, et al. for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-31.
[56] Degl' Innocenti A, Elmfeldt D, Hansson L, et al. Cognitive function and health-related quality of life in elderly patients with hypertension - Baseline data from the Study on COgnition and Prognosis in the Elderly (SCOPE). Blood Pressure 2002;11:157-165.
[57] Psaty BM, Lumley T, Furberg CD. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534-44.
[58] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. Lancet 2003;362:1527–35.
[59] Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until March 2003. J Hypertens 2003;21:1055-76.
[60] Pylypchuk GB. ACE inhibitor-versus angiotensin II blocker-induced cough and angioedema. Ann Pharmacother 1998;32:1060-6.
[61] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
[62] Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.
[63] Punzi HA. Safety update: focus on cough. Am J Cardiol 1993;72:45H-8H.
[64] Sharif MN, Evans BL, Pylypchuk GB. Cough induced by quinapril with resolution after changing to fosinopril. Ann Pharmacother 1994;28:720-1.
[65] Germino FW, Lastra J, Pool P, et al. Evaluation of the cough profile of fosinopril in hypertensive patients with ACE inhibitor-associated cough-a pilot study. Curr Ther Res 1993;54:469-75.
[66] Tanser PH, Campbell LM, Carranza J, et al. Candesartan cilexetil is not associated with cough in hypertensive patients with enalapril-induced cough. Multicentre Cough Study Group. Am J Hypertens 2000;13:214-8.
[67] Lacourciere Y, Brunner H, Irwin R, et al. Effects of modulators of the renin-angiotensin-aldosterone system on cough. J Hypertens 1994;12:1387-93.
[68] Chan P, Tomlinson B, Huang TY, et al. Double-blind comparison of losartan, lisinopril, and metolazone in elderly hypertensive patients with previous angiotensin-converting enzyme inhibitor-induced cough. J Clin Pharmacol 1997;37:253-7.
[69] Paster RZ, Snavely DB, Sweet AR, et al. Use of losartan in the treatment of hypertensive patients with a history of cough induced by angiotensin-converting enzyme inhibitors. Clin Ther 1998;20:978-89
[70] Lacourciere Y, Bittar N, Blanchard E, et al. The incidence of cough: a comparison of lisinopril, placebo and telmisartan, a novel angiotensin II antagonist. Int J Clin Pract 1999;53:99-103.
[71] Benz J, Oshrain C, Henry D, et al. Valsartan, a new angiotensin II receptor antagonist: a double-blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. J Clin Pharmacol 1997;37:101-7.
[72] Punzi HA. Safety update: focus on cough. Am J Cardiol 1993;72:45H-8H.
[73] Conigliaro RL, Gleason PP. Losartan-induced cough after lisinopril therapy. Am J Health-Syst Pharm 1999;56:914-5. Letter.
[74] van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. Arch Intern Med 1998;158:2063-5.

[75] Boxer M. Accupril- and Cozaar-induced angioedema in the same patient (letter). J Allergy Clin Immunol 1996;98:471.
[76] Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan (letter). N Engl J Med 1995;333:1572.
[77] Sharma PK, Yium JJ. Angioedema associated with angiotensin II receptor antagonist losartan. South Med J 1997;90:552-3.
[78] Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. Pharmacotherapy 1998;18:866-8.
[79] Rivera JO. Losartan-induced angioedema. Ann Pharmacother 1999;33:933-5.
[80] Cha YJ, Pearson VE. Angioedema due to losartan. Ann Pharmacother 1999;33:936-8.
[81] Rupprecht R, Vente C, Grafe A, Fuchs T. Angioedema due to losartan. Allergy 1999;54:81-2.
[82] Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. Ann Pharmacother 2000;34:526-8.
[83] Kyrmizakis DE, Papadakis CE, Liolios AD, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. Arch Otolaryngol Head Neck Surg 2004;130:1416-9.
[84] Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med 2004;164:910-3.
[85] Abdi R, Dong VM, Lee CJ, Ntoso KA. Angiotensin II receptor blocker-associated angioedema: on the heels of ACE inhibitor angioedema. Pharmacotherapy. 2002;22:1173-5.
[86] Chiu AG, Krowiak EJ, Deeb ZE. Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology. Laryngoscope 2001;111:1729-31.
[87] Bakris GL, Siomos M, Richardson D, et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. Kidney Int 2000;58:2084-92.
[88] Esmail ZN, Loewen PS. Losartan as an alternative to ACE inhibitors in patients with renal dysfunction. Ann Pharmacother 1998;32:1096-8.

Contact Person: Elaine Furmaga, PharmD, Clinical Pharmacy Specialist, VHA PBM-SHG