

VA/DoD Drug Class Review: Angiotensin II Receptor Antagonists (AIIRAs)

Department of Defense Pharmacoeconomic Center (DoD PEC)
Department of Veterans Affairs Pharmacy Benefits Management
Strategic Healthcare Group (VA PBM) and the VA Medical Advisory Panel (VA MAP)

Introduction

Seven angiotensin II receptor antagonists (AIIRAs) are currently available in the United States: losartan potassium (Cozaar®, Merck), valsartan (Diovan®, Novartis), irbesartan (Avapro®, Sanofi / Bristol-Myers Squibb), candesartan cilexetil (Atacand®, AstraZeneca), telmisartan (Micardis®, Boehringer Ingelheim), eprosartan (Teveten®, Biovail Pharmaceuticals), and olmesartan medoxomil (Benicar™, Sankyo Pharma Inc/Forest). (See table 1). None of the AIIRAs are available generically, and patent expiration is not expected for several years (after 2009).

All seven AIIRAs are available in combination with hydrochlorothiazide (HCTZ): losartan potassium/HCTZ (Hyzaar®, Merck), valsartan/HCTZ (Diovan HCT®, Novartis), candesartan cilexetil/HCTZ (Atacand HCT®, AstraZeneca), irbesartan/HCTZ (Avalide®, Bristol-Myers Squibb), telmisartan/HCTZ (Micardis HCT®, Boehringer-Ingelheim), and olmesartan/HCTZ (Benicar HCT™, Sankyo Pharma Inc/Forest), and eprosartan/HCTZ (Teveten®, Biovail Pharmaceuticals). (See table 2)

Table 1: Angiotensin II Receptor Antagonists available in the U.S

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval date
Candesartan cilexetil	Atacand (AstraZeneca)	4 mg, 8 mg, 16 mg, 32 mg tablets	6/4/98
Eprosartan	Teveten (Biovail)	400 mg, 600 mg tablets	10/22/99
Irbesartan	Avapro (Sanofi / Bristol-Myers Squibb)	75 mg, 150 mg, 300 mg tablets	9/30/97
Losartan potassium	Cozaar (Merck)	25mg, 50 mg, 100 mg tablets	4/14/95
Olmesartan	Benicar (Sankyo / Forest)	5 mg, 20 mg 40 mg tablets	4/25/02
Telmisartan*	Micardis (Boehringer-Ingelheim)	20 mg, 40 mg, 80 mg tablets	11/10/98
Valsartan	Diovan (Novartis)	40 mg, 80 mg, 160 mg, 320 mg tablets	12/23/96

*All of the AIIRAs are available in bulk packages, with the exception of telmisartan. Telmisartan is available in strip packs of 28 tablets.

Table 2: AIIRA / Hydrochlorothiazide (HCTZ) combinations available in the U.S

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval date
Candesartan / HCTZ	Atacand HCT (AstraZeneca)	16/12.5 mg, 32/12.5 mg tablets	9/5/00
Eprosartan / HCTZ	Teveten HCT (Biovail)	600/12.5 mg, 600/25 mg tablets	11/01/01
Irbesartan / HCTZ	Avalide (Sanofi / Bristol-Myers Squibb)	150/12.5 mg, 300/12.5 mg tablets	5/9/00
Losartan / HCTZ	Hyzaar (Merck)	50/12.5 mg, 100/25 mg tablets	8/24/98
Olmesartan / HCTZ	Benicar HCT(Sankyo / Forest)	20/12.5 mg 40/12.5 mg, 40/25 mg tablets	6/5/03
Telmisartan / HCTZ	Micardis HCT(Boehringer-Ingelheim)	40/12.5 mg, 80/12.5 mg tablets	11/17/00
Valsartan / HCTZ	Diovan HCT(Novartis)	80/12.5 mg, 160/12.5 mg, 160/25 mg tablets	01/17/02

Background: The AIIRAs are effective in lowering blood pressure and all 7 AIIRAs are approved for the treatment of hypertension. In addition, some AIIRAs have demonstrated positive outcomes in treating patients with conditions such as heart failure, diabetic nephropathy, and in the post myocardial infarction setting. Approximately 42% of veterans have a diagnosis of hypertension. Both heart failure (HF) and diabetic nephropathy are prevalent conditions in the veteran patient population with a high rate of morbidity and mortality if left untreated.

There are a number of antihypertensive classes of medications available for the treatment of hypertension that have demonstrated a reduction in the cardiovascular complications of hypertension. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that a thiazide-type diuretic be used in most patients with hypertension, either as monotherapy or in combination with other drug classes including the angiotensin-converting enzyme inhibitors (ACEI), AIIRAs, beta-blockers, or calcium channel blockers.

According to medication utilization data, approximately 60% of veteran patients with hypertension are prescribed an ACEI for treatment of this condition. In addition, ACEIs are considered standard therapy for patients with heart failure and are recommended in patients with diabetes and renal disease. Treatment with an ACEI has been associated with a persistent cough, resulting in discontinuation of the drug in many patients. An AIIRA is recommended in patients who are unable to tolerate an ACEI, where an ACEI is indicated. The recommendations to use an AIIRA are based on clinical trials demonstrating the following: a reduction in cardiovascular death and heart failure hospitalizations in patients on standard therapy and who are intolerant to an ACEI; a similar benefit as an ACEI in patients with left ventricular dysfunction or signs of heart failure after an acute myocardial infarction in reducing all-cause mortality; and a reduction in the composite doubling of serum creatinine, development of end-stage renal disease or all-cause death in patients with diabetic nephropathy.

FDA-Approved Indications and Off-Label Uses

All of the AIIRAs are approved for the treatment of hypertension, either alone or in conjunction with other agents. Losartan is the only AIIRA approved to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy.

The AIIRAs have also been studied in patients with DM and microalbuminuria or nephropathy. Two of the AIIRAs, irbesartan and losartan, have additional indications for diabetic nephropathy in type 2 diabetic patients.

In addition to hypertension, valsartan is also labeled for heart failure in patients intolerant of ACE inhibitors. Although candesartan is not currently FDA-approved for treating heart failure, AstraZeneca has submitted a supplemental NDA for heart failure, based on the results of one large clinical trial program published in September 2003 (CHARM programme).

The results of one large clinical trial published in November 2003 supports the use of valsartan as an alternative to ACE inhibitors in patients with acute myocardial infarction (MI) and left ventricular (LV) dysfunction (VALIANT). This indication is not currently FDA-approved, however, Novartis has filed a supplemental NDA with the FDA requesting expansion of the label to include improvement in survival and a reduction in cardiovascular events in patients at high risk after surviving a heart attack.

None of the AIIRAs are approved for use in the pediatric population.

Table 3: FDA-approved indications

Drug	FDA-Approved Indications			
	Hypertension	*Hypertension with Left Ventricular Hypertrophy	**Diabetic Nephropathy	***Heart Failure
Candesartan	X			
Eprosartan	X			
Irbesartan	X		X	
Losartan	X	X	X	
Olmesartan	X			
Telmisartan	X			
Valsartan	X			X

*Left ventricular hypertrophy indication for losartan is as follows: Losartan is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.

**Diabetic Nephropathy labeling for losartan is stated as follows: Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension.

**Diabetic Nephropathy labeling for irbesartan is stated as follows: Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria. Irbesartan reduces the rate of progression to nephropathy, as measured by the occurrence of doubling of serum creatinine and end stage renal disease (need for dialysis or renal transplant).

***Heart Failure labeling for valsartan is stated as follows: Treatment of heart failure (NYHA class II-IV) in patients intolerant of ACE inhibitors.

Methods

This review is limited to the seven individual AIIRAs, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Formulations of an AIIRA in combination with HCTZ are not included in this review.

Hypertension Trials: The AIIRAs have been used clinically for several years for treating hypertension and are mentioned in JNC 7 as a proven therapy for reducing blood pressure. Efficacy determinations will thus be limited to published clinical trials and meta-analyses. In a number of trials, AIIRAs have been shown to be superior to placebo for treating hypertension, and have also been compared with ACE inhibitors. Due to the large volume of information, only randomized, double-blinded, controlled, head to head trials of an individual AIIRA(s) vs AIIRA(s) will be discussed in the review. This review will not address efficacy of AIIRAs in comparison to ACE inhibitors.

Outcome trials in other conditions: Use of AIIRAs in patients with other conditions, including left ventricular hypertrophy (LVH), heart failure, diabetic nephropathy, and in patients following myocardial infarction will be limited to published trials enrolling large numbers of patients in a randomized, controlled manner incorporating placebo and/or active controls. Those trials evaluating “hard” outcomes, in contrast to surrogate markers or “soft” outcomes (outcomes which do not cause irrevocable damage), are considered to be clinically important. Trials with surrogate endpoints are only briefly reviewed. Examples of hard outcomes include stroke, all-cause mortality, cardiovascular mortality, hospitalization for HF, or composite of doubling of serum creatinine and development of end stage renal disease (ESRD), dialysis, or renal transplantation. Examples of “soft” outcomes are changes in laboratory tests (e.g urinary albumin excretion), or time to onset of diabetic nephropathy (this is a problem in that many trials (MARVAL, CALM) are of too short duration to show a difference.) Although surrogate markers of kidney outcome risk, such as proteinuria can be improved with lower blood pressure, surrogate markers may not accurately predict more clinically significant events such as doubling of SCr, need for dialysis or renal transplant, or death due to kidney failure. Trials with surrogate markers will be mentioned briefly, but more interest is placed on trials with hard outcomes.

This review is limited to information published up to and including December 2003.

Pharmacology 63-65,127,128, 66-72,131

- The renin-angiotensin-aldosterone system (RAAS) is a key component in the regulation of blood pressure. Renin is released from the juxtaglomerular cells in response to decreased renal perfusion. Renin cleaves angiotensinogen to form angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) into angiotensin II. Angiotensin II activates angiotensin II receptors. Angiotensin II receptors of known clinical relevance are characterized as AT₁ and AT₂. Effects mediated by the activation of AT₁ receptors are vasoconstriction (coronary, renal, cerebral), sodium retention (aldosterone production), water retention (vasopressin release), activation of sympathetic nervous system, constriction of the efferent arteriole in the kidney, growth (remodeling and restructuring of vessel walls, glomerular cells, and myocardium), inhibition of apoptosis (cell death), and increases in platelet aggregation and thrombosis. AT₂ receptors function to oppose the effects of AT₁ receptors. AT₂ receptor functions include vasodilation, inhibition of cell growth, promotion of cell differentiation, and apoptosis.
- ACEIs decrease production of angiotensin II and inhibit the breakdown of bradykinin.
- AIIRAs block the effects of angiotensin II at the AT₁ receptor and do not affect bradykinin.
- AIIRA receptor blocking capacity to AT₁ can be described as insurmountable or surmountable. Insurmountable blockade is suppression of agonist response despite escalations in agonist concentration. Surmountable is the reverse. Insurmountable response may be due to slow dissociation of the drug from the receptor. Whether insurmountable blocking capacity is superior is unknown.
- A T:P ratio of at least 0.5 for once daily dosing of hypertension medications is essential for once daily dosing. All seven AIIRAs have a T:P ratio > 0.5. Telmisartan and candesartan appear to have the highest T:P ratios, however, the clinical significance of this has not been established.

Pharmacokinetics

The pharmacokinetic profiles of the seven AIIRAs are included in table 4.

Table 4: Pharmacokinetic properties

Parameter	Losartan	Valsartan	Irbesartan	Candesartan	Telmisartan	Eprosartan	Olmesartan
Pro-Drug	EXP 3174 (active metabolite)	No	No	Candesartan (active metabolite)	No	No	Olmesartan (active metabolite)
AT1 receptor Antagonism	Parent- Competitive EXP 3174- insurmountable	Partially In-surmountable	In-surmountable	In-surmountable	In-surmountable	Competitive	In-surmountable
Bioavailability (%)	33	25	60-80	34-56	30-60	13-15	26
Protein binding (%)	Parent- 98.7 EXP 3174- 99.8	95	90	99.5	99.5	98	99
Elimination Fecal (%) Urinary (%)	60 35	83 13	80 20	67 33	>98	90 7	50-65 35-50
Dose adjustment Cl_{cr}<30ml/min Hepatic failure	No 50% initial dose	No No	No No	No No	No No	No No	No No
Half-life (hr)	Parent- 2 EXP 3174- 6-9	6	11-15	9	24	5-9	13
Onset of BP effect (hr)	2-3	2	2	2-4	3	No data	1 week
Maximum BP effect (hr)	6	4-6	3-6	6-8	3-9	3	2-4 weeks
Hemodialyzable	No	No	No	No	No	No	Unknown
Starting Dose (HTN)	50 mg QD	80 mg QD	150 mg QD	16 mg QD	40 mg QD	600 mg QD	20 mg QD
Maximum Dose	100 mg/day	320 mg/day	300 mg/day	32 mg/day	80 mg/day	800 mg/day	40 mg/day

T:P ratio	0.58-0.78 (50-100 mg)	0.69-0.76 (80-160 mg)	> 0.6 (≥ 150 mg)	0.8 (8-16 mg)	≥ 0.97 (20-80 mg)	0.67 (600 mg)	0.60-0.80 (2.5-80mg)
Food-drug interaction	No	No	No	No	No	No	No
Demonstrated drug-drug interaction	Lithium, Indomethacin, Rifampin, Fluconazole	Lithium		Lithium	Digoxin		
CYP450 Metabolism	Metabolized by 2C9, 3A4	Unknown	Conjugation oxidation by 2C9	No	Some inhibition of 2C19	No	No

Dosing and Administration

All the AIIAs are indicated for once daily dosing in hypertension. The package inserts for losartan, candesartan and eprosartan state twice daily dosing may be required in some instances. Once vs. twice daily dosing has been compared for candesartan and eprosartan, respectively, with similar efficacy and tolerability.

For heart failure, package labeling for valsartan states BID dosing. Candesartan has been studied for HF in one large clinical trial that used QD dosing. For diabetic nephropathy, irbesartan and losartan are dosed once daily in doses similar to that used in hypertension.

Table 5: Dosing according to package labeling for HTN, HF, or diabetic nephropathy ⁶⁶⁻⁷²

Generic	Renal/Hepatic Adjustments	Usual Dose (Range)
Losartan	hepatic failure: ↓ initial dose 50%	HTN: 50 mg QD (25-100 mg qd or divided bid) Diabetic Nephropathy: 100 mg QD
Valsartan	No	HTN: 80 mg QD (80-320 mg qd) HF: 160 mg BID Post MI (non FDA-approved): 160 mg BID
Irbesartan	No	HTN: 150 mg QD (75-300 mg qd) Diabetic Nephropathy: 300 mg QD
Candesartan	No	HTN: 16 mg QD (4-32 mg qd or divided bid) HF (non FDA-approved): 32 mg QD
Telmisartan	No	HTN: 40 mg QD (20-80 mg qd)
Eprosartan	No	HTN: 600 mg QD (400-800 qd or divided bid)
Olmesartan	5, 20, 40	HTN: 20mg QD (5-40mg qd)

Abbreviations; HTN = Hypertension; HF = Heart Failure

Efficacy

Efficacy for hypertension will be reviewed. For hypertension, since the drugs in this class are superior to placebo, only head-to-head and active comparator trials will be considered. Additionally, efficacy for large trials examining outcomes in hypertension, heart failure (including those post MI), and diabetic nephropathy will be discussed.

Hypertension:

Comparative trials among AIIRAs¹¹⁻²² (Head to head trials of AIIRAs are included in this review; see Appendix A at end of document) All studies were performed in patients with mild-moderate hypertension. Results of individual comparison trials suggest that losartan may not be as effective as other AIIRAs at comparable doses. Candesartan recently received approval to include labeling that states candesartan 32mg lowered SBP and DBP an average of 2 to 3 mm Hg more than losartan 100mg, comparing QD dosing of the two agents. One study with olmesartan vs. three other AIIRAs at the usual starting doses showed that olmesartan was more effective than losartan and valsartan in reduction of diastolic and systolic ambulatory blood pressure monitoring. It is unknown if the difference in blood pressure reduction would be apparent at other doses, or with other AIIRAs. However, a meta-analysis of candesartan, irbesartan, losartan, and valsartan was performed on 43 trials including 11,281 patients showed that the absolute weighted average reductions in DBP and SBP were 8.2-8.9 mm Hg and 10.4-11.8 mm Hg, respectively and were similar with all AIIRAs evaluated. Treatment with an AIIRA resulted in 48-55% patients achieving BP response. This was increased to 56-70% when a diuretic was added to therapy.

Hypertension Efficacy Discussion: All AIIRAs are approved for hypertension and appear to be similar in efficacy to the ACEIs (data not shown). A few trials have shown, at comparable doses, that losartan may be slightly less effective than the other AIIRAs. However, in a meta-analysis of 43 trials including candesartan, irbesartan, losartan, and valsartan, blood pressure reduction was similar with all AIIRAs evaluated.²² One study with olmesartan vs. three other AIIRAs at the usual starting doses showed that olmesartan was more effective than losartan and valsartan in reduction of diastolic and systolic ambulatory blood pressure monitoring.²¹ It is unknown if the difference in blood pressure reduction would be apparent at other doses, or with other AIIRAs.

Hypertension Efficacy Conclusion: All AIIRAs are equally effective for treating hypertension when titrated to blood pressure goals. Efficacy is increased when an AIIRA is combined with HCTZ.

Outcomes Trials

AIIRAs have been evaluated in several trials using hard clinical endpoints as well as surrogate endpoints (see table below). Endpoint trials using telmisartan are underway. There are no known published outcomes trials for eprosartan or olmesartan.

Table 6: Summary of Outcomes/Endpoint Trials with the AIIRAs.

ARB	Candesartan	Irbesartan	Losartan	Telmisartan	Valsartan
HF	CHARM (+ ACEI)	<i>I-PRESERVE</i>	ELITE-II HEAAL		Val-HeFT
DM/DN	CALM	IDNT	RENAAL	<i>DETAIL</i>	MARVAL
HTN/DM/MA		IRMA 2			
HTN/LVH			LIFE		
HTN/LVH/DM			LIFE		
HTN/CV risk					VALUE (vs. amlodipine)
HTN/elderly	SCOPE				
Post-MI			OPTIMAAL		VALIANT
CV disease				TRANSCEND (ACEI intolerant)	
CAD/CVA/PVD/ DM				ONTARGET (+ ramipril)	

italicized = not published/completed

DM: diabetic mellitus; DN: diabetic nephropathy; MA: microalbuminuria; LVH: left ventricular hypertrophy

Hypertension Outcomes Trials

- Losartan:** In addition to hypertension, losartan is labeled to reduce the risk of stroke in patients with hypertension and LVH; the evidence of benefit does not apply to black patients. The Losartan Intervention for Endpoint reduction in hypertension study (LIFE) compared atenolol with losartan and reported that losartan significantly reduced the composite endpoint of cardiovascular death, MI, and stroke in 9,193 patients with HTN and signs of LVH by 12% (RRR 12%; CI 2-22).²³ The reduction in the primary endpoint was driven solely by a reduction in stroke. Significant reductions in the composite primary endpoint were also seen with losartan in the prespecified subgroup of 1,195 patients with concomitant DM (RRR 24%; CI 2-42).²⁴ LVH and hypertension are strong independent risk factors for cardiovascular morbidity and death. Most patients required more than 2 agents to reach target BP, which is consistent with the results of other trials. The details of these studies are presented in Table 7 below and in Appendix B at the end of this document.
- A substudy of 1,326 patients from the LIFE study with isolated systolic HTN demonstrated a reduction in the primary outcome measure of cardiovascular death, MI, and stroke by 25% (RR 0.75 CI 0.56-1.01, P=0.06) compared to atenolol, adjusted for risk and degree of LVH.²⁵
- Another substudy of LIFE in 6,886 patients without clinically evident vascular disease reported a statistically significant reduction in stroke with losartan compared to atenolol (RR 0.66 CI 0.53-0.82, P<0.001), although the difference in cardiovascular death or MI were not statistically significant.²⁶
- Although the results below show that an AIIRA may be preferable to a β -adrenergic blocker in patients with HTN and LVH in decreasing the risk of stroke or lowering CV mortality in a subgroup of patients with DM, it is still unclear whether an AIIRA is preferred over an ACEI in this patient population.

Table 7: Summary results from the LIFE Trial

Outcomes	Losartan (n=4605)	Atenolol (n=4588)	Adjusted Hazard Ratio	RRR (95% CI)*	P value	NNT
Composite end point cardiovascular mortality, stroke, and MI	508 (11%)	588 (13%)	0.87 (CI 0.77-0.98)	13% (2 to 22)	0.021	56
Stroke	5%	7%	0.75 (CI 0.63-0.89)	25% (11 to 36)	0.001	59

*RRR = Relative Risk Reduction; was adjusted for Framingham risk score and degree of LVH at baseline.

- Candesartan:** A trial with candesartan compared to placebo (with open-label addition of antihypertensive therapy as needed) in elderly patients with mild to moderate HTN did not show a statistically significant difference in the primary endpoints of major cardiovascular events, or a composite of cardiovascular death, non-fatal stroke, and non-fatal MI, although there was a significant decrease in non-fatal stroke with candesartan. (SCOPE trial).²⁷
- Valsartan:** Another outcome study, Valsartan Antihypertensive Long-term Use Evaluation (VALUE), is currently being conducted comparing valsartan to amlodipine in 15,314 patients with essential HTN who are at high risk for coronary events, and will evaluate the impact of treatment on cardiac morbidity and mortality.²⁸

Hypertension Outcomes Trials Conclusion: The results of one well-conducted clinical trial support the use of losartan for reducing the risk of stroke in patients with hypertension and LVH; this benefit does not extend to black patients. Losartan is indicated for use in this condition by the FDA. There is insufficient evidence to support the use of candesartan to reduce major cardiovascular events or valsartan in patients at high risk for cardiovascular morbidity and mortality.

Heart Failure Outcomes Trials with AIIRAs:²⁹⁻⁴⁴

- Valsartan:** To date, valsartan is the only AIIRA that has received FDA approval for use in HF (in patients intolerant of an ACEI). The indication is based on the results of the Val-HeFT (Valsartan Heart Failure Treatment) study, which was supported by the manufacturer. The trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF on standard therapy (diuretics: 85%; ACEI: 93%; β -adrenergic blockers: 35%; and digoxin 67%). Baseline left ventricular ejection fraction (LVEF) was 27%. Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily) or placebo. Mean follow-up was 23 months. The two primary endpoints were all-cause mortality and the combined endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). Overall mortality was similar, occurring in 19.7% of patients in the valsartan group and 19.4% of patients on placebo (P=0.80). The combined primary endpoint occurred in 28.8% and 32.1% of patients on valsartan and placebo, respectively and the difference was statistically significant (RR 0.87 CI 0.77-0.97, P=0.009; ARR 3.3%; NNT=31). This included a 24% reduction in hospitalizations for HF (13.8% valsartan vs. 18.2% placebo; P < 0.001; ARR 4.4%; NNT=23). 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). (See Table 8).
- According to a subgroup analysis, there was a statistically significant increase in the risk of mortality (P=0.009) and a non-significant trend toward an increased risk of combined morbidity and mortality (P=0.10) in patients receiving valsartan in conjunction with an ACEI and β -adrenergic blocker. Patients who were not on an ACEI or β -adrenergic blocker experienced a statistically significant reduction in mortality (P=0.012).³⁰ Patients on valsartan but not on an ACEI (n=366), had a statistically significant lower risk of death (RR 0.67, CI 0.42-1.06, P=0.017) and a statistically significant lower risk of the combined endpoint (RR 0.56, CI 0.39-0.81, P<0.0001).³¹ In patients on an ACEI alone (i.e., without a β -adrenergic blocker), there was a significant reduction in the combined endpoint (P=0.002) and a nonsignificant reduction in mortality with valsartan compared to placebo.³⁰

Table 8: Summary results of the Val-HeFT study

Outcomes	Valsartan (n=2511)	Placebo (n=2499)	RR*	P value	NNT
All-cause mortality	495 (19.7%)	484 (19.4%)	1.02 (98% CI: 0.88-1.18)	0.80	-
Combined all-cause mortality and morbidity **	723 (28.8%)	801 (32.1%)	0.87 (97.5% CI: 0.77-0.97)	0.009	31
CHF hospitalizations	348 (13.8%)	455 (18.2%)	0.76 (CI not reported)	<0.001	23

*RR = relative risk.

**Morbidity defined as cardiac arrest with resuscitation, HF hospitalization, or requiring intravenous inotropic agents or vasodilators for over 4 hours.

- Losartan:** In the ELITE³² pilot trial (Evaluation of Losartan in the Elderly) study, the AIIRA losartan was compared to an ACEI, captopril, in 722 patients with NYHA class II to IV HF and a LVEF < 40%. Patients were randomized to losartan (up to 50mg) once daily (n=352) or captopril (up to 50mg) three times daily (n=370) for 48 weeks. Seventy-five percent of patients in the losartan group and 71% of patients in the captopril group received target doses. The majority of patients were prescribed diuretics and 55% were taking digoxin at the time of study enrollment. The primary endpoint of the study was the effect of treatment on serum creatinine (\geq 0.3mg/dL increase). There was no difference between treatment groups in the rise in serum creatinine during continued treatment. The secondary endpoints of a composite of death and/or hospitalization for HF occurred in 9.4% of patients on losartan and 13.2% on captopril (32% RR (CI-4% to +55%, 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 (4.8% with losartan vs 8.7% with captopril; $P=0.035$), which was driven by a reduction in sudden cardiac death. The unexpected finding of a survival benefit for losartan over captopril was based on a secondary analysis of 49 deaths. 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. More patients in the captopril group (20.8%) withdrew from the study due to adverse events compared to patients in the losartan group (12.2%). Cough was reported in 3.8% of patients taking captopril compared to 0% in losartan treated patients.³² The favorable mortality rate in the losartan group was not hypothesized *a priori*. Therefore, replication of the results was attempted in ELITE II.³³

- ELITE II³³ enrolled 3,152 symptomatic HF patients to evaluate the effects of losartan 50mg once daily (n=1574) compared to captopril 50mg three times daily (n=1570) on the primary endpoint of overall mortality and secondary endpoint of cardiac events (sudden cardiac death or resuscitated cardiac arrest). The patients were ACEI naïve. There was no significant difference in all-cause mortality between the treatment groups (17.7% on losartan vs. 15.9% on captopril, HR 1.13; CI 0.95-1.35; $P=0.16$). There was no difference between the groups in sudden death or resuscitated cardiac arrest, or hospital admissions. However, this was a superiority trial not designed to detect equivalence between groups. Therefore, losartan and captopril cannot be concluded to be the same. Patients receiving captopril had significantly more adverse effects resulting in discontinuation of the drug than patients on losartan ($P<0.001$).³³ Several researchers have speculated that the dose of losartan was sub-optimal in this study. One trial (HEEAL) is underway comparing losartan 50 mg with losartan 150 mg.
- **Candesartan:** The RESOLVD Pilot Study compared candesartan, enalapril, and the combination of the two agents in 768 patients with NYHA class II to IV HF with a LVEF < 40%. Patients were placed on candesartan (4, 8, or 16mg), candesartan (4 or 8mg) plus enalapril (20mg), or enalapril (20mg) for 43 weeks. The primary endpoints were exercise tolerance, ventricular function, quality of life, neurohormone levels, and tolerability. There was no significant difference between the treatment groups in results of the six-minute walk test, NYHA functional class, or quality of life. There was a trend toward an increase in ejection fraction, although not significant, in the patients treated with the combination of 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. There appeared to be a benefit of combination therapy on the patient's neurohormonal profile.³⁴ 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.³⁵ Mortality was higher in the group taking candesartan alone (6.1%) vs those receiving combination therapy with candesartan and enalapril (3.7%). This trial was insufficiently powered to detect changes in relevant clinical endpoints.
- Three separate trials comprised the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) program, where candesartan, titrated to 32 mg (although the median dose was 24 mg), was added to standard heart failure therapy in patients with symptomatic heart failure. The primary outcome was a composite of cardiovascular death or HF hospitalization. See Table 9 for details of the CHARM trials.
- The CHARM Alternative study randomized 2028 patients with LVEF $\leq 40\%$ who were intolerant of ACEIs to candesartan or placebo, in addition to standard HF therapies. The median follow-up was 34 months. The most common reason for ACEI intolerance was cough, which had occurred in 70% of the participants. Candesartan showed a significant 23% relative risk reduction in the primary endpoint of cardiovascular mortality and heart failure hospitalization, which was driven by a reduction in HF hospitalization⁴⁰
- The CHARM Added study randomized 2548 patients with LVEF $\leq 40\%$ to candesartan in addition to standard HF therapy, which included ACEIs. The inclusion criteria were similar to Val-HeFT. Beta-blocker therapy was administered in 55% of the study participants. After a median follow-up of 41 months, candesartan resulted in a 15% relative risk reduction in cardiovascular death or hospital admission for heart failure. Patients who were receiving triple therapy with candesartan, ACEI and beta-blocker also benefited, which is in contrast to the results of the Val-Heft trial above.⁴¹

- The CHARM Preserved trial was unique in that 3023 HF patients with preserved LV function, defined as an ejection fraction > 40% were evaluated; this patient population had not been previously evaluated in a large trial. Only one endpoint reached statistical significance; candesartan therapy resulted in a reduced hospital admission rate.⁴²
- The CHARM Overall³⁹ trial combined the results of the separate 3 CHARM trials to determine overall mortality as the primary endpoint. Candesartan showed a 9% relative risk reduction in overall mortality, which was of borderline significance. Twenty-three patients would need to be treated with candesartan for 3 years to prevent one cardiovascular death or CHF hospitalization.

Table 9: Summary Results of the CHARM trials

Primary Outcomes	Candesartan	Placebo	Unadjusted Hazard Ratio (95% CI)	P value
CHARM Alternative				
CV death or CHF hospitalization	334/1013 (33.0%)	406/1015 (40.0%)	0.77 (0.67-0.89)	0.0004 (ARR 7%; NNT=14)
CV death	219/1013 (21.6%)	252/1015 (24.8%)	0.85 (0.7-1.02)	0.072
CHF hospitalization	207/1013 (20.4%)	286/1015 (28.2%)	0.68 (0.57-0.81)	<0.001
CHARM-Added				
CV death or CHF hospitalization	483/1276 (37.9%)	538/1272 (42.3%)	0.85 (0.75-0.96)	0.011 (ARR 4.4%; NNT=23)
CV death	302/1276 (23.7%)	347/1272 (27.3%)	0.84 (0.72-0.98)	0.029
CHF hospitalization	309/1276 (24.2%)	356/1272 (28.0%)	0.83 (0.71-0.96)	0.014 (ARR 3.8%; NNT=27)
CHARM Preserved				
CV death or CHF hospitalization	333/1514 (22%)	366/1509 (24.3%)	0.89 (0.77-1.03)	0.118
CV death	170/1514 (11.2%)	170/1509 (11.3%)	0.99 (0.80-1.22)	0.918
CHF hospitalization	241/1514 (15.9%)	276/1509 (18.3%)	0.85 (0.72-1.01)	0.072
CHARM Overall				
All-Cause mortality (1° endpoint)	886/3803 (23%)	945/3796 (25%)	0.91 (0.83-1.00)	0.055
CV death or CHF hospitalization (2° endpoint)	1150/3803 (30.2%)	1310/3796 (34.5%)	0.84 (0.77-0.91)	<0.0001
CV death (2° endpoint)	693/3803 (18.2%)	796/3796 (20.3%)	0.88 (0.79-0.97)	0.012
CHF hospitalization (2° endpoint)	757/3801 (19.9%)	1369/3796 (24.2%)	0.84 (0.72-0.87)	<0.0001 (ARR 4.3%; NNT=23)

CV = cardiovascular

- **Meta-analyses:** The AIIRAs have yet to be shown to be equivalent or superior to the ACEIs in patients with HF. According to a recent meta-analysis of 12,469 patients from 17 trials, the AIIRAs were not found to be superior to an ACEI in reducing mortality or hospitalizations. There was a trend toward improved mortality and hospitalizations with an AIIRA compared to placebo in patients not on an ACEI, and the combination of an AIIRA and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone. The results of the ELITE II and Val-HeFT trials were included in the meta-analysis.³⁶ In a previous meta-analysis of 1,896 patients, losartan contributed to a mortality benefit compared to a control group of either placebo or an ACEI, but this meta-analysis did not include the more recent outcome trials with an AIIRA in patients with HF (ELITE II and Val-HeFT).³⁷ In Val-HeFT, combination with an ACEI and an AIIRA significantly reduced the combined primary endpoint in patients not on a beta-adrenergic blocker, although the reduction in mortality was not significant.³⁰

HF Outcomes Trials Discussion: (See Appendix C for study summaries). The Val-HeFT trial evaluated whether an AIIRA plus ACEI would reduce clinical events compared to an ACEI alone. The addition of valsartan to standard HF therapy did not affect all-cause mortality, but there was a significant 13.3% reduction in the combined endpoint of all-cause mortality and morbidity, which was driven by CHF hospitalization. Concomitant therapy affected the results. There was benefit when valsartan was added if patients were not receiving an ACEI or beta-blockers, but increased death and hospitalization if patients were receiving both an ACEI and beta-blocker. Valsartan is FDA approved for treating HF in patients intolerant of an ACEI.

The ELITE II trial was conducted to evaluate whether losartan was superior to captopril in reducing clinical events. Since ELITE II was not designed as an equivalency study, the conclusion is that losartan is not superior to captopril, and in fact the data showed trends favoring the ACEI.

An early pilot trial of candesartan for heart failure (RESOLVD) was prematurely discontinued. The CHARM program conducted in over 7000 patients found candesartan, in addition to standard HF therapies, resulted in a statistically significant reduction in cardiovascular death/HF hospitalization in patients with a LVEF <40%. This benefit was seen in patients who were intolerant of ACEIs, and when candesartan was added to ACEIs. The results were not statistically significant in patients with preserved LV function. Candesartan is not currently approved by the FDA for use in HF, but is under review, with an action anticipated by June 2004.

Current national guidelines for HF recommend using an ACEI as first line for HF, and reserving AIIRAs for patients unable to take ACEIs, however, they were released prior to the availability of the CHARM results. Since the benefits of an ACEI in conjunction with a beta-adrenergic blocker is well-defined, an AIIRA should not be prescribed prior to an ACEI but should be considered if the patient is intolerant to an ACEI or unable to take a beta-adrenergic blocker. Results of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) studies confirm this recommendation. According to the results of CHARM-Added, an AIIRA may be beneficial in combination with an ACEI and beta-adrenergic blocker in reducing cardiovascular death and HF hospitalizations, however, the effect on all-cause mortality requires further study.

HF Outcomes Trials Conclusion: Both candesartan and valsartan have convincing data to show benefit in patients with HF, especially in patients who are intolerant of ACEIs. Valsartan has an FDA indication for HF, while candesartan does not. The CHARM trials used a candesartan dose titrated to 32 mg once daily, in contrast to the Val-HeFT study where valsartan was titrated to a dose of 160 mg bid. The CHARM-Added and Val-HeFT trials represented the most similar patient populations and study design. It is difficult to determine the relative clinical effectiveness between candesartan and valsartan for HF, as differing primary endpoints were used, (cardiovascular mortality was used in CHARM, and all-cause mortality was evaluated in Val-HeFT). If the secondary endpoint of HF hospitalization is used 22 patients would need to be treated with valsartan for 23 months, and 13 patients would need to be treated with candesartan for 41 months to prevent one hospitalization for HF. The use of losartan for HF is not approved by the FDA, and the results of the ELITE II trial are less supportive of its use for HF than candesartan or valsartan.

Acute MI Outcomes Trials with AIIRAs⁴³⁻⁴⁴

- Losartan:** Losartan (target dose 50mg qd) was recently compared to captopril (target dose 50mg tid) in 5477 high-risk (i.e., signs and symptoms of HF or Q-wave MI) patients with acute MI (OPTIMAAL; Optimal Trial in Myocardial Infarction with the Angiotensin II antagonist Losartan). After a mean follow-up of 2.7 years, the primary endpoint of all-cause mortality occurred in 18% of patients on losartan and 16% of patients on captopril (RR 1.13 CI 0.99-1.28, P=0.07). There was also not a statistically significant difference between treatment groups in the secondary (i.e., sudden cardiac death or resuscitated cardiac arrest) and tertiary (i.e., fatal or non-fatal reinfarction) endpoints.⁴³⁻ Due to the study design, superiority or non-inferiority of losartan relative to captopril was not shown. Several researchers have speculated that the dose of losartan was sub-optimal in this study.
- Valsartan:** The Valsartan in Acute Myocardial Infarction Trial (VALIANT)⁴⁴ evaluated the effects on mortality of valsartan (target dose of 160 mg BID), captopril (target dose of 50 mg TID) and the combination of valsartan and captopril (target dose of 80 mg bid and 50 mg TID, respectively) in 14,808 high-risk (i.e. signs and symptoms of acute HF, or LV systolic function) patients with an acute MI. Valsartan was as effective as captopril in reducing the primary end-point of all-cause mortality in post-MI patients (19.9% mortality in the valsartan group vs 19.5% in the captopril group; hazard ratio for death 1.00 (0.90-1.11; p=0.98). The combination of captopril plus valsartan resulted in an increased incidence of adverse events, without improving survival (19.3% mortality in the combination vs 19.5% with captopril). Similar results were seen for the composite secondary endpoint of fatal and nonfatal cardiovascular events. (See table 10).
- VALIANT also showed that the combination of an ACE, AIIRA and a beta-blocker did not lead to higher mortality (unlike in Val-HeFT). Triple therapy was used in over 6,000 patients. Valsartan was at least as effective as captopril in reducing the risk of major cardiovascular events.

Table 10: Summary results of the VALIANT trial

Outcomes	Captopril (n=4909)	Valsartan (n=4909)	Combination (n=4885)	Hazard Ratio compared with captopril (97.5% CI)	P Value
1° Endpoint: All-cause mortality	958 (19.5%)	979 (19.9%)	941 (19.3%)	VAL: 1.00 (0.90- 1.11) Combo: 0.98 (0.89- 1.09)	VAL: 0.98 Combo: 0.73
2° Endpoint: Combined CV death, recurrent MI, HF hospitalization	1567 (31.9%)	1529 (31.1%)	1518 (31.1%)	VAL: 0.95 (0.88- 10.3) Combo: 0.97 (0.89- 1.03)	VAL: 0.20 Combo: 0.37

Acute MI Outcomes Conclusion: (See Appendix D for study summaries). The results of one large clinical trial support that valsartan, 160 mg BID, was as effective as captopril in reducing overall mortality in patients with acute MI and symptomatic HF. Novartis has filed a supplemental NDA with the FDA seeking approval for a new indication for valsartan to improve survival and reduce cardiovascular events in patients at high risk after surviving a heart attack, based on the results of the VALIANT trial. A trial with losartan conducted in similar patients was not able to show benefits above that achieved with captopril.

Diabetic Nephropathy Outcomes Trials

Irbesartan: In the IRMA 2 trial (Irbesartan Microalbuminuria type 2 Diabetes Mellitus in Hypertensive Patients) 590 type 2 diabetics with hypertension and microalbuminuria were randomized to irbesartan 150 mg, irbesartan 300 mg or placebo. The patients had normal glomerular filtration rate (GFR), but early renal disease. The trial lasted 2 years. The primary endpoint of time to progression from microalbuminuria to onset of diabetic nephropathy (overt proteinuria) was significantly reduced with the 300 mg irbesartan treatment group (5.2% vs 14.9%, respectively, $p<0.001$). The 150 mg irbesartan dose was less effective. The benefit of the 300 mg irbesartan dose was similar, regardless of blood pressure or glycemic control.⁴⁵

The renoprotective effect of irbesartan was also evaluated in the IDNT (Irbesartan Type 2 Diabetic Nephropathy Trial), where 1715 patients with type 2 diabetes and nephropathy received either irbesartan 300 mg qd, amlodipine 10 mg or placebo controlled antihypertensive agents (ACEIs were excluded) in a randomized manner for 2.6 years. The primary endpoint was the time to first occurrence of a composite of mortality, doubling of SCr, and ESRD (defined as renal transplantation, permanent dialysis, or $\text{SCr} \geq 6$). Secondary endpoints included cardiovascular, rather than renal outcomes. Irbesartan was associated with a risk of the primary composite endpoint that was 20% lower vs placebo ($p=0.02$) and 23% lower vs amlodipine ($p=0.006$) (relative risk). There was no significant difference with irbesartan when only death or ESRD was considered. Irbesartan efficacy compared to amlodipine was primarily due to a delay in the doubling of SCr. The irbesartan group had low enrollment of African Americans, compared to the other groups.⁴⁶ An FDA Advisory committee questioned the use of doubling of SCr as a marker for renal disease progression. However, based on the results of these two trials, the FDA granted approval for irbesartan labeling to include treatment of “diabetic nephropathy with an elevated serum creatinine and proteinuria. Irbesartan reduces the rate of progression to nephropathy, as measured by the occurrence of doubling of serum creatinine and end stage renal disease (need for dialysis or renal transplant)”. (See Table 11).

Table 11: Summary Results of the IDNT trial

Endpoint	Results	RR (95% CI)	P Value
Primary Composite Endpoint (mortality, SCr doubling, ESRD)			
IRB vs placebo	IRB: 189/579 (32.6%) vs P: 222/569 (39%)	0.80 (0.66-0.97)	0.02
IRB vs AML	IRB 189/579 (32.6%) vs AML: 233/567 (41.1%)	0.77 (0.63-0.93)	0.006
Doubling of SCr			
IRB vs placebo	IRB: 98/579 (16.9%) vs P:135 /569 (23.7%)	0.67 (0.52-0.87)	0.003
IRB vs AML	IRB: 16.9% vs AML: 233/567 (25.4%)	0.63 (0.48-0.81)	<0.001
ESRD			
IRB vs placebo	IRB 82/579 (14.2%) vs P: 101/569 (17.8%)	0.77 (0.57-1.03)	0.07
IRB vs AML	IRB 14.2% vs AML 104//567 (18.3%)	0.77 (0.57-1.03)	0.07
Death from any cause			
IRB vs placebo	IRB 87/579 (15%) vs P: 93/569 (16.3)	0.92 (0.69-1.23)	0.57
IRB vs AML	IRB 15% vs AML:83/567 (14.6%)	1.04 (0.77-1.40)	0.80

IRB = irbesartan; AML = amlodipine; P= placebo

Losartan: Losartan was evaluated in 1500 type 2 diabetics with proteinuria (nephropathy) in the Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. Losartan 50 mg qd (which could be increased to 100 mg qd for blood pressure control) was compared to placebo in addition to anti-hypertensive medications for 3 years. The antihypertensive drugs excluded ACEIs. The primary endpoint was a composite of doubling of SCr, ESRD (need for chronic dialysis or renal transplantation), or death. In the losartan group, 71% received a dosage of 100 mg qd. Losartan reduced the risk of the primary composite endpoint by 16% compared to placebo ($p=0.02$). Losartan decreased the progression to ESRD by 28% ($p=0.002$) and reduced the doubling of SCr by 25% ($p=0.006$) vs conventional controlled placebo group, but had no effect on the rate of death

($p=0.88$). Losartan is labeled for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension. (See Table 12).

Table 12: Summary Results of the RENAAL Trial

Outcomes	Losartan (n=751)	Placebo (n=762)	RRR (95% CI)	P Value
1° Endpoint: Composite of doubling of SCr, ESRD, or death	327 (44%)	359 (47%)	16% (2 to 28)	0.02
2° Endpoint: Doubling of SCr	162 (22%)	198 (26%)	25% (8 to 39)	0.006
2° Endpoint: ESRD	147 (20%)	194(26%)	28% (11 to 42)	0.002
2° Endpoint: Death	158 (21%)	155 (20.2%)	-2 (-27 to 19)	0.9

A side-by-side comparison of the IDNT and RENAAL trial is included in Table 13.

Table 13: Summary Results of the IDNT and RENAAL trials

Parameter	IDNT*	RENAAL
Drug	Irbesartan	Losartan
Entry criteria	Type 2 DM HTN Proteinuria Increased SCr	Type 2 DM Proteinuria Increased SCr
N	1715	1513
Comparators	Irbesartan 300 mg (579) Amlodipine 10 mg (567) Placebo (569)	Losartan 50-100 mg (751) Placebo (762)
Mean duration	2.6 yrs	3.4 yrs
1° Endpoint	SCr doubling ESRD Death (Composite)	SCr doubling ESRD Death (Composite)
Results Absolute (% reaching 1° endpoint)	Irbesartan 33% Placebo 39%	Losartan 43.5% Placebo 47.1%
Results Relative (% reaching 1° endpoint vs placebo)	Irbesartan 20% (CI 0.66-0.97)	Losartan 16% (CI 0.72-0.98)
P value	0.02	0.02
Results (Relative risk)	SCr: 33% ↓ vs placebo ESRD: 23% ↓ vs placebo Death: NSD	SCr: 25% ↓ vs placebo ESRD: 28% ↓ vs placebo Death: NSD

* amlodipine results not shown in table.

Other Renal Endpoint Trials

The Microalbuminuria Reduction with Valsartan (MARVAL) study was a recent trial in 332 patients with type 2 DM and microalbuminuria (with or without HTN) that compared the percent change in UAE rate from baseline to 24 weeks with valsartan (mean dose 122mg) or amlodipine (mean dose 8mg). Doses were titrated to a target BP of 135/85 mm Hg. The UAE rate in patients on valsartan was 56% (CI 0.496-0.63) of baseline compared to 92% (CI 0.817-1.037) of baseline with amlodipine ($P<0.001$). Results were similar in the patients who were normotensive

vs. hypertensive at baseline. In evaluating the secondary endpoint of the study, significantly more patients on valsartan demonstrated a return to normoalbuminuria (UAE rate < 20 $\mu\text{g}/\text{min}$) compared to patients on amlodipine (29.9% vs. 14.5%, respectively; 15.4% difference, CI 0.056-0.258; $P < 0.001$).⁴⁸ This study was not powered to evaluate mortality. In a study evaluating 147 normotensive (BP $\leq 150/90$ mm Hg) patients with type 2 DM, there was a relative reduction of 43% in UAE rate with losartan 100mg compared to placebo at 10 weeks.⁴⁹

Studies comparing an ACEI to an AIIRA

Candesartan: The Candesartan and Lisinopril Microalbuminuria (CALM) study compared the effects of candesartan 16mg, lisinopril 20mg, or the combination on UAE and BP in 197 patients with HTN, type 2 DM, and microalbuminuria for a total of 24 weeks. There was a statistically significant reduction in BP in all treatment groups, with the greatest reduction in patients on combination therapy. Urinary albumin:creatinine ratio was reduced with candesartan (24%, CI 0-0.43; $P=0.05$), lisinopril (39%, CI 0.20-0.54; $P < 0.001$), and combination therapy (50%, CI 0.36-0.61; $P < 0.001$). 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.⁵⁰

Losartan: In the COOPERATE trial, 263 patients with non-diabetic renal disease were randomized to losartan 100mg, trandolapril 3mg, or the combination. The combined primary endpoint of doubling serum creatinine concentration or ESRD was reduced in the combination group compared with those on losartan (HR 0.40, CI 0.17-0.69; $P=0.016$) or trandolapril (HR 0.38, CI 0.18-0.63; $P=0.018$).⁵¹ In another study, losartan 50mg was compared to enalapril 20mg in 93 patients with HTN. There were similar reductions in blood pressure and a significant reduction in UAE rate with the two agents. The effect on UAE was more evident in the patients with baseline microalbuminuria.⁵² Losartan was also compared to enalapril in a study of 16 patients with type 1 DM and nephropathy for 2 months. The blood pressure was decreased in both groups. There was not a statistically significant difference between losartan 100mg and enalapril 20mg in the reduction in UAE.⁵³ In another trial comparing losartan with enalapril in 92 patients with HTN and type 2 DM with early nephropathy, blood pressure and UAE significantly decreased in both treatment groups after one year.⁵⁴

Valsartan: In a study comparing valsartan with captopril in 122 patients with type 2 DM and microalbuminuria, valsartan demonstrated a similar reduction in UAE rate as captopril after 1 year of follow-up.⁵⁵

Diabetic Nephropathy Discussion: Nephropathy is characterized by proteinuria and decreasing glomerular filtration rate. In both type 1 and 2 diabetics, the presence of albuminuria is associated with increased cardiovascular morbidity and mortality. Diabetic patients are more likely to die of cardiovascular events than renal events. If microalbuminuria (urinary albumin excretion 30 to 300 mg/24 hr) is found, screening for possible vascular disease and measures to reduce all cardiovascular risk factors (e.g. lowering of LDL cholesterol, antihypertensive therapy, smoking cessation, exercise, etc) are indicated. Hypertension and renal disease are both independent risk factors for cardiovascular events.

Surrogate markers of kidney outcome risk such as proteinuria can be improved with lower BP, but these surrogate markers may not accurately predict more clinically significant events such as doubling of SCr, need for dialysis or renal transplant, or death due to kidney failure. RENAAL and IDNT were designed to look at renal outcomes, not cardiovascular outcomes. The composite outcomes in both the RENAAL and IDNT trials have been accepted by the nephrology community as the gold standard for evaluating drug treatment of nephropathy; the endpoints are similar to those used in the landmark 1993 Collaborative Trial, which first showed the benefit of ACEIs in slowing renal disease progression. Candesartan (CALM) and valsartan (MARVAL) evaluated a surrogate outcome, albumin excretion rate and were only 24 weeks in duration.

Several trials have evaluated the use of an ACEI in patients with type 1 DM or type 2 DM with proteinuria or diabetic nephropathy with favorable results.⁵⁶⁻⁵⁸ In 94 patients with type 2 DM (HbA_{1c} 10.4%) and microalbuminuria, there was an absolute risk reduction of 30% (95% CI, 15-45%) in the development of overt proteinuria (UAE rate $\geq 300\text{mg}/24\text{hr}$) with enalapril 10mg compared to placebo ($P < 0.001$) after 5 years (NNT=3).⁵⁹ This benefit was extended to 7 years in a follow-up evaluation.⁶⁰

From the results of the trials discussed above, it appears that an AIIRA is an effective treatment for patients with type 2 DM and microalbuminuria or nephropathy.⁶¹ Losartan and irbesartan recently received FDA approval in the treatment of nephropathy in patients with type 2 DM and HTN. However, long-term outcome trials comparing an ACEI to an AIIRA are needed to determine if these agents provide similar benefit in treating patients with DM and microalbuminuria or nephropathy and if combination therapy provides any significant benefit over an ACEI alone. Therefore, an ACEI is preferred in patients with DM and microalbuminuria or nephropathy and an AIIRA may be considered in patients who are unable to tolerate an ACEI.

Diabetic Nephropathy Conclusion

(See Appendix E for study comparisons). Losartan and irbesartan have both been studied in type 2 diabetic patients with nephropathy and were shown to reduce the primary outcome used in both studies (RENAAL, and IDNT), which is the well-accepted composite of SCr doubling, ESRD and mortality. Over 1500 patients were enrolled in both trials. Losartan was effective in reducing the risk of doubling of SCr and reducing ESRD progression, but had no effect on mortality. Similar results were seen with irbesartan. The relative benefit was 20% with irbesartan and 16% for losartan. Both irbesartan and losartan are labeled for use in diabetic patient with nephropathy. An additional study with irbesartan, IRMA-2 supports that a dose of 300 mg is more effective than 150 mg qd in patients with DM and microalbuminuria.

Candesartan and valsartan have been evaluated in two separate trials (CALM and MARVAL) assessing urinary albumin excretion rate. Less than 350 patients were enrolled in these trials. Candesartan and valsartan both showed positive results in reducing microalbuminuria, however, the short duration of these trials (24 weeks) did not establish whether these findings would translate into clinical benefit. Neither candesartan nor valsartan have FDA-approved labeling for use in diabetic nephropathy.

Other Outcomes Trials under investigation

DETAIL (Diabetics exposed to telmisartan and enalapril), which is comparing an AIIRA and an ACE in patients with mild to moderate hypertension and diabetic nephropathy, is planned for completion in 2005.

HEAAL (Heart Failure endpoint Evaluation with the Angiotensin II Antagonist Losartan) is a study comparing losartan 50 mg and 150 mg dosages in a heart failure population.

I-PRESERVE (Irbesartan in Heart Failure Preserved Systolic Function) will compare irbesartan with placebo in patients > age 60 years with a diagnosis of HF and a LV ejection fraction >45%. The primary end points are death and hospitalization for cardiovascular disease.

ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) is underway in patients with coronary artery disease, peripheral vascular disease, or diabetes with end-organ damage. Telmisartan 80 mg, ramipril 10 gm and the combination of telmisartan 80 mg and ramipril 10 mg are being compared. To date, over 20,000 patients have been enrolled, with study completion expected by 2007.

TRANSCEND: (Telmisartan Randomized Assessment Study in ACE-I Intolerant Patients with Cardiovascular Disease) will investigate telmisartan or placebo in patients unable to tolerate ACEIs, comparing the primary endpoint of a composite of cardiovascular death, MI, stroke or HF hospitalization.

VALUE (Valsartan antihypertensive long-term use evaluation). Head to head comparison of valsartan vs amlodipine in 15,314 hypertensive patients with at least one additional risk factor for cardiovascular events.

Safety / Tolerability^{1,23,30,32,46,47,62-86}

Serious Side Effects^{32,34,39,41,87-103}

Angioedema—Angioedema has been reported with AIIRAs but to a much lesser degree than ACEIs. This may be due to the fact that ACEIs have been available for a longer period of time and have been used in more patients; or this phenomenon could be provoked through a mechanism not triggered by AIIRAs. The exact mechanism is unknown; in ACEIs, it is thought to be related to bradykinin accumulation. The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2%. In a large, multicenter, randomized controlled 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.⁴¹ There have been a number of published case reports of angioedema in patients treated with an AIIRA. In approximately one third of these cases, the patients previously experienced angioedema with an ACEI. Therefore, an AIIRA should be used with caution in patients who have previously experienced angioedema.

Renal Failure—In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system, treatment with AIIRAs and ACEIs has been associated with acute renal failure. These drugs are capable of reducing intraglomerular filtration pressure by causing dilation of the efferent renal arterioles. These agents can cause renal failure in a patient with bilateral renal artery stenosis or severe cardiac insufficiency.

Hyperkalemia—AIIRAs, like ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to potassium reabsorption. According to information from manufacturers, rises in potassium levels have been associated with these drugs, but clinical significance is either minor or not addressed. This low incidence could also be due to the shorter time frame that AIIRAs have been available. It is unclear at this time if treatment with an AIIRA would be an appropriate alternative in patients who develop hyperkalemia on an ACEI. In SOLVD, hyperkalemia with potassium levels greater than 5.5 mmol/L was reported in 6.4% of patients on enalapril compared to 2.5% of patients on placebo. In the ELITE Study, an increase in serum potassium of ≥ 0.5 mmol/L above baseline was observed in 22.7% patients receiving captopril compared to 18.8% of patients on losartan. The proportion of patients with potassium levels ≥ 5.5 mmol/L did not differ significantly among the treatment groups in the RESOLVD Pilot Study. 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.³⁹ The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on lisinopril compared to valsartan with renal insufficiency. In patients with a $GFR \leq 60$ mL/min/1.73 m², there was a significant increase of 0.28 mEq/L ($P = 0.04$) above baseline (4.6 mEq/L). The increase of 0.12 mEq/L seen with valsartan in this subgroup was not significant ($P = 0.1$).

Adverse Event Profile

- The AIIRA adverse effect profile is similar to that of placebo in clinical trials.
- No AIIRA has a specific, dose-dependent adverse effect that can be attributed to the drug itself.
- All the AIIRAs appear to be well tolerated.
- Published, long-term safety/tolerability data are not available for olmesartan.
- **Cough:** ACEIs have an incidence of cough ranging from 5 to 39%. Unlike ACEIs, AIIRAs have an incidence of cough comparable to placebo (1.6-3.4%). In the ELITE Study, 3.8% of patients on an ACEI withdrew from the study due to complaints of cough compared to 0% of patients treated with an AIIRA. 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.⁴¹ A number of trials evaluating candesartan, losartan, telmisartan, or valsartan in patients with previous ACEI induced cough showed that patients treated with an AIIRA complained of cough similar to that seen with placebo (15.6%-36.7% AIIRA, 9.7%-31.4% placebo), but statistically significantly less than seen when an ACEI was included (60-97%).¹³⁴⁻¹³⁹ In trials specifically evaluating cough as a side effect, cough was reported in 1.5%-12.9% of

patients on eprosartan compared to 5.4%-23% of patients receiving an ACEI.¹⁴⁰⁻¹⁴³ Use of an AIIRA can be considered in patients who are unable to tolerate treatment with an ACEI due to cough, although there is a slight chance that patients may develop a cough with an AIIRA.

- Adverse experiences have generally been mild and transient in nature and have rarely required drug discontinuation. The overall incidence of adverse events is comparable to placebo as shown in Table 14. In addition, the AIIRAs have been studied in large [candesartan (n>6000), irbesartan (n>500), losartan (n>9000), and valsartan (n>7000)], long-term (> 1 year in duration), randomized, multicenter, controlled, outcome trials with discontinuation due to adverse events either less than (irbesartan) or similar to (losartan) placebo in patients with diabetic nephropathy, or greater than placebo (candesartan, valsartan) in patients with HF. The AIIRAs candesartan, losartan, irbesartan, and valsartan, have been shown to result in less discontinuations due to adverse events compared to active control in these large trials including patients with HF (losartan), elderly patients with HTN (candesartan), HTN and LVH (losartan), HF post-MI (losartan, valsartan), and diabetic nephropathy (irbesartan).^{27,30,32,33,43,44,45,47} Publications of pooled analyses of the safety and tolerability of irbesartan (n~1900) and losartan (n~2900) showed that patients on these agents experienced adverse events similar to placebo.¹⁴⁴ An integrated analysis of safety from seven studies of 6 to 12 weeks duration in ~2500 patients (5,888 patient months) on olmesartan demonstrated a similar incidence of treatment-emergent adverse events compared to placebo, with the exception of dizziness that occurred in 2.8% on olmesartan vs. 0.9% on placebo (P=0.01).¹¹⁵ The long-term tolerability of telmisartan was demonstrated in a 52-week trial with over 300 patients where patients on telmisartan experienced fewer side effects related to treatment compared to an ACEI.¹⁴⁵ The long-term safety of eprosartan was evaluated in an open-label trial of over 500 patients who completed 12 months and ~300 patients on eprosartan for 24 months. It was reported that the safety profile of eprosartan was similar to short-term placebo-controlled trials.¹⁴⁶ Published, post-marketing surveillance data of over 12,000 patients on valsartan identified no unexpected serious adverse events.¹⁴⁷ Candesartan, losartan, and valsartan have been studied most extensively in long-term outcome trials. Irbesartan has also been studied in a long-term outcome trial but with fewer patients. Eprosartan, telmisartan, and olmesartan do not have published safety results from long-term outcome trials but have demonstrated that they are safe with either collective data from short-term trials (olmesartan), or an open-label (eprosartan) or randomized controlled trial (telmisartan) lasting one year or longer evaluating the safety and efficacy of these agents in approximately 300-500 patients.
- Losartan decreases serum uric acid and increases urinary uric acid secretion. A study was conducted in 63 patients with hypertension to determine if the uricosuric effects of acute and chronic doses of losartan increase the risk of urate nephropathy in the presence of thiazide-induced hyperuricemia. The authors concluded that administration of losartan to patients with hypertension did not increase the risk of urate nephropathy, even in the presence of thiazide-induced hyperuricemia. A cross-over comparison trial of 13 hypertensive patients with hyperuricemia and gout were treated with irbesartan or losartan and found losartan to have statistically significantly lower serum uric acid levels compared with irbesartan.¹⁴⁸ In another trial of 58 patients with HTN comparing eprosartan with losartan, an increase in uric acid excretion was seen with losartan but not with eprosartan.¹⁶ The decrease in serum uric acid was not significantly different at week 4 between the two groups. The clinical significance of these effects is unknown.
- There does not seem to be any discernable difference in adverse effects (AE) or adverse effect dropout rates (AE_{DO}) among drugs. See table below:

Table 14: AIIRA Adverse Events and Dropout Rates^{7,9,11-12,14,72,100-115}

	Losartan	Valsartan	Irbesartan	Candesartan	Telmisartan	Eprosartan	Olmesartan
AE % (n)	26.7 – 46.8 (2371)	15 – 46.6 (1350)	43.7 – 56 (1419)	11.3 – 54 (554)	54.8 – 69.9 (365)	45.5 – 64 (276)	42.2 (2540)
AE % Placebo (n)	27.9 – 52.0 (727)	17 – 63.4 (746)	52.7 – 56 (821)	15.9 – 61 (257)	48.7 – 69.1 (157)	51.7 – 57 (198)	42.7 (555)
AE _{DO} % (n)	2.3 – 14.4 (2371)	0.73 – 2.3 (1052)	0 – 2.5 (569)	1.2 – 3.7 (285)	1.4 – 6.9 (478)	3.3 – 6.3 (276)	2.4 (3278)
AE _{DO} % Placebo (n)	3.7 – 18.6 (727)	2.1 – 3.3 (598)	1.3 – 3.4 (282)	3.5 – 4.8 (148)	6.7 – 9.2 (214)	7.5 – 10.5 (198)	2.7 (1179)

*AE included clinical, laboratory and ineffective therapeutic effect.

Drug Interactions^{65-72,116-126}

- Candesartan, losartan, telmisartan, and valsartan have been reported to have potentially significant drug interactions where monitoring may be required.
- **Losartan:** Losartan may increase the reabsorption of lithium; monitor levels and for signs of toxicity. The antihypertensive effect of losartan may be decreased with concomitant administration of indomethacin. Patients should be monitored for change in blood pressure control. Fluconazole has increased losartan AUC (66%) and C_{max} (30%) and decreased E-174 (the active metabolite of losartan) AUC (43%) and C_{max} (56%). The clinical significance of this drug interaction is unknown, although it has been recommended to monitor patients for continued control of HTN. Rifampin decreased the AUC of losartan (35%) and E-174 (40%). The half-life of both losartan and E-174 are decreased 50% by rifampin. It is recommended that blood pressure control be monitored due to this drug interaction. Phenobarbital decreases the AUC of losartan and E-174 by 20%. This drug interaction is thought to have minor clinical significance.
- **Telmisartan:** The manufacturer states that telmisartan has been shown to increase peak and trough digoxin levels by 49% and 20%, respectively. This data being based on a study in healthy volunteers. In a subgroup analysis of digoxin levels in 49 patients participating in the REPLACE trial, the change in digoxin levels ranged from -0.1 to +0.6nmol/L. Four patients with therapeutic digoxin levels prior to the addition of telmisartan experienced a change in levels to outside the therapeutic range after addition of the telmisartan. There did not appear to be a difference in safety when these patients were analyzed. However, as recommended in the manufacturer's product information, it is prudent to monitor trough digoxin levels at steady-state in patients receiving digoxin in conjunction with telmisartan. Telmisartan has some inhibition of CYP2C19, possibly inhibiting the metabolism of drugs metabolized by CYP2C19, clinical significance unknown. Warfarin trough plasma concentrations may decrease slightly, although this did not result in a change in INR.
- **Valsartan:** Valsartan may increase the reabsorption of lithium; monitor levels and for signs of toxicity. Cimetidine increased the AUC (7%) and C_{max} (51%) of valsartan, although this was considered to be clinically insignificant.
- **Candesartan:** Candesartan decreased trough warfarin plasma concentrations, although the prothrombin time did not change. Increased lithium concentrations have been reported, thus lithium concentrations should be monitored when co-administered with candesartan.
- **Irbesartan:** Irbesartan has some oxidation by CYP2C9 in vitro. Nifedipine inhibits CYP2C9 but clinical studies have not shown pharmacokinetic changes with irbesartan.
- Potassium-sparing diuretics and potassium supplements used in conjunction with AIIRAs may increase the risk of hyperkalemia.

Special Populations

- Pregnancy risk factor C (first trimester); D (second and third trimesters)
- Drugs that act directly on the renin-angiotensin-aldosterone system have been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.
- It is not known if AIIRAs are excreted in human milk, but they are known to be present in rat milk. Risks to the fetus versus benefits to the mother must be assessed.
- None of the AIIRAs are approved for use in pediatric patients.
- See Table 5 under the dosing and administration for information on hepatic and renal failure dosing of AIIRAs.

Other Factors

Other factors include place in therapy, clinical practice guideline recommendations, dosing/administration, compliance/convenience issues, and current usage.

Place in Therapy^{23-62,64,129,130}

- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines recommend using a thiazide diuretic for most patients with uncomplicated HTN. Other classes (ACEIs, AIIRAs, beta-adrenergic blockers, calcium channel blockers) may be considered in combination or for treatment of patients with compelling indications.
- The ACEIs have well documented beneficial effects in the treatment and prevention of HF. Losartan has been shown to be effective in the treatment of HF. Data with valsartan has also shown a benefit in patients with HF however, there appears to be a detrimental effect in patients treated with an AIIRA in conjunction with an ACEI and a beta-adrenergic blocker. While there is evidence as to the effectiveness of the AIIRAs in HF, more data is needed to support the use of AIIRAs for this condition over an ACEI. An AIIRA has not been shown to provide better outcomes in high-risk patients with acute MI compared to treatment with an ACEI.
- The ACEIs have been shown to be beneficial in slowing the progression of diabetic nephropathy in patients with type 1 or 2 DM and microalbuminuria. The ACEIs also provide a renal protective effect in patients with type 1 DM and nephropathy. Outcome trials in patients with type 2 DM and microalbuminuria or nephropathy have shown that an AIIRA can prevent the decline in renal function. At this time, long-term outcome trials comparing an ACEI to an AIIRA are needed to determine if these agents provide similar benefit in treating patients with DM and microalbuminuria or nephropathy. There is evidence to suggest that combination of an ACEI and AIIRA may be beneficial in patients with type 2 DM and microalbuminuria, however combination therapy has not been shown to be significantly different than an ACEI alone in this patient population.
- An AIIRA may be considered for use only in those patients who have an indication for an ACEI and who are intolerant

Clinical Practice Guidelines¹³²

Hypertension: The JNC 7 guidelines recommend that thiazide diuretics be used in patients with uncomplicated HTN. There are data to suggest the AIIRAs may be beneficial in other disease states (e.g., type 2 DM with microalbuminuria or nephropathy, HF), although the AIIRAs have not been shown to be superior to the ACEIs in these patients.

CHF: The 2001 ACC/AHA Guidelines for Evaluation and Management of Chronic Heart Failure are evidence based and state the following regarding the use of AIIRAs. These guidelines considered the results of the Val-HeFT trial, but were published prior to the availability of the CHARM trials. Guidelines from the Heart Failure Society of America have not been updated since 1999, but an update is underway.

- AIIRAs should not be considered equivalent to or superior to ACEIs in treating HF
- AIIRAs should not be used in treating HF in patients with no prior use of an ACEI
- AIIRAs should not be substituted for ACEI in patients who are tolerating ACEIs with no difficulty
- AIIRAs should be considered instead of ACEIs in patients who are intolerant of ACEIs due to angioedema or intractable cough
- The role of AIIRAs as an adjunct to ACEI in HF remains to be defined
- The benefit of an AIIRA in patients with HF taking an ACEI and a beta-blocker requires further study

Utilization – See individual VA or DoD pre-decisional analysis.

Conclusion

Hypertension: All seven AIIRAs are labeled for use in hypertension and appear equally effective for lowering blood pressure. Losartan has an additional indication to reduce the risk of stroke in hypertensive patients with left ventricular hypertrophy that does not apply to black patients.

Heart Failure: Valsartan is labeled for use in HF patients intolerant of ACEIs in a dose of 160 mg BID. For hypertension, valsartan is dosed once daily (usual dosage is 80 mg qd). Candesartan is not approved for use in HF, but the results of one large trial support its use, and this indication is under review at the FDA. The candesartan dose used in the CHARM trials was 32 mg qd. Candesartan may be dosed qd or bid in hypertension, but qd dosing

is more common (usual dose is 16 mg QD). Losartan is not approved for use in HF patients, and the results of one trial were insufficient to recommend its routine use for this indication. Valsartan is not approved for use in high-risk patients after an acute MI but a supplemental NDA has been filed with the FDA for this indication and its use is supported by a long-term outcome trial. Losartan is not approved for use in patients post-MI and its use is not supported by the results of a long-term outcome trial.

Diabetic Nephropathy: Both irbesartan (dose 300 mg qd) and losartan (dose 50-100 mg qd) are labeled for use in type 2 diabetic patients with nephropathy, based on two trials evaluating hard outcomes. The usual doses of each drug for hypertension are irbesartan, 150 mg qd and losartan 50 mg qd. Neither candesartan nor valsartan are labeled for use in diabetic nephropathy, and, there is insufficient evidence at this time to support their use for this indication, as only surrogate outcomes have been measured.

References:

1. UHC Drug Monographs. Angiotensin II Receptor Antagonists. August 1998.
2. Larochelle P, Flack JM, Marbury TC, et al. Effects and tolerability of irbesartan versus enalapril in patients with severe hypertension. *Irbesartan Multicenter Investigators. Am J Cardiol* 1997;80:1613-5.
3. Mimran A, Ruilope L, Kerwin L, Nys M, Owens D, Kassler-Taub K, Osbakken M. A randomised, double-blind comparison of the angiotensin II receptor antagonist, irbesartan, with the full dose range of enalapril for the treatment of mild-to-moderate hypertension. *J Hum Hypertens* 1998;12:203-8.
4. Lacourciere Y. A multicenter, randomized, double-blind study of the antihypertensive efficacy and tolerability of irbesartan in patients aged > or = 65 years with mild to moderate hypertension. *Clin Ther* 2000;22:1213-24.
5. Sega R. Efficacy and safety of eprosartan in severe hypertension. *Eprosartan Multinational Study Group. Blood Press* 1999;8:114-21.
6. Smith DH, Matzek KM, Kempthorne-Rawson J. Dose response and safety of telmisartan in patients with mild to moderate hypertension. *J Clin Pharmacol* 2000;40:1380-90.
7. Holwerda NJ, Fogari R, Angeli P. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. *J Hypertens* 1996;14:1147-51.
8. Tikkanen I, Omvik P, Jensen HA. Comparison of the angiotensin II antagonist losartan with the angiotensin converting enzyme inhibitor enalapril in patients with essential hypertension. *J Hypertens* 1995;13:1343-51.
9. Zanchetti A, Omboni S, Biagio CD. Candesartan cilexetil and enalapril are of equivalent efficacy in patients with mild to moderate hypertension. *J Hum Hypertens* 1997;11(suppl 2):S57-S59.
10. Ball KJ, Williams PA, Stumpe KO. Relative efficacy of an angiotensin II antagonist compared with other antihypertensive agents. *Olmesartan medoxomil versus antihypertensives. J Hypertens* 2001;19(suppl 1):S49-56.
11. Hedner T, Oparil S, Rasmussen K, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. *Am J Hypertens* 1999;12:414-7.
12. Kassler-Taub K, Littlejohn T, Elliott W. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. *Am J Hypertens* 1998;11:445-53.
13. Oparil S, Guthrie R, Lewin AJ, et al. An elective-titration study of the comparative effectiveness of two angiotensin II receptor blockers, irbesartan and losartan. *Clin Ther* 1998;20(3):398-409.
14. Andersson OK, Neldam S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. *Blood Press* 1998;7:53-9.
15. Gradman AH, Lewin A, Bowling BT, et al. Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. *Heart Disease* 1999;1:52-7.
16. Puig JG, Mateos F, Buno A, et al. Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens* 1999;17:1033-9.
17. Mallion JM, Siche JP, Lacourciere Y. ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. *J Hum Hypertens* 1999;13:657-64.
18. Monterroso VH, Rodriguez Chavez V, Carbajal ET, et al. Use of ambulatory blood pressure monitoring to compare antihypertensive efficacy and safety of two angiotensin II receptor antagonists, losartan and valsartan. *Losartan Trial Investigators. Adv Ther* 2000;17:117-31.
19. Bakris G, Gradman A, Reif M, et al. for the CLAIM Study Investigators. Antihypertensive efficacy of candesartan in comparison to losartan: the CLAIM study. *J Clin Hypertens (Greenwich)* 2001;3:16-21.
20. Manolis AJ, Grossman E, Jelakovic B, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. *Losartan Trial Investigators. Clin Ther* 2000;22:1186-203.
21. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens* 2001;3:283-91,318.
22. Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertens* 2000;13:418-26.
23. 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.
24. 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.

25. Kjeldsen SE, Dahlöf B, Devereux RB, et al. for the LIFE Study Group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. A Losartan Intervention For Endpoint Reduction (LIFE) substudy. *JAMA* 2002;298:1491-8.
26. Devereux RB, Dahlöf B, Kjeldsen SE, et al., for the LIFE Study Group. Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease: a substudy of the LIFE randomized trial. *Ann Intern Med* 2003;139:169-77.
27. Lithell H, Hansson L, Skoog I, et al., SCOPE Study Group. The Study of Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875-86.
28. Kjeldsen SE, Julius S, Brunner H, et al. Characteristics of 15,314 hypertensive patients at high coronary risk. The VALUE trial. The Valsartan Antihypertensive Long-term Use Evaluation. *Blood Press* 2001;10:83-91.
29. Novartis *Diovan* gets heart failure claim but is second line to ACEI inhibitors. *FDC Rep.* 2002; 64(Aug 19).
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. Greenberg BH. Role of angiotensin receptor blockers in heart failure not yet RESOLVD. *Circulation* 1999;100:1032-4.
36. 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.
37. Sharma D, Buyse M, Pitt B, Rucinska EJ and the Losartan Heart Failure Mortality Meta-analysis Study Group. Meta-analysis of observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan in heart failure. *Am J Cardiol* 2000;85:187-92.
38. Swedberg K, Pfeffer M, Granger C et al. Candesartan in heart failure-assessment of reduction in mortality and morbidity (CHARM): rationale and design. *Charm-Programme Investigators. J Card Fail* 1999;5:276-82.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. (VALIANT). *N Engl J Med* 2003;349:1893-906.
45. 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.
46. 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.
47. 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.
48. Viberti G, Wheeldon NM, for the MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. *Circulation* 2002;106:672-8.
49. Zandbergen AAM, Baggen MGA, Lamberts SWJ, et al., Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med* 2003;139:90-6.
50. 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.
51. 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.
52. Nielsen S, Døllerup 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.
53. 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.
54. 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.
55. 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.
56. Kasiske BL, Kalil RSN, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993;118:129-38.
57. Vivian EM, Goebig ML. Slowing the progression of renal disease in diabetic patients. *Ann Pharmacother* 2001;35:452-63.

58. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62.
59. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;118:577-81.
60. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1996;156:286-9.
61. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003; 26(Suppl 1):S80-2.
62. Burnier M, Brunner HR. Comparative antihypertensive effects of angiotensin II receptor antagonists. *J Am Soc Nephrol* 1999;10:S278-S82.
63. Song JC, White CM. Pharmacologic, pharmacokinetic, and therapeutic differences among angiotensin II receptor antagonists. *Pharmacotherapy* 2000;20(2):130-9.
64. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000;355(2):637-45.
65. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. *Am J Hypertens* 2000;13:18S-24S.
66. Package insert. Losartan. Merck & Co., Inc. Whitehouse Station, NJ;2003:7882922.
67. Package insert. Valsartan. Novartis Pharmaceuticals Corp. East Hanover, NJ;2002:T2002-77.
68. Package insert. Irbesartan. Bristol-Myers Squibb Sanofi-Synthelabo Partnership. New York, NY;2002:V4-641H.
69. Package insert. Candesartan. AstraZeneca. Wilmington, DE;2003:610002-09.
70. Package insert. Telmisartan. Boehringer Ingelheim Pharmaceuticals. Ridgefield, CT;1998:MC-PI-11.
71. Package insert. Eprosartan. Solvay Pharmaceuticals, Inc. Buffalo Grove, IL;1999:50186US2.
72. Package insert. Olmesartan. Sankyo Pharma, Inc. New York, NY;2001:P1800601.
73. Shahinfar S, Simpson RI, Carides AD, et al. Safety on losartan in hypertensive patients with thiazide-induced hyperuricemia. *Kidney Int* 1999;56(5):1879-85.
74. Gavras HP, Salerno CM. The angiotensin II type 1 receptor blocker losartan in clinical practice: a review. *Clin Ther* 1996;18(6):1058-67.
75. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs* 1996;51(5):820-45.
76. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997;54(2):299-311.
77. Pool J, Oparil S, Hedner T, et al. Dose-responsive antihypertensive efficacy of valsartan, a new angiotensin II receptor blocker. *Clin Ther* 1998;20(6):1106-14.
78. Gillis JC, Markham A. Irbesartan: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the management of hypertension. *Drugs* 1997;54(6):885-902.
79. McClellan KJ, Gao KL. Candesartan cilexetil: a review of its use in essential hypertension. *Drugs* 1998;56(5):847-68.
80. Sharpe M, Jarvis B, Goa KL. Telmisartan: a review of its use in hypertension. *Drugs* 2001;61(10):1501-29.
81. Plosker GL, Foster RH. Eprosartan: a review of its use in the management of hypertension. *Drugs* 2000;60(1):177-201.
82. Weber M. Clinical efficacy of eprosartan. *Pharmacotherapy* 1999;19(4 Pt 2):95S-101S.
83. Conigliaro RL, Gleason PP. Losartan-induced cough after lisinopril therapy. *Am J Health-Syst Pharm* 1999;56:914-5. Letter.
84. Sever PS, Holzgreve H. Long-term efficacy and tolerability of candesartan cilexetil in patients with mild to moderate hypertension. *J Hum Hypertens* 1997;11 (suppl 2):S69-73.
85. Levine B. Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension. *Curr Med Res Opin* 2001;17:8-17.
86. Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther* 1999;6:161-6.
87. Pylypchuk GB. ACE inhibitor-versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998;32:1060-6.
88. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998;158:2063-5.
89. Boxer M. Accupril- and Cozaar-induced angioedema in the same patient (letter). *J Allergy Clin Immunol* 1996;98:471.
90. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan (letter). *N Engl J Med* 1995;333:1572.
91. Sharma PK, Yium JJ. Angioedema associated with angiotensin II receptor antagonist losartan. *South Med J* 1997;90:552-3.
92. Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsartan. *Pharmacotherapy* 1998;18:866-8.
93. Rivera JO. Losartan-induced angioedema. *Ann Pharmacother* 1999;33:933-5.
94. Cha YJ, Pearson VE. Angioedema due to losartan. *Ann Pharmacother* 1999;33:936-8.
95. Rupprecht R, Vente C, Grafe A, Fuchs T. Angioedema due to losartan. *Allergy* 1999;54:81-2.
96. Irons BK, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 2003;37:1024-7.
97. Lo K. Angioedema associated with candesartan. *Pharmacotherapy* 2002; 22:1176-9.
98. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000;34:526-8.
99. 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.
100. 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.
101. Gradman AH, Arcuri KE, Goldberg AI, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. *Hypertension* 1995;25:1345-50.
102. MacKay JH, Arcuri KE, Goldberg AI, et al. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. *Arch Intern Med* 1996;156:278-85.
103. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine er, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol* 1995;75:793-5.
104. Oparil S, Dyke S, Harris F, et al. The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension. *Clin Ther* 1996;18(5):797-810.

105. Black HR, Graff A, Shute D. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. *J Hum Hypertens* 1997;11:483-9.
106. Pool JL, Guthrie RM, Littlejohn TW. Dose-related antihypertensive effects of irbesartan in patients with mid-to-moderate hypertension. *Am J Hypertens* 1998;11:462-70.
107. Man in't Veld AJ. Clinical overview of irbesartan: expanding the therapeutic window in hypertension. *J Hypertens* 1997;15(suppl 7):S27-S33.
108. Kochar M, Guthrie R, Triscari J, et al. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens* 1999;12:797-805.
109. Reif M, White W, Fagan T, et al. Effects of candesartan cilexetil in patients with systemic hypertension. *Am J Cardiol* 1998;82:961-5.
110. Franke H. Antihypertensive effects of candesartan cilexetil, enalapril and placebo. *J Hum Hypertens* 1997;11(suppl 2):S61-S62.
111. Elliott HL. The efficacy and safety of telmisartan compared to atenolol and placebo in patients with hypertension [abstr]. *Am J Hypertens* 1998;11(4):E116.
112. Smith DHG, Neutel JM, Morganstern P. Once-daily telmisartan compared with enalapril in the treatment of hypertension. *Adv Ther* 1998;15(4):229-40.
113. Lacourciere Y, Lenis J, Orchard R, et al. A comparison of the efficacies and duration of action of the angiotensin II receptor blocker telmisartan and amlodipine. *Blood Press* 1998;3:295-302.
114. Gradman AH, Gray J, Maggiamo F, et al. Assessment of once-daily eprosartan, an angiotensin II antagonist, in patients with systemic hypertension. *Clin Ther* 1999;21(3):442-52.
115. Neutel JM. Clinical studies of CS-866, the newest angiotensin II receptor antagonist. *Am J Cardiol* 2001;87(suppl):37C-43C.
116. Hedner T, Himmelman A. The efficacy and tolerance of one or two daily doses of eprosartan in essential hypertension. *J Hypertens* 1999;17:129-36.
117. Stangier J, Su CPF, Hendriks MGC, et al. The effect of telmisartan on the steady-state pharmacokinetics of digoxin in healthy male volunteers. *J Clin Pharmacol* 2000;40:1373-9.
118. Oakes ML. Micardis® tablets (telmisartan) drug information unit response. Boehringer Ingelheim Pharmaceuticals, Inc. October 15, 2001.
119. Goldberg MR, Lo MW, Deutsch PJ, et al. Phenobarbital minimally alters plasma concentrations of losartan and its active metabolite. *Clin Pharmacol Ther* 1996; 59:268-74.
120. Blanche P, Raynaud E, Kerob D, et al. Lithium intoxication in an elderly patient after combined treatment with losartan (letter). *Eur J Clin Pharmacol* 1997; 52:501.
121. Kazierad DJ, Martin DE, Blum RA, et al. Effect of fluconazole on the pharmacokinetics of eprosartan and losartan in healthy male volunteers. *Clin Pharmacol Ther* 1997; 62:417-25.
122. Williamson KM, Patterson HP, McQueen RH, et al. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 1998; 63:316-23.
123. Conlin P, Moore T, Swartz S, et al. Effect of indomethacin on blood pressure lowering by captopril and losartan in hypertensive patients. *Hypertension* 2000; 36:461-5.
124. Leung M, Remick R. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* 2000; 20:392-3.
125. Schmidt EK, Antonin KH, Flesch G, et al. An interaction study with cimetidine and the new angiotensin II antagonist valsartan. *Eur J Clin Pharmacol* 1998;53:451-8.
126. Jonkman JH, van Lier JJ, van Heiningen PNM, et al. Pharmacokinetic drug interaction studies with candesartan cilexetil. *J Hum Hypertens* 1997; 11(suppl 2):S31-5.
127. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertension* 1999;12:S205-S213.
128. Hawkins DW, Bussey HI, Prisant LM. Hypertension, in: Dipiro JT, Talbert RL, Yee GC, et al (eds): *Pharmacotherapy: A Pathophysiologic Approach*. 3rd ed. Stamford, CT, Appleton and Lange, 1997, p. 197-198.
129. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL 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(19):2560-2572.
130. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. *Am J Health-Syst Pharm* 2001;58:671-83.
131. See S, Stirling AL. Candesartan cilexetil: an angiotensin II receptor blocker. *Am J Health-Syst Pharm* 2000;57:739-46.
132. VHA/DoD Clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. Washington DC: Office of Quality and Performance and the Veteran Affairs and Department of Defense Development Work Group, Veterans Health Administration, Department of Veterans Affairs; May 1999.
133. Zuschke CA, Keys I, Munger MA, et al. Candesartan cilexetil: comparison of once-daily versus twice daily administration for systemic hypertension. Candesartan Cilexetil Study Investigators. *Clin Ther* 1999;21:464-74.
134. Tanser PH, Campbell LM, Carranza J, Karrash J, Toutouzas P, Watts R. Candesartan cilexetil is not associated with cough in hypertensive patients with enalapril-induced cough. Multicentre Cough Study Group. *Am J Hypertens* 2000;13(2):214-8.
135. Lacourciere Y, Brunner H, Irwin R, et al. Effects of modulators of the renin-angiotensin-aldosterone system on cough. *J Hypertens* 1994;12(12):1387-1393.
136. Chan P, Tomlinson B, Huang TY, Ko JT, Lin TS, Lee YS. 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(3):253-7
137. 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(5):978-89
138. 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(2):99-103.
139. Benz J, Oshrain C, Henry D, Avery C, Chiang YT, Gatlin M. 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(2):101-7.

140. Gavras I, Gavras H. Effects of eprosartan versus enalapril in hypertensive patients on the renin-angiotensin-aldosterone system and safety parameters: results from a 26-week, double-blind, multicentre study. Eprosartan Multinational Study Group. *Curr Med Res Opin* 1999;15(1):15-24.
141. Elliot WJ. Double-blind comparison of eprosartan and enalapril on cough and blood pressure in unselected hypertensive patients. *J Hum Hypertens* 1999; 13(6):413-417
142. Rake EC, Breeze E, Fletcher AE. Quality of life and cough on antihypertensive treatment: a randomised trial of eprosartan, enalapril and placebo. *J Hum Hypertens* 2001; 15(12):863-7.
143. Breeze E, Rake EC, Donoghue MD, Fletcher AE. Comparison of quality of life and cough on eprosartan and enalapril in people with moderate hypertension. *J Hum Hypertens* 2001; 15(12):857-62.
144. Simon TA, Gelarden RT, Freitag SA, Kassler-Taub KB, Davies R. Safety of irbesartan in the treatment of mild to moderate systemic hypertension. *Am J Cardiol* 1998; 82(2):179-82.
145. Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. *Am J Ther* 1999;6(3): 161-6.
146. Levine B. Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension. *Curr Med Res Opin* 2001;17(1)8-17.
147. Biswas PN, Wilton LV, Shakir SW. The safety of valsartan: Results of a postmarketing surveillance study on 12 881 patients in England. *J Hum Hypertens* 2002; 16(11):795-803
148. Wurznner G, Gerster JC, Chiolero A, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001;19(10):1855-60.

Prepared by: DoD PEC: Angela Allerman, PharmD, BCPS; VA PBM: Elaine Furmaga, PharmD

Points of contact: : DoD PEC: Angela Allerman, PharmD, BCPS; VA PBM: Elaine Furmaga, PharmD

Version 3, last major revision April 2004

Check for updated versions at: www.vapbm.org or www.pec.ha.osd.mil

Appendix A: Summary of comparative trials of AIIRAs (AIIRAs vs AIIRAs)

1. **Telmisartan vs. Losartan:** Compared telmisartan 40 mg QD, telmisartan 80mg QD, losartan 50 mg QD, and placebo in a 6-week trial of 223 patients. During the 18-24 hour period after dosing (by ABPM), telmisartan 40 mg and telmisartan 80 mg had significantly greater reductions in DBP (-6.8 mm Hg and -7.1 mm Hg) than losartan 50 mg (-3.7 mm Hg), $P < 0.05$. For 24 hour mean blood pressure reduction, telmisartan 40 mg and telmisartan 80 mg had significantly greater reductions in DBP (-7.4 mm Hg and -8.4 mm Hg) than losartan 50 mg (-4.9 mm Hg), $P < 0.05$. However, trough supine DBP reduction was only significantly greater in the telmisartan 80mg group (-9.7 mm Hg) compared to losartan 50mg (-6.0 mm Hg), $P < 0.05$.
2. **Irbesartan vs. Losartan:** Compared irbesartan 150 mg QD and losartan 50 mg QD in an 8-week trial of 432 patients. At week 4, if sitting DBP at trough was ≥ 90 mm Hg, the daily dose of either drug was doubled. The mean change in trough sitting DBP at week 8 was significantly greater in the irbesartan group (-10.2 mm Hg) than in the losartan group (-7.9 mm Hg), $P < 0.02$.
3. **Irbesartan vs. Losartan:** Compared irbesartan 150 mg QD, irbesartan 300 mg QD, losartan 100 mg QD, and placebo in an 8-week trial of 567 patients. After 8 weeks, the antihypertensive effect of irbesartan 150 mg did not differ significantly from losartan 100 mg. Reduction from baseline trough sitting DBP with irbesartan 300 mg was greater than losartan 100 mg by 3 mm Hg ($P < 0.01$).
4. **Valsartan vs. Losartan:** Compared valsartan 80 mg QD, losartan 50 mg QD, and placebo in an 8-week trial of 1,369 patients. After 4 weeks, doses in all groups were doubled. No significant difference was seen between valsartan and losartan in trough sitting SBP/DBP. Valsartan showed a slight increase in response rate to losartan (61.6% vs. 54.5%) that reached statistical significance at 8 weeks ($P = 0.021$).
5. **Valsartan vs. Losartan:** Compared losartan 50mg QD to valsartan 80mg QD in 187 patients for 6 weeks by ABPM. Both losartan and valsartan significantly reduced mean SeDBP at 6 weeks (-7.2 ± 5.0 mm Hg and -6.0 ± 7.6 mm Hg, respectively; $P \leq 0.001$) compared to baseline. The response rate (SeDBP < 90 mm Hg; SeDBP ≥ 90 mm Hg and a decrease of ≥ 10 mm Hg) was 54% with losartan and 46% with valsartan.
6. **Candesartan vs. Losartan:** Compared candesartan 8 mg QD, candesartan 16 mg QD, losartan 50 mg QD, and placebo in an 8-week trial of 337 patients. After 8 weeks, no significant difference was seen between candesartan 8 mg versus losartan 50 mg. Candesartan 16 mg had a significantly greater drop in DBP (a difference of -3.7 mm Hg) than losartan 50 mg ($P = 0.013$). There was no significant difference in response rates between any of the active treatment groups.
7. **Candesartan vs. Losartan:** Compared candesartan 16 mg QD and losartan 50 mg QD in an 8-week trial of 332 patients. After 4 weeks, if DBP was > 90 mm Hg, patients were titrated to candesartan 32 mg or losartan 100 mg. At week 8, candesartan resulted in a significantly greater drop in DBP (-11.0 mm Hg) than losartan (-8.9 mm Hg), $P = 0.016$.
8. **Candesartan vs. Losartan:** Compared candesartan 32 mg QD and losartan 100 mg QD in an 8-week trial of 654 patients. At week 8, candesartan lowered trough SBP and DBP significantly more than losartan (-13.3/10.9 vs. -9.8/8.7 mm Hg, respectively; $P < 0.001$). Peak SBP and DBP were also significantly lower with candesartan compared with losartan ($P < 0.05$). A significantly higher percent of patients ($P < 0.05$) on candesartan responded and were controlled (62.4% and 56.0%, respectively) than patients treated with losartan (54.0% and 46.9%, respectively).
9. **Candesartan vs. Losartan:** Compared candesartan 8 to 16 mg QD, losartan 50 to 100mg QD, and losartan/HCTZ QD in a 12-week trial of 1161 patients. After 6 weeks, if DBP was ≥ 90 mm Hg, patients were titrated to the higher dose. At 12 weeks, candesartan similarly decreased SeSBP/SeDBP -15.8/13.1 mm Hg compared to -14.4/12.4 mm Hg with losartan. A greater BP reduction of > 2.5 mm Hg was seen with losartan/HCTZ compared to either monotherapy.
10. **Eprosartan vs. Losartan:** Compared eprosartan 600 mg QD and losartan 50 mg QD in a 4-week trial of 60 patients. The primary endpoint was effect on uric acid metabolism. Blood pressure efficacy was a secondary endpoint. There was no significant difference in blood pressure efficacy observed between eprosartan and losartan.
11. **Olmесartan vs. Losartan, Valsartan, Irbesartan:** Compared olmesartan 20 mg QD ($n = 147$), losartan 50 mg QD ($n = 150$), valsartan 80 mg QD ($n = 145$), irbesartan 150 mg QD ($n = 146$) in an 8-week trial evaluating cuff blood pressures and ABPM. There was a significantly greater decrease in the primary efficacy variable of cuff SeDBP with olmesartan (-11.5 mm Hg) compared with losartan (-8.2 mm Hg, $P = 0.0002$), valsartan (-7.9 mm Hg, $P < 0.0001$) or irbesartan (-9.9 mm Hg, $P = 0.0412$). The decreases in SeSBP were not statistically significantly different. The mean decrease in DBP by ABPM was statistically significantly greater with olmesartan (-8.5 mm Hg) compared to losartan (-6.2 mm Hg, $P < 0.05$) and valsartan (-5.6 mm Hg, $P < 0.05$), but not compared with irbesartan (-7.4 mm Hg, $P = 0.087$). The mean decrease in SBP by ABPM was statistically significantly greater with olmesartan (-12.5 mm Hg) compared to losartan (-9.0 mm Hg, $P < 0.05$) and valsartan (-8.1 mm Hg, $P < 0.05$), and similar to the reduction with irbesartan (-11.3 mm Hg).

Abbreviations: ABPM = ambulatory blood pressure monitoring; SeDBP=seated diastolic blood pressure; SeSBP=seated systolic blood pressure

Appendix B: Hypertension outcomes trials with AIIRAs

Trial	Regimens	Methods	Results	Comments																		
LIFE ²³ R, dm, DD, PG Supported by Merck and Co.	Losartan (LOS) vs atenolol (ATEN)	9193 pts (92% white) w/HTN (DBP 95-115 mm Hg or SBP 160-200 mm Hg or both) and LVH (by ECG) Excluded secondary HTN, MI or stroke in past 6 months, angina, HF or LVEF < 40% LOS: n=4605: 9% 50mg, 18% 50mg + other Rx, 2% 100mg, 48% 100mg + other Rx ATEN: n=4588 10% 50mg, 20% 50mg + other Rx, 2% 100mg, 42% 100mg + other Rx Rx titrated to BP < 140/90 mm Hg ACEI use prohibited Mean age: 67 years Mean F/U: 4.8 years PEP: Composite CV death, MI, stroke	<u>PEP developed in:</u> LOS 508 (11%) vs. ATEN 588 (13%); (AHR 0.87, CI 0.77-0.98, P=0.021); ARR: 1.79% No diff in CV death or MI when analyzed separately Fatal or non-fatal stroke was stat sig ↓ with LOS (5%) vs. ATEN (6.7%) (AHR 0.75, CI 0.63-0.89, P=0.001); ARR: 1.70% PEP HR 0.85 (P=0.009) if not adjusted for Framingham risk score and severity of LVH <i>NNT for PEP: 56</i> <i>NNT for stroke: 59</i> <table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>LOS</td> <td>4605</td> <td>508 (11%)</td> <td>0.021</td> <td>1.79%</td> <td>56</td> </tr> <tr> <td>ATEN</td> <td>4588</td> <td>588 (13%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	LOS	4605	508 (11%)	0.021	1.79%	56	ATEN	4588	588 (13%)				Additional outcome measures: total mortality, hospitalization due to angina or HF, resuscitated cardiac arrest, coronary or peripheral revascularization, new-onset DM; no stat sig difference in these endpoints except for 25% ↓ rate of new-onset DM (P=0.001) (LOS 6% vs ATEN 8%; 24% RRR (CI 12-36; NNT 52). <u>Mean BP</u> LOS 144.1/81.3 mm Hg (↓ 30.2/16.6) ATEN 145.4/80.9 mm Hg (↓ 29.1/16.8) Mean dose LOS 82mg Mean dose ATEN 79mg At least 44% of LOS and 38% of ATEN patients also received a diuretic 23% LOS and 27% ATEN were not taking study drugs More pts on ATEN stopped treatment due to ADE vs. LOS (P<0.0001)
Tx	N	PEP	P	ARR	NNT																	
LOS	4605	508 (11%)	0.021	1.79%	56																	
ATEN	4588	588 (13%)																				
LIFE ²⁴ (Diabetes) R, dm, DD, PG Supported by Merck and Co.		1195 pts (86% white) w/HTN (DBP 95-115 mm Hg or SBP 160-200 mm Hg or both), LVH (by ECG), DM Exclusion criteria as listed in LIFE LOS: n=586 8% 50mg, 14% 50mg + other Rx, 1% 100mg, 50% 100mg + other Rx ATEN: n=609 5% 50mg, 16% 50mg + other Rx, 1% 100mg, 46% 100mg + other Rx Mean age: 67 years Mean F/U: 4.7 years PEP: Composite CV death, MI, stroke	<u>PEP developed in:</u> LOS 103 (18%) vs. ATEN 139 (23%); (AHR 0.76, CI 0.58-0.98, P=0.031); ARR: 5.25% No diff in MI or stroke when analyzed separately CV mortality was stat sig ↓ with LOS vs. ATEN (AHR 0.63, CI 0.42-0.95, P=0.028) PEP HR 0.73 (P=0.017) if not adjusted for Framingham risk score and severity of LVH <i>NNT for PEP: 19.1</i> <table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>LOS</td> <td>586</td> <td>103 (18%)</td> <td>0.031</td> <td>5.25%</td> <td>19</td> </tr> <tr> <td>ATEN</td> <td>609</td> <td>139 (23%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	LOS	586	103 (18%)	0.031	5.25%	19	ATEN	609	139 (23%)				Total mortality stat sig ↓ with LOS vs. ATEN (P=0.002) <u>Mean BP</u> LOS 146/79 mm Hg (↓ 31/17) ATEN 148/79 mm Hg (↓ 28/17) <u>Mean Glucose</u> LOS 9.41 mmol/L (↑ 0.05) ATEN 9.52 mmol/L (↑ 0.05) Clinical albuminuria reported in 8% and 11% of patients on LOS and ATEN, respectively 27% LOS and 32% ATEN were not taking study drugs; open label AIIRA or ACEI could have been used after study drug discontinued
Tx	N	PEP	P	ARR	NNT																	
LOS	586	103 (18%)	0.031	5.25%	19																	
ATEN	609	139 (23%)																				

Abbreviations: AHR: adjusted hazard ratio; R = randomized, DM = double masked; DD = double dummy

Appendix C: Heart Failure Outcomes trials for AIIARs

Trial	Regimen	Methods	Results	Comments																																																			
<p>VALHeFT³⁰</p> <p>R, D B, placebo controlled MC Supported by Novartis</p>	<p>Valsartan (VAL) + standard care vs Placebo + standard care</p> <p>Standard care could include ACEI, diuretics, digoxin and beta blockers</p>	<p>N=5010; mean age 62 yrs LVEF <40% Mean duration 23 months</p> <p>Val dose: initial was 40 mg BID titrated to 160 mg BID Usual care: ACEI 93%, BB 36%, ACEI + BB 30% diuretics 86%, dig 67% PEP: all-cause mortality; combined mortality and morbidity (hosp for CHF, cardiac arrest, IV inotropes for 4 hours);</p>	<p>PEP Results</p> <table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td colspan="6">All-cause mortality</td> </tr> <tr> <td>Val</td> <td>2511</td> <td>495 (19.7%)</td> <td rowspan="2">0.80</td> <td rowspan="2">0.3</td> <td rowspan="2">NA</td> </tr> <tr> <td>P</td> <td>2488</td> <td>484 (19.4%)</td> </tr> <tr> <td colspan="6">Combined mortality and morbidity</td> </tr> <tr> <td>Val</td> <td>2511</td> <td>723 (28.8%)</td> <td rowspan="2">0.009</td> <td rowspan="2">3.1</td> <td rowspan="2">31</td> </tr> <tr> <td>P</td> <td>2488</td> <td>801 (32.1%)</td> </tr> <tr> <td colspan="6">Hospitalization for HF (2° Endpoint)</td> </tr> <tr> <td>Val</td> <td>2488</td> <td>348 (13.8%)</td> <td rowspan="2"><0.001</td> <td rowspan="2">4.4</td> <td rowspan="2">23</td> </tr> <tr> <td>P</td> <td>2511</td> <td>455 (18.2%)</td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	All-cause mortality						Val	2511	495 (19.7%)	0.80	0.3	NA	P	2488	484 (19.4%)	Combined mortality and morbidity						Val	2511	723 (28.8%)	0.009	3.1	31	P	2488	801 (32.1%)	Hospitalization for HF (2° Endpoint)						Val	2488	348 (13.8%)	<0.001	4.4	23	P	2511	455 (18.2%)	<ul style="list-style-type: none"> ➤ NSD in all-cause mortality ➤ Val was sig better than placebo in the combined endpoint ➤ Benefit of vals was driven solely by stroke reduction ➤ 63% of pts were NYHA II ➤ Subgroup analysis showed VAL + BB + ACEI had increased mortality ➤ In the 7% of pts not receiving an ACEI, an ARB was beneficial (44% reduction in the combined endpoint and a 33.1% reduction in mortality. ➤ Mean VAL dose: 254 mg ➤ Target VAL dose was achieved in 84% ➤ Standard dose of captopril was 80 mg
Tx	N	PEP	P	ARR	NNT																																																		
All-cause mortality																																																							
Val	2511	495 (19.7%)	0.80	0.3	NA																																																		
P	2488	484 (19.4%)																																																					
Combined mortality and morbidity																																																							
Val	2511	723 (28.8%)	0.009	3.1	31																																																		
P	2488	801 (32.1%)																																																					
Hospitalization for HF (2° Endpoint)																																																							
Val	2488	348 (13.8%)	<0.001	4.4	23																																																		
P	2511	455 (18.2%)																																																					
<p>CHARM Overall³⁹</p> <p>R, DB, Co, PG, MC Supported by AstraZeneca</p>	<p>Candesartan (C) vs placebo</p>	<p>7601 pts; mean age 66yrs NYHA class: 45% II, 52% III, 3% IV EF < 40%: 57%; EF ≥ 40%: 43% F/U: median 37.7 months C (mean 24mg at 6 months) 41% ACEI, 55% BB, 83% diuretics, 43% dig, 17% SPL PEP: all-cause mortality</p>	<table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>C</td> <td>3803</td> <td>886 (23%)</td> <td>0.055</td> <td>1.6%</td> <td>63</td> </tr> <tr> <td>P</td> <td>3796</td> <td>945 (25%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	C	3803	886 (23%)	0.055	1.6%	63	P	3796	945 (25%)				<ul style="list-style-type: none"> ➤ C DC'd in 23% ➤ 63% at target dose (32mg) at 6 months ➤ P=0.032 for covariate adjusted HR for PEP ➤ Survival benefit not seen in pts w/EF > 40% 																																	
Tx	N	PEP	P	ARR	NNT																																																		
C	3803	886 (23%)	0.055	1.6%	63																																																		
P	3796	945 (25%)																																																					
<p>CHARM Alternative⁴⁰</p> <p>R, DB, PC Supported by AstraZeneca</p>	<p>Candesartan (C) vs placebo</p>	<p>2028 pts; mean age 66yrs NYHA class: 48% II, 48% III, 4% IV Mean EF: 30% F/U: median 33.7 months C (mean 23mg at 6 months) 55% BB (64% at 6 months), 85% diuretics, 45% dig, 25% SPL PEP: CV death or HF hosp</p>	<table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>C</td> <td>1013</td> <td>334 (33%)</td> <td>0.0004</td> <td>7.0%</td> <td>14</td> </tr> <tr> <td>P</td> <td>1015</td> <td>406 (40%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	C	1013	334 (33%)	0.0004	7.0%	14	P	1015	406 (40%)				<ul style="list-style-type: none"> ➤ C DC'd in 24% ➤ 3 pts w/angioedema (previous angioedema w/ACEI) ➤ 59% at target dose (32mg) at 6 months 																																	
Tx	N	PEP	P	ARR	NNT																																																		
C	1013	334 (33%)	0.0004	7.0%	14																																																		
P	1015	406 (40%)																																																					
<p>CHARM Added⁴¹</p> <p>R, DB, PC Supported by AstraZeneca</p>	<p>Candesartan (C) vs placebo</p>	<p>2548 pts; mean age 64yrs NYHA class: 24% II, 73% III, 3% IV Mean EF: 28% F/U: median 41 months C (mean 24mg at 6 months) 100% ACEI, 55% BB (64% at 6 months), 90% diuretics, 58% dig, 17% SPL PEP: CV death or HF hosp</p>	<table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>C</td> <td>1276</td> <td>483 (38%)</td> <td>0.011</td> <td>4.4%</td> <td>23</td> </tr> <tr> <td>P</td> <td>1272</td> <td>538 (42%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	C	1276	483 (38%)	0.011	4.4%	23	P	1272	538 (42%)				<ul style="list-style-type: none"> ➤ C DC'd in 25% ➤ 61% at target dose (32mg) at 6 months ➤ ACEI near target doses ➤ Sig benefit PEP in subanalysis of pts w or w/o BB or ACEI ➤ 73% NYHA class III 																																	
Tx	N	PEP	P	ARR	NNT																																																		
C	1276	483 (38%)	0.011	4.4%	23																																																		
P	1272	538 (42%)																																																					

<p>CHARM Preserved⁴² R, DB, PC Supported by AstraZeneca</p>	<p>Candesartan (C) vs placebo</p>	<p>3023 pts; mean age 67 yrs NYHA class: 61% II, 37% III, 2% IV EF >40% F/U: mean 36.6 months C (mean 25mg at 6 months) 20% ACEI, 56% BB, 75% diuretics, 29% dig, 11% SPL, 31% CCB PEP: CV death or HF hosp</p>	<table border="1"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>C</td> <td>1514</td> <td>333 (22%)</td> <td>0.118</td> <td>2.2%</td> <td>NA</td> </tr> <tr> <td>P</td> <td>1509</td> <td>366 (24%)</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Tx	N	PEP	P	ARR	NNT	C	1514	333 (22%)	0.118	2.2%	NA	P	1509	366 (24%)				<ul style="list-style-type: none"> ➤ C DC'd in 22% ➤ 67% at target dose (32mg) at 6 months
Tx	N	PEP	P	ARR	NNT																	
C	1514	333 (22%)	0.118	2.2%	NA																	
P	1509	366 (24%)																				

ACEI=angiotensin-converting enzyme inhibitor; AIIRA=angiotensin II receptor antagonist; ARR=absolute risk reduction; BB=beta-blockers; C=candesartan; CCB=calcium channel blocker; Co=controlled; CV=cardiovascular; DB=double-blind; DC=discontinued; dig=digoxin; EF=ejection fraction; F/U=follow-up; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; NNT=number needed to treat; P=placebo; PC=placebo-controlled; PEP=primary endpoint; PG=parallel-group; R=randomized; Sig=significant; SPL=spironolactone; Tx=treatment

Appendix D: Acute Myocardial Infarction Outcomes Trials with AIIRAs

Trial	Regimens	Methods	Results	Comments																								
<p>VALIANT ⁴⁴</p> <p>R, DB, active controlled, parallel-group</p> <p>Supported by Novartis.</p>	<p>Valsartan (VAL) vs Captopril (CAP) vs Valsartan + Captopril</p> <p>VAL: dose titrated to 160 mg BID</p> <p>VAL + CAP: VAL dose titrated to 80 mg BID; CAP titrated to 50 mg TID</p> <p>CAP: dose titrated to 50 mg TID</p>	<p>14,808 patients hospitalized with acute MI who were at high risk (LV systolic dysfunction and/or signs of HF, including rales/dyspnea)</p> <p>LVSD was defined as an EF <35% via echo</p> <p>Randomization occurred within 12 hours to 10 days post-MI.</p> <p>Other ACEs or ARBs were D/C'd at least 12 hours before randomization; 70.4% of patients in the combination group were also receiving beta blockers, 91.3% received aspirin concomitantly</p> <p>Mean duration: 24.7 months</p> <p>Mean age: 64.8 years; 69.9% male; 93.5% Caucasian</p> <p>PEP: all-cause mortality</p>	<p>PEP: all-cause mortality VAL 979 (19.0%); CAP 958 (19.5%); VAL + CAP 941 (19.3%)</p> <p>PEP results:</p> <table border="1" data-bbox="856 428 1417 607"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P value (vs CAP)</th> <th>ARR</th> <th>NNT</th> </tr> </thead> <tbody> <tr> <td>CAP</td> <td>4090</td> <td>958 (19.5%)</td> <td>----</td> <td></td> <td></td> </tr> <tr> <td>VAL</td> <td>4090</td> <td>979 (19.9%)</td> <td>0.98</td> <td>0.4%</td> <td>NA</td> </tr> <tr> <td>VAL + CAP</td> <td>4885</td> <td>941 (19.3%)</td> <td>0.73</td> <td></td> <td></td> </tr> </tbody> </table> <p>Since VAL was not superior to CAP, a non-inferiority analysis was done which showed VAL to be noninferior to CAP</p> <p>In the VAL+CAP group, 6,882 patients were also receiving beta-blockers. There was no significant difference in all-cause mortality in these patients receiving triple therapy when compared to captopril alone (p=0.41).</p> <p>Mean blood pressure at 1 yr: VAL 127/75 mmHg CAP 127/76 mmHg VAL + CAP 125/75 mmHg</p>	Tx	N	PEP	P value (vs CAP)	ARR	NNT	CAP	4090	958 (19.5%)	----			VAL	4090	979 (19.9%)	0.98	0.4%	NA	VAL + CAP	4885	941 (19.3%)	0.73			<p>The trial was designed so that if valsartan was not superior to captopril, a non-inferiority analysis was pre-specified to determine whether valsartan could be considered to be as effective as captopril</p> <p>Entry criteria were similar to the SAVE trial (Survival and Ventricular Enlargement), a key trial showing ACE inhibitors are of benefit in HF post MI.</p> <p>Val-HeFT and CHARM-added were conducted in chronic heart failure patients, a different patient population (↓ LVEF, dyspnea, ankle edema, fatigue) than VALIANT.</p> <p>Mean doses: CAP: 117 mg VAL: 247 mg VAL+CAP: 116 mg valsartan and 107 mg captopril.</p> <p>Target doses were reached in approximately 55% of patients in the monotherapy groups, but 47% in the combination group.</p> <p>Discontinuations due to adverse event: CAP: 7.7% VAL: 5.8% (p<0.05 vs CAP) CAP+VAL 9% (p<0.05 vs CAP)</p> <p>Hypotension and renal dysfunction were the most common AEs in the VAL group, and cough, rash and taste disturbance were the most common AEs in the CAP group.</p>
Tx	N	PEP	P value (vs CAP)	ARR	NNT																							
CAP	4090	958 (19.5%)	----																									
VAL	4090	979 (19.9%)	0.98	0.4%	NA																							
VAL + CAP	4885	941 (19.3%)	0.73																									

<p>OPTIMAAL⁴³</p> <p>DB, R, PG (European study)</p> <p>Supported by Merck and Co.</p>	<p>Losartan (LOS) target dose 50 mg qd Vs Captopril (CAP) target dose 50 mg TID</p>	<p>5477 patients ≥50 years</p> <p>Confirmed acute MI and signs/symptoms of HF during the acute phase or a new Q-wave anterior MI or reinfarction</p> <p>Primary endpoint: all-cause mortality</p> <p>Mean follow-up: 2.7 yrs</p> <p>Mean age: 67 years; 70% male; 98% Caucasian</p>	<p>PEP developed in: LOS 499 (18%) vs. CAP 447 (16%); (RR 1.13 (95% CI 0.99-1.28; p=0.07)</p> <table border="1" data-bbox="856 337 1417 407"> <thead> <tr> <th>Tx</th> <th>N</th> <th>PEP</th> <th>P</th> <th>RRI</th> <th>NNH</th> </tr> </thead> <tbody> <tr> <td>LOS</td> <td>2744</td> <td>499 (18%)</td> <td rowspan="2">0.07</td> <td rowspan="2">13% (-1 to 28)</td> <td rowspan="2">Not significant</td> </tr> <tr> <td>CAP</td> <td>2733</td> <td>447 (16%)</td> </tr> </tbody> </table> <p>RRI = relative risk increase; NNH = Number needed to harm</p> <p>There was no significant difference in the secondary endpoints of sudden cardiac death/ resuscitated cardiac arrest; (LOS 239 (8.7%) vs CAP 203 (7.4%); RR 1.19 (0.99-1.43; p=0.07) or the tertiary endpoint of fatal or non-fatal re-infarction (LOS 384 (14%) vs CAP 379 (13.9%) RR 1.03 (0.89-1.18; p=0.7).</p> <p>For the non-primary endpoint of cardiovascular death, captopril had significantly fewer cardiovascular deaths than losartan (CAP 363 (13.3%) vs LOS 420 (15.3%), RR 1.17 (1.01-1.34; p=0.03).</p>	Tx	N	PEP	P	RRI	NNH	LOS	2744	499 (18%)	0.07	13% (-1 to 28)	Not significant	CAP	2733	447 (16%)	<p>LOS did not satisfy criteria for non-inferiority, since the RR exceeded the pre-set boundary of 1.10.</p> <p>Fewer LOS patients D/C'd therapy due to AEs compared to CAP (LOS 202 (7%) vs CAP 387 (14%); p<0.0001</p> <p>At study end, 83% of LOS reached target dose; 81% of CAP reached target dose Mean LOS dose: 45 mg qd Mean CAP dose: 44 mg TID</p> <p>Author conclusion: losartan did not show superiority or non-inferiority relative to captopril.</p>
Tx	N	PEP	P	RRI	NNH														
LOS	2744	499 (18%)	0.07	13% (-1 to 28)	Not significant														
CAP	2733	447 (16%)																	

Abbreviations: DB=double-blind; R = randomized; PG=parallel group, PEP: primary endpoint

Appendix E: Diabetic Nephropathy Trials with AIIRAs

Trial	Regimens	Methods	Results	Comments
IRMA 2 ⁴⁵ R, DB, PC Supported by BMS and Sanofi-Synthelabo		590 pts w/HTN, type 2 DM, persistent microalbuminuria, sCr nmt 1.5mg/dl men/1.1mg/dl women (194 IRB 300mg, 195 IRB 150mg, 201 PL) Mean age: 58 years HbA _{1c} : IRB 300mg 7.1%, IRB 150mg 7.3%, PL 7.1% Pts on ACEI excluded F/U: 2yrs PEP: time to onset DN (persistent albuminuria in overnight specimens, with UAE rate >200µg/min and at least 30%> BL)	PEP developed in: IRB 300mg (5.2%; HR 0.3, CI 0.14-0.61; P<0.001 vs. PL); ARR: 9.7% IRB 150mg (9.7%; HR 0.61, CI 0.34-1.08; P=0.08 vs. PL); ARR:5.2% PL (14.9%) <i>NNT for PEP: 10 IRB 300mg; 19 IRB 150mg</i>	Secondary Endpoints <u>UAE rate</u> IRB 300mg ↓ 38% IRB 150mg ↓24% PL ↓2% (P<0.001 both IRB vs. PL; P<0.001 IRB 300mg vs. IRB 150mg) ↓ CrCl Initial and sustained ↓ CrCl not stat sig between groups <u>Average trough BP</u> IRB 300mg 141/83 mm Hg IRB 150mg 143/83 mm Hg PL 144/83 mm Hg (P=0.004 vs. IRB)
IDNT ⁴⁶ R, DB, PC Supported by BMS and Sanofi-Synthelabo		1715 pts w/ type 2 DM and DN (579 IRB 300mg, 567 AML 10mg, 569 PL controlled HTN) Mean age: 59 years HbA _{1c} : IRB 300mg 8.1%, AML 10mg 8.2%, PL 8.2% Pts on ACEI excluded F/U: mean 2.6yrs PEP: composite doubling BL sCr, ESRD, or all-cause death	IRB ↓ PEP by 20% (RR 0.80, CI 0.66-0.97) vs. PL (P=0.02); ARR: 6.4% IRB ↓ PEP 23% (RR 0.77, CI 0.63-0.93) vs. AML (P=0.006); ARR:8.5% <i>NNT for PEP: 16 IRB 300mg</i>	Secondary Endpoints <u>Doubling sCr</u> IRB ↓ 33% vs. PL (P=0.003) IRB ↓ 36% vs. AML (P<0.001) <u>ESRD</u> IRB ↓ 23% vs. PL and AML (P=0.07) <u>Death from any cause</u> IRB ↓ 8% vs. PL; AML ↓ 12% vs. PL Not stat sig between groups BP: not stat sig IRB vs. AML
RENAAL ⁴⁷ R, DB, PC Supported by Merck and Co.		1513 pts w/ type 2 DM and DN [751 LOS 50-100mg (71% 100mg/d), 762 PL) Mean age: 60 years HbA _{1c} : LOS 8.5%, PL 8.4% Pts on ACEI excluded F/U: mean 3.4yrs PEP: composite doubling BL sCr, ESRD, or death	LOS ↓ PEP 16% (RR 0.84, CI 0.72-0.98) vs. PL (P=0.02); ARR:3.6% <i>NNT for PEP: 28 LOS 50-100mg</i>	Secondary Endpoints <u>CV morbidity and mortality</u> LOS ↓ 10% vs. PL (P=0.26) <u>UAC ratio</u> LOS ↓ 35% (P<0.001) <u>Rate of decline in renal function</u> LOS ↓ 18% vs. PL (P=0.01) <u>Doubling sCr</u> LOS ↓ 25% vs. PL (P=0.006) <u>ESRD</u> : LOS ↓ 28% vs. PL (P=0.02) No effect on death rate vs. PL BP: not stat sig LOS vs. PL

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

