Angiotensin II Receptor Antagonists: Recommendations for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information 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 VA/DoD Angiotensin II Receptor Antagonists Drug Class Review at www.pbm.va.gov or http://vaww.pbm.va.gov for additional discussion and for recommendations on dosing, potential drug interactions, side effects, and precautions of the angiotensin II receptor antagonists.

Recommendations for Use of an Angiotensin II Receptor Antagonist in Patients with Heart Failure (HF)

Patients with systolic HF [i.e., reduced left ventricular ejection fraction (LVEF) with current or prior symptoms of 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.

- An angiotensin II receptor antagonist is recommended in patients with systolic HF [or HF/evidence of systolic dysfunction after acute myocardial infarction (MI)] who are intolerant to an ACEI*
- Combination therapy with an angiotensin II receptor antagonist may be considered in patients with systolic HF and persistent symptoms despite maximized standard therapy (combination therapy in patients with HF/evidence of systolic dysfunction after acute MI is not routinely recommended due to an increased risk for adverse events without a survival benefit)

Recommendations for Use of an Angiotensin II Receptor Antagonist in Patients with Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD)

Standard therapy for patients with DM and CKD includes treatment with an ACEI. Treatment with an angiotensin II receptor antagonist has been shown to reduce the combined endpoint of increasing sCr, end-stage kidney disease (ESKD), and death in patients with type 2 DM and nephropathy with hypertension (HTN) and/or on antihypertensive medications. As such an angiotensin II receptor antagonist is a treatment option in this patient population.

- An angiotensin II receptor antagonist may be considered a treatment option in patients with type 2 DM and nephropathy (e.g., macroalbuminuria) with HTN
- An angiotensin II receptor antagonist may be considered in patients with DM and CKD or nondiabetic kidney disease with proteinuria who are intolerant to an ACEI*
- Combination therapy with an ACEI and angiotensin II receptor antagonist should be considered only after evaluation of risk vs. benefit

Recommendations for an Angiotensin II Receptor Antagonist in Patients with HTN

An angiotensin II receptor antagonist is effective for lowering blood pressure in the treatment of hypertension. There have been mixed results with an angiotensin II receptor antagonist and their effect on CV morbidity and mortality in patients with HTN and/or cardiovascular (CV) disease or high CV risk [reduced CV morbidity and mortality vs. treatment with a beta-blocker or conventional treatment, no difference compared to an ACEI or dihydropyridine calcium channel blocker (CCB), and a nonsignificant reduction compared to placebo in patients with CV disease or high risk DM who were ACEI intolerant]. At this time, consensus recommendations consider an angiotensin II receptor antagonist to be an option in patients intolerant to an ACEI.

- An angiotensin II receptor antagonist may be considered for the treatment of HTN in a patient who is intolerant to an ACEI*

*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 kidney dysfunction, hyperkalemia, or angioedema with an ACEI, or where treatment with an ACEI is limited due to kidney dysfunction, as these adverse events have also occurred with the use of an angiotensin II receptor antagonist [refer to Executive Summary and Discussion for review of the literature]

Executive Summary
(Refer to Discussion section for review of the literature)

Summary of recommendations for use of an angiotensin II receptor antagonist in patients with systolic HF with or without recent MI

Heart Failure

- The ACEIs have well documented beneficial effects in the treatment and prevention of HF. The absence of data that angiotensin II receptor antagonists are superior to ACEIs 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 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 in the management of patients with HF. One trial reported results that 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 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, another trial demonstrated 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.

Heart Failure with Acute Myocardial Infarction

- 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 or CV endpoints compared to an angiotensin II receptor antagonist alone and resulted in an increase in adverse events; therefore combination therapy with an ACEI and angiotensin II receptor antagonist is not routinely recommended in this patient population.

Summary of recommendations for use of an angiotensin II receptor antagonist in patients with DM and CKD

Type 2 Diabetic Nephropathy

- There is good evidence that treatment with an angiotensin II receptor antagonist in patients with type 2 DM with nephropathy (with HTN or on additional antihypertensive medications) reduced the composite endpoints of doubling sCr, ESKD, or death. The ACEIs have been shown to decrease surrogate endpoints in this patient population, with results from one comparison trial in patients with early nephropathy demonstrating an angiotensin II receptor antagonist to be noninferior to treatment with an ACEI.

Diabetes and Chronic Kidney Disease

- There is good evidence that in patients with type 1 DM nephropathy, an ACEI decreases the rate of decline in kidney function and reduces the combined risk of death, dialysis, or transplantation; and in patients with type 1 or 2 DM and microalbuminuria or nondiabetic kidney disease, an ACEI slows the progression of kidney disease. Treatment with an angiotensin II receptor antagonist has also been shown to prevent the decline in kidney function in patients with type 2 DM and microalbuminuria. In general, it is recommended that an angiotensin II receptor antagonist be used in patients with DM and CKD or nondiabetic kidney disease who are intolerant to an ACEI.
- Combination therapy with an ACEI and angiotensin II receptor antagonist should be considered only after evaluation of the risk vs. benefit. It has been recommended that combination therapy may be considered in patients with type 2 DM and persistent high-level macroalbuminuria to further reduce proteinuria. In patients with vascular disease or high risk DM, combination therapy with an ACEI and angiotensin II receptor antagonist increased the secondary endpoint of risk for dialysis, doubling sCr, and death when compared to an ACEI alone. The evidence for an ACEI in combination with an angiotensin II receptor antagonist in slowing the progression of nondiabetic kidney disease is also limited. Further study is needed to determine the long-term outcome of combination therapy with an ACEI and angiotensin II receptor antagonist in patients with DM and CKD, or in patients with nondiabetic kidney disease.

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

Hypertension

- Thiazide-type diuretics are recommended as initial therapy for most patients with uncomplicated HTN; another class of antihypertensive agents 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 considered in a patient who is intolerant to an ACEI for the management of HTN

Additional Considerations

ACEI Induced Cough

- Use of an angiotensin II receptor antagonist may be considered in patients who have a specific indication for an ACEI (e.g., systolic HF, evidence of HF with recent MI, DM and CKD) where an angiotensin II receptor antagonist has either been reported to be similar 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 being treated with an ACEI for the management of HTN who develop cough associated with an ACEI may experience improvement if switched to fosinopril; or consideration of treatment with an angiotensin II receptor antagonist may be appropriate.

Angioedema

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

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 kidney dysfunction who develop hyperkalemia on an ACEI and who have an indication for an ACEI.

Kidney 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 kidney dysfunction or in a patient who develops kidney 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.

Discussion

Heart Failure Discussion:

According to the American College of Cardiology and American Heart Association (ACC/AHA) guidelines[1] and the VA PBM-MAP The Pharmacologic Management of Chronic Heart Failure (refer to document located under Clinical Guidance/VA National Clinical Practice Guidelines at www.pbm.va.gov or http://vaww.pbm.va.gov), an angiotensin II receptor antagonist is recommended in patients with systolic HF on standard therapy who are unable to tolerate therapy with an ACEI.

Combination of an angiotensin II receptor antagonist and an ACEI may be considered to decrease HF hospitalizations; however, there are conflicting data as to the effect of this combination on all-cause mortality. In addition, patients with recent New York Heart Association (NYHA) class IV HF and current class III or IV symptoms and LVEF $\leq$ 35%, should be considered as a candidate for an aldosterone antagonist (provided the patient has preserved kidney 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 Evaluation of Losartan in Elderly Study (ELITE),[3] the angiotensin II receptor antagonist losartan (titrated to 50mg once daily) was compared to an ACEI, captopril (titrated to 50mg three times daily), 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 three times daily (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. Several researchers speculated that the dose of losartan may have been suboptimal in these trials.[5]

It was for this reason that the Heart Failure endpoint Evaluation with the Angiotensin II Antagonist Losartan (HEAAL) study[6] was undertaken to determine the effect of losartan 50 mg compared with losartan 150 mg on all-cause mortality and HF hospitalizations in 3846 patients with HF and LVEF $\leq$ 40%, who were intolerant to an ACEI (86% reported intolerance due to cough). Seventy-two percent of patients received concomitant treatment with beta-adrenergic blockers. After a median of 4.7 years of follow-up, treatment with losartan 150 mg (mean 129$\pm$39 mg) resulted in a 10% decrease in the risk for death or HF hospitalization compared to patients randomized to losartan 50 mg (mean 46$\pm$11 mg) [losartan 150 mg 828 (43.0%) vs. losartan 50 mg 889 (46.3%); HR 0.90 95% CI 0.82-0.99; P=0.027). The secondary endpoint of all-cause mortality did not differ between treatment groups; although, there was a significant reduction in HF hospitalizations in patients treated with the higher dose of losartan (HR 0.87 95% CI 0.76-0.98; P=0.025). Hyperkalemia, hypotension, kidney impairment, and angioedema all occurred more frequently in the losartan 150 mg treatment group compared to the 50 mg dose, with no difference in discontinuations due to these adverse events. Losartan is not currently FDA approved for use in HF; the target dose studied in the HEAAL trial is higher than the maximum recommended dose used for other indications.

The Valsartan Heart Failure Treatment (Val-HeFT)[7] 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 per 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).[7] 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 angiotensin II receptor antagonist compared to placebo.[8] FDA approval for valsartan is for treatment of NYHA class II-IV HF and that valsartan significantly reduced hospitalizations for HF. The product information also includes a statement that there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI.

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial[9] randomized 2548 patients with LVEF ≤ 40% (mean LVEF 28%; NYHA class: II 24%; III 73%; IV 3%) to candesartan (61% achieved target dose at 6 months; mean dose 24mg per 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 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[10] randomized 2028 patients with LVEF ≤ 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, to candesartan 4mg once daily titrated to a target dose of 32mg once daily (59% achieved target dose at 6 months; mean dose 23mg per 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 ≤ 40% to reduce the risk of death from cardiovascular causes and to reduce HF hospitalizations. Candesartan is also approved for use in combination with an ACEI.

The CHARM-Preserved trial[11] 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 Overall program[12] 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%). The primary outcome of all-cause mortality was reduced with candesartan (63% achieved target dose at 6 months; mean dose 24mg per day), although the result did not achieve statistical significance. The secondary endpoint of combined CV death or HF hospitalization was significantly reduced by 16% compared to placebo. When data of patients with low LVEF (≤ 40%) from the CHARM program (i.e., from CHARM Added and CHARM Alternative) were evaluated (N=4576), there was a reduction in the primary endpoint of CV death or HF hospitalization (with a reduction when each endpoint was analyzed separately), as well as a reduction in all-cause mortality (HR 0.88 95% CI 0.79-0.98; P=0.018) with candesartan compared to the placebo group.[13]

Results of CHARM-Alternative[10] and HEAAL[6] confirm the recommendation from Val-HeFT[7] to use an angiotensin II receptor antagonist in patients who are intolerant of an ACEI. The results of CHARM-Added[9] 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] Similar results were found in another meta-analysis of 27,495 patients, with no difference in all-cause mortality between treatment with an angiotensin II receptor antagonist compared to an ACEI (HR 1.06 95% CI 0.56-1.62), no difference in death between combination with an angiotensin II receptor antagonist and ACEI compared to an ACEI alone (HR 0.98 95% CI 0.84-1.15), and a 17% reduction in HF hospitalizations with combination therapy compared to an ACEI alone (RR 0.83 95% CI 0.71-0.97).[15]

Table 1. Results of CHARM, Val-HeFT, and HEAAL 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 (24.2%)	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%)	0.76	<0.001	4.4%	23
HEAAL						
Outcomes	**Losartan 150 mg (N=1927)**	**Losartan 50 mg (N=1919)**	**HR (95% CI)**	**P value**	**ARR[c]**	**NNT[c] (4.7 years)**
All-cause mortality	635 (33.0%)	665 (34.7%)	0.94 (CI 0.84-1.04)	0.24		
Death or HF hospitalization[b]	828 (43.0%)	889 (46.3%)	0.90 (CI 0.82-0.99)	0.027	3.4%	30
HF hospitalizations	450 (23.4%)	503 (26.2%)	0.87 (CI 0.76-0.98)	0.025	2.9%	35

[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

Heart Failure with Acute Myocardial Infarction 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.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT)[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. Valsartan is FDA approved to reduce CV mortality in patients with left ventricular failure or left ventricular dysfunction following MI.

According to results of Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),[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 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

Diabetes and Chronic Kidney Disease Discussion:

In patients with DM and HTN, the American Diabetes Association (ADA) recommends treatment with an ACEI or angiotensin II receptor antagonist, with addition of other drug classes (e.g., diuretics, CCBs, beta-adrenergic blockers) as needed for additional blood pressure reduction; with data to support use of an ACEI in patients with type 1 DM with albuminuria or type 2 DM and microalbuminuria and evidence for use of an angiotensin II receptor antagonist in type 2 DM and macroalbuminuria, to slow the progression of CKD.[18] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) states that diuretics, ACEIs, beta-adrenergic 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-adrenergic blocker, CCB, or angiotensin II receptor antagonist may be considered as additional or alternative therapy.

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. 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 there are clinical trial data to support use of an angiotensin II receptor antagonist 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.[18]

The National Kidney Foundation (NKF) guideline on the management of HTN in DM and CKD recommends treatment with an ACEI or angiotensin II receptor antagonist, usually in combination with a diuretic, for the management of HTN due to their effect on slowing the progression of CKD in patients with type 1 or 2 DM; with strong evidence for use of an ACEI in patients with type 1 DM and macroalbuminuria and for an angiotensin II receptor antagonist in type 2 DM and macroalbuminuria.[33] These recommendations are consistent with the NKF guidelines on HTN in CKD.[34] It is also recommended that an ACEI be used in patients with nondiabetic kidney disease to slow the progression of kidney disease.[34,35] The NKF 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. 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 would be reasonable to reduce proteinuria in patients with HTN and diabetic kidney disease with persistent high-level macroalbuminuria[33] as it has been shown to further reduce proteinuria.[36] However, further study is needed to determine the long-term outcome of combination therapy with an ACEI and angiotensin II receptor antagonist as one trial of patients with vascular disease or high risk DM, combination therapy with an ACEI and angiotensin II receptor antagonist was shown to increase the secondary endpoint of risk for dialysis, doubling sCr, and death when compared to an ACEI alone.[37]

The recommendation to use an angiotensin II receptor antagonist in patients with type 2 DM and nephropathy is based on the results of two long-term outcome trials in this patient population. The Irbesartan Type 2 Diabetic Nephropathy (IDNT)[38] and Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[39] trials both evaluated the effect of an angiotensin II receptor antagonist on the primary endpoint of composite all-cause mortality, doubling of sCr, and ESKD. 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.[38] 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.[39] Both trials demonstrated a reduction in the primary endpoint with an angiotensin II receptor antagonist compared to placebo[38,39] and, in IDNT, this endpoint was also significantly reduced compared to amlodipine.[38] The secondary endpoints evaluating cardiac events were not statistically significantly different with an angiotensin II receptor antagonist compared to placebo.[38,39] Refer to Table 3.

Table 3. Results of IDNT and RENAAL Trials in Patients with HTN and Type 2 Diabetic Nephropathy[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, ESKD, 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
ESKD	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, ESKD, 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
ESKD	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] ESKD=end-stage kidney 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. 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.[40-44] The Candesartan and Lisinopril Microalbuminuria (CALM) study compared the effects of

candesartan 16mg, lisinopril 20mg, or the combination on urinary albumin excretion (UAE) 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.[45] 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.[46-49] This benefit has also been seen with the combination of an ACEI and nondihydropyridine CCB compared to treatment with either agent alone in a long-term trial of patients with type 2 DM and nephropathy.[50]

A meta-analysis of data with the ACEIs and the angiotensin II receptor antagonists in patients with diabetic nephropathy showed a significant reduction in all-cause mortality with the ACEIs vs. placebo (RR 0.79; 95% CI 0.63-0.99; P=0.04); a difference that was not statistically significant when the angiotensin II receptor antagonists were compared to placebo (RR 0.99; 95% CI 0.85-1.17; P=0.95). The reduction in doubling of sCr and ESKD were not significant (P=0.08 and P=0.07, respectively) with the ACEIs compared to placebo or no treatment. With the angiotensin II receptor antagonists, the reduction in doubling of sCr (P=0.004), ESKD (P=0.001), microalbuminuria to macroalbuminuria (P=0.001), and regression from microalbuminuria to normoalbuminuria (P=0.02) were significant compared to placebo or no treatment. The reduction in progression from microalbuminuria to macroalbuminuria (P=0.0007), and regression from 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 kidney 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 antagonists.[51] A systematic review and meta-analysis of 127 trials evaluating an angiotensin II receptor antagonist or ACEI on kidney outcomes reported a nonsignificant reduction with an ACEI or angiotensin II receptor antagonist on doubling sCr and a significant decrease in ESKD when compared with other antihypertensive treatment groups, with no difference in the degree of change in blood pressure. When comparing an ACEI or angiotensin II receptor antagonist to placebo, there was a benefit in reducing ESKD and doubling sCr that was associated with a reduction in BP.[52] A systematic review and meta-analysis of 21 trials including 654 patients with proteinuria evaluated the antiproteinuric effect of combination with an angiotensin II receptor antagonist and an ACEI and reported a further reduction in proteinuria with the addition of an angiotensin II receptor antagonist compared to an ACEI alone. This was accompanied by a slight increase in potassium (0.11 mEq/L) that was statistically significant. The effect on long-term outcomes was not evaluated.[53] Another meta-analysis evaluated the effect of an angiotensin II receptor antagonist alone or in combination with an ACEI on proteinuria in 6181 patients from 49 trials and reported that an angiotensin II receptor antagonist reduced proteinuria compared to placebo, with the combination providing further reduction in proteinuria compared to either agent as monotherapy. The effect of an angiotensin II receptor antagonist or the combination of an angiotensin II receptor antagonist with an ACEI on long-term outcomes was also not evaluated in this meta-analysis.[36]

Hypertension Discussion:

According to the JNC 7 2003 guidelines[21] a thiazide-type diuretic is recommended as initial therapy for most patients with uncomplicated HTN. Other classes (ACEIs, angiotensin II receptor antagonists, beta-adrenergic blockers, CCBs) that have demonstrated positive outcomes in randomized controlled trials may be considered in combination or for treatment of patients with compelling indications. The VA/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) concur with the recommendations of JNC 7; in addition, these guidelines recommend that an angiotensin II receptor antagonist may be considered in patients with uncomplicated HTN who are intolerant to an ACEI.

The European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 HTN guidelines consider a thiazide-type diuretic, ACEI, angiotensin II receptor antagonist, beta-adrenergic blocker, or CCB as appropriate first-line therapy for hypertension. In addition, an angiotensin II receptor antagonist may be considered preferable (along with consideration of other medications listed) in the following conditions: LVH: ACEI, CCB, angiotensin II receptor antagonist; microalbuminuria: ACEI, angiotensin II receptor antagonist; kidney dysfunction: ACEI, angiotensin II receptor antagonist; previous stroke: any agent that lowers BP; previous MI: beta-adrenergic blocker, ACEI, angiotensin II receptor antagonist; HF: diuretics, beta-adrenergic blocker, ACEI, angiotensin II receptor antagonist, aldosterone antagonist; recurrent atrial fibrillation: angiotensin II receptor antagonist, ACEI; kidney failure/proteinuria: ACEI, angiotensin II receptor antagonist, loop diuretics; metabolic syndrome: ACEI, angiotensin II receptor antagonist, CCB; DM: ACEI, angiotensin II receptor antagonist; ACEI induced cough: angiotensin II receptor antagonist.[54] The NICE 2006 HTN guideline recommends a thiazide-type diuretic or CCB first-line if > 55 years of age or black; and an ACEI (or angiotensin II receptor antagonist if an ACEI is not tolerated) first-line if < 55 years of age. Combination therapy should include the addition of a thiazide diuretic, CCB, or ACEI (or angiotensin II receptor antagonist if an ACEI is not tolerated).[55] The Canadian Hypertension Education Program 2009 recommends a thiazide diuretic as initial therapy in uncomplicated HTN; an ACEI (not in black patients), long-acting CCB, angiotensin II receptor antagonist, or beta-adrenergic blocker (in patients < 60 years of age) are also considered appropriate first-line therapy in patients with HTN.[56]

A systematic review of benefits and harms of first-line antihypertensive therapies concluded that first-line therapy with a thiazide diuretic reduced morbidity and mortality (e.g., mortality, stroke, CHD, CV events), with the ACEIs reducing mortality, stroke, CHD, CV events, and the CCBs decreasing stroke and CV events; with the stronger evidence to support treatment with a thiazide diuretic. No randomized controlled trials with an angiotensin II receptor antagonist compared to placebo or no treatment were found.[57] In a meta-analysis of first-line

therapies for HTN that included comparison trials, an angiotensin II receptor antagonist was not significantly more effective for any of the treatment outcomes (total or CV mortality, CV events, stroke, HF, or CHD) compared to a low-dose thiazide diuretic.[58] Another meta-analysis found no difference in all-cause mortality with an angiotensin II receptor antagonist vs. active controls.[59] A recent meta-analysis reported a significant reduction in the risk of stroke with an angiotensin II receptor antagonist; however, there was a nonsignificant increase in MI with an angiotensin II receptor antagonist compared to controls.[60]

According to randomized controlled trials in patients with HTN, treatment with an angiotensin II receptor antagonist reduced hospitalization for stroke and hospitalization for MI (candesartan) compared to conventional treatment,[61] reduced nonfatal stroke (candesartan) vs. open-label antihypertensive therapy,[62] and decreased combined death, CV and cerebrovascular events (eprosartan) compared to a dihydropyridine CCB.[63] In patients at high CV risk or CV disease, treatment with an angiotensin II receptor antagonist has been shown to reduce the composite death, MI, stroke (losartan) compared to a beta-blocker,[64] and decrease CV morbidity and mortality (valsartan) vs. conventional treatment;[65,66] there was no difference in CV morbidity and mortality (telmisartan) compared to an ACEI,[67] or with telmisartan compared to placebo in patients intolerant to an ACEI,[68] or with valsartan[69] or candesartan[70] compared to a dihydropyridine CCB; no significant difference in reducing major adverse CV events (candesartan) compared to conventional therapy;[71] and no significant reduction in the rate of CV events with valsartan compared to placebo, although there was a decrease in development of DM in patients with impaired glucose intolerance.[72] Although the reduction in CV events appear largely driven from the reduction in stroke, there was no difference in recurrent stroke when treatment with an angiotensin II receptor antagonist (telmisartan) was compared to placebo.[73]

In summary, an angiotensin II receptor antagonist is effective for lowering blood pressure in the treatment of hypertension. There have been mixed results with an angiotensin II receptor antagonist in patients with HTN and/or CV disease or high CV risk; an angiotensin II receptor antagonist has been shown to reduce CV morbidity and mortality in patients with high CV risk when compared to treatment with a beta-blocker or conventional treatment, with no difference compared to an ACEI or dihydropyridine CCB (per controlled clinical trials including patients in the U.S.), and a nonsignificant reduction compared to placebo in patients with CV disease or high risk DM who were ACEI intolerant. At this time, consensus recommendations consider an angiotensin II receptor antagonist to be an option in patients intolerant to an ACEI.

ACEI Induced Cough Discussion:

The incidence of cough with an ACEI is estimated to be anywhere from 0.5 to 39%.[74] 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, HF, 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.[75] In V-HeFT II, 37% of HF patients on enalapril complained of cough compared to 29% receiving hydralazine and isosorbide dinitrate.[76] 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.[77-80]

On the other hand, the incidence of cough associated with the angiotensin II receptor antagonists is reported to be similar to placebo (1.6-3.4%).[74] In a systematic review of head-to-head comparison trials of an ACEI and angiotensin II receptor antagonist, cough was reported in 0 to 23% (mean 10%) of patients treated with an ACEI and 0 to 13% (mean 3%) of patients receiving an angiotensin II receptor antagonist.[81] In a large comparison study of valsartan 160 mg daily and lisinopril 20 mg daily in patients with HTN, dry cough was reported in 1.0% of patients on valsartan and in 7.2% of patients treated with lisinopril ($P<0.001$).[82] The TRANSCEND trial enrolled patients who were intolerant to an ACEI, with cough as the reported reason for ACEI intolerance in 88.2% (i.e., 5225 patients) enrolled in the trial. Cough was subsequently reported as the reason for discontinuation in 15 (0.51%) of patients treated with telmisartan compared to 18 (0.61%) patients in the placebo group.[68] In patients with HF 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 with HF 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.[10] 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%).[83-90] 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.[90]

Angioedema Discussion:

The incidence of angioedema in patients taking an ACEI 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.[10] In a large trial of 5926 patients at high CV risk intolerant to an ACEI, 75 (1.3%) of patients were intolerant due to angioedema or anaphylaxis. Of the 2954 patients randomized to telmisartan, angioedema was reported as the reason for discontinuation in 2 patients (0.07%) compared to 3 patients (0.10%) on placebo (P=0.660).[73] A systematic review of 61 trials comparing an angiotensin II receptor antagonist with an ACEI reported angioedema (in 3 of the studies) in only those patients who were treated with an ACEI.[81] There have been a number of published case reports of angioedema in patients treated with an angiotensin II receptor antagonist.[74,91-103] In approximately one third of these cases, the patients previously experienced angioedema with an ACEI. A systematic review found the risk for angioedema to be 9.4% (95% CI 2 to 17%) of patients on an angiotensin II receptor antagonist who previously experienced angioedema on an ACEI; and 3.5% (95% CI 0 to 9.2%) of patients with previously confirmed angioedema on an ACEI.[104] Therefore, an angiotensin II receptor antagonist should be used with caution in patients who have previously experienced angioedema.[91,99,100,102,104]

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.[75] 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] 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.[9] The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients with mild kidney impairment on lisinopril compared to valsartan; in patients with moderate kidney dysfunction (with a 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).[105]

Kidney Failure Discussion:

In patients whose kidney 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 kidney 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 sCr ($\geq$ 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 kidney dysfunction or in a patient who develops kidney dysfunction as a result of treatment with an ACEI.[106]

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