VA/DoD Drug Class Review
Angiotensin II Receptor Antagonists (AIIRAs)
Update February 2010

Department of Veterans Affairs Pharmacy Benefits Management Services (VA PBM),
VA Medical Advisory Panel (VA MAP), and VISN Pharmacist Executives (VA VPEs)
Department of Defense Pharmacoeconomic Center (DoD PEC)

Introduction

Seven angiotensin II receptor antagonists (AIIRAs) are currently available in the United States: candesartan (Atacand®, AstraZeneca), eprosartan (Teveten®, Abbott), irbesartan (Avapro®, Bristol-Myers Squibb/Sanofi Aventis), losartan (Cozaar®, Merck), olmesartan (Benicar™, Daiichi Sankyo Pharma), telmisartan (Micardis®, Boehringer Ingelheim), valsartan (Diovan®, Novartis). (See table 1).[1-7] None of the AIIRAs is available generically, with the first patent expiration not expected until 2010.

All seven AIIRAs are available in combination with hydrochlorothiazide (HCTZ): losartan/HCTZ (Hyzaar®, Merck), valsartan/HCTZ (Diovan HCT®, Novartis), candesartan/HCTZ (Atacand HCT®, AstraZeneca), irbesartan/HCTZ (Avalide®, Bristol-Myers Squibb), telmisartan/HCTZ (Micardis HCT®, Boehringer Ingelheim), and olmesartan/HCTZ (Benicar HCT™, Daiichi Sankyo Pharma), and eprosartan/HCTZ (Teveten HCT®, Abbott). (See table 2)[8] Two AIIRAs are available in combination with amlodipine: amlodipine/olmesartan (Azor™, Daiichi Sankyo Pharma) and amlodipine/valsartan (Exforge™, Novartis); one in combination with amlodipine and HCTZ:amlodipine/valsartan/HCTZ (Exforge HCT™, Novartis); and one in combination with aliskiren: aliskiren/valsartan (Valturna®, Novartis). (See table 3).[8]

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

Generic	Brand (Manufacturer)	Strengths & formulations	Initial FDA approval
Candesartan	Atacand (AstraZeneca)	4 mg, 8 mg, 16 mg, 32 mg tablets	6/4/98
Eprosartan	Teveten (Abbott)	400 mg, 600 mg tablets	10/22/99
Irbesartan	Avapro (Bristol-Myers Squibb/Sanofi Aventis)	75 mg, 150 mg, 300 mg tablets	9/30/97
Losartan	Cozaar (Merck)	25mg, 50 mg, 100 mg tablets	4/14/95
Olmesartan	Benicar (Daiichi Sankyo)	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 blister-sealed packs of 30 tablets as 3 X 10 cards.

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

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval
Candesartan / HCTZ	Atacand HCT (AstraZeneca)	16/12.5 mg, 32/12.5 mg, 32/25 mg tablets	9/5/00
Eprosartan / HCTZ	Teveten HCT (Abbott)	600/12.5 mg, 600/25 mg tablets	11/01/01
Irbesartan / HCTZ	Avalide (Bristol-Myers Squibb	150/12.5 mg, 300/12.5 mg, 300/25 mg tablets	5/9/00
Losartan / HCTZ	Hyzaar (Merck)	50/12.5 mg, 100/12.5 mg, 100/25 mg tablets	8/24/98
Olmesartan / HCTZ	Benicar HCT(Sankyo / Forest)	20/12. 5mg 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, 80/25 mg tablets	11/17/00
Valsartan / HCTZ	Diovan HCT(Novartis)	80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg tablets	1/17/02

Table 3: Other fixed-dose combinations with an AIIRA available in the U.S.

Generic	Brand (Manufacturer)	Strengths & formulations	FDA approval
Amlodipine/Olmesartan	Azor (Daiichi Sankyo)	5/20 mg, 5/40 mg, 10/20 mg, 10/40 mg tablets	9/26/07
Amlodipine/Valsartan	Exforge (Novartis)	5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg tablets	6/20/07
Amlodipine/Valsartan/HCTZ	Exforge HCT (Novartis)	5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg tablets	4/30/09
Aliskiren/Valsartan	Valturna (Novartis)	150/160 mg, 300/320 mg tablets	9/17/09

Background

The AIIRAs are effective in lowering blood pressure and all seven AIIRAs are approved for the treatment of hypertension (HTN).[1-7] In addition, some AIIRAs have demonstrated positive outcomes and are approved for use in the treatment of patients with heart failure (HF),[1,7] diabetic nephropathy,[3,4] in patients with hypertension and left ventricular hypertrophy (LVH),[4] and in the post myocardial infarction (MI)[7] setting. Approximately 47% of veterans have a diagnosis of hypertension.

There are a number of classes of medications available for the treatment of hypertension that have resulted in a reduction in the cardiovascular complications of hypertension. The seventh report of the Joint National Committee[9] on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the VA/DoD Clinical Practice Guideline on the Management of Hypertension in Primary Care (2004)[10] recommend a thiazide-type diuretic as initial therapy in most patients with hypertension, or in combination with other drug classes including the angiotensin-converting enzyme inhibitors (ACEI), AIIRAs, beta-blockers, or calcium channel blockers (CCB). Since the publication of JNC 7, other hypertension treatment guidelines have made alternate recommendations: European Society of Hypertension/European Society of Cardiology (2007)[11] recommends that a thiazide-type diuretic, ACEI, AIIRA, beta-blocker, or CCB are all appropriate first-line therapy for hypertension; National Institute for Health and Clinical Excellence (2006)[12] recommends a thiazide-type diuretic or CCB first-line if > 55 years of age or black; or an ACEI first-line if < 55 years of age. The recent update of the Canadian Hypertension Education Program guideline (2009) recommends a thiazide as first-line therapy in patients with hypertension without compelling indications for another class of antihypertensive medication; an ACEI (except in black patients), a long-acting CCB, AIIRA, or beta-blocker (in patients < 60 years of age) are also considered appropriate first-line therapy for hypertension.[13]

In addition, ACEIs are considered standard therapy for patients with heart failure with reduced ejection fraction (unless contraindicated or not tolerated) according to the 2009 Update of the American College of Cardiology/American Heart Association 2005 Guideline for the Diagnosis and Management of Chronic Heart Failure in the Adult[14] and the VHA PBM-MAP Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice (2007).[15] An ACEI is also recommended in patients with concomitant diabetes mellitus (DM) and/or hypertension, and kidney disease (or AIIRA in patients with concomitant hypertension and type 2 diabetic nephropathy), as per the American Diabetes Association Standards of Medical Care in Diabetes (2009),[16] National Kidney Foundation KDOQI Clinical Practice Guidelines in patients with DM and Chronic Kidney Disease (2007)[17] and in Hypertension with Chronic Kidney Disease (2004),[18] and the VA/DoD Clinical Practice Guideline for Management of Chronic Kidney Disease in Primary Care (2008).[19]

Treatment with an ACEI has been associated with a persistent cough, sufficiently distressing to cause discontinuation of the drug in some patients.[20] An AIIRA is generally recommended in patients who are unable to tolerate an ACEI, where an ACEI is indicated.[10,14,19] 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 with HF on standard therapy and who are intolerant to an ACEI;[21] a similar benefit as an ACEI in patients with left ventricular dysfunction or signs of HF after an acute MI in reducing

all-cause mortality;[22] and a reduction in the composite doubling of serum creatinine (sCr), development of end-stage kidney disease or all-cause death in patients with diabetic nephropathy.[23,24]

According to medication utilization data from 2006, over 60% of veteran patients with hypertension were prescribed an ACEI for treatment of this condition, with 11.2% of patients with hypertension prescribed an AIIRA. In addition, ACEIs were prescribed in 64% of patients with a diagnosis of HF, increasing to 78% when treatment with an ACEI or AIIRA was given. Utilization of an ACEI or AIIRA is included as a component of VA Performance Measures for patients with HF or reduced left ventricular (LV) function post MI as follows: 95% of patients with HF at hospital discharge; 95% of patients post MI with a LV ejection fraction < 40% at hospital discharge. According to recent utilization data, nearly 285,000 veterans are prescribed an AIIRA. When looking at the total number of prescriptions for either an AIIRA or an ACEI in the VA, an AIIRA accounts for approximately 17% of the prescriptions within these two drug classes.

FDA-Approved Indications

All of the AIIRAs are approved for the treatment of hypertension, either alone or in conjunction with other agents.[1-8] Losartan is the only AIIRA approved to reduce the risk of stroke in patients with hypertension and LVH; although, there is evidence that this benefit does not apply to black patients.[4,25]

The AIIRAs have also been studied in patients with type 2 DM and nephropathy. Two of the AIIRAs, irbesartan and losartan, have additional indications for diabetic nephropathy in type 2 diabetic patients.[3,4,23,24]

Valsartan and candesartan are approved for treating patients with heart failure.[1,7,21,26-28] Valsartan is also approved for reducing cardiovascular (CV) mortality in patients with LV failure or LV dysfunction post MI.[7,23]

Losartan and valsartan include recommendations for dosing in pediatric patients > 6 years of age for the treatment of hypertension.[4,7]

Table 4: FDA-approved indications[1-7]

	FDA-Approved Indications				
Drug	**Hypertension**	**Hypertension with LVH[a]**	**Diabetic Nephropathy[b]**	**Heart Failure[c]**	**Post MI[d]**
Candesartan	X			X	
Eprosartan	X				
Irbesartan	X		X		
Losartan	X	X	X		
Olmesartan	X				
Telmisartan	X				
Valsartan	X			X	X

[a]Left ventricular hypertrophy indication for losartan: 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.
[b]Diabetic Nephropathy labeling for losartan: Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension. Losartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplant).
[b]Diabetic Nephropathy labeling for irbesartan: 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).
[c]Heart Failure labeling for valsartan: Treatment of heart failure (NYHA class II-IV); significantly reduced hospitalizations for heart failure. There is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI.
[c]Heart Failure labeling for candesartan: Treatment of heart failure (NYHA class II-IV) in patients with LV systolic dysfunction (ejection fraction ≤ 40%) to reduce cardiovascular death and to reduce heart failure hospitalizations; there is also an added effect on these outcomes when used with an ACEI.
[d]Post MI labeling for valsartan: In clinically stable patients with left ventricular failure or left ventricular dysfunction following MI, indicated to reduce cardiovascular mortality.

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, amlodipine, and/or aliskiren 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,[1-7,29] and have also been compared with ACEIs with similar efficacy.[20,30-38] 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 ACEI.

Outcome trials in other conditions: Use of AIIRAs in patients with other conditions, including LVH, heart failure, diabetic nephropathy, and in patients following myocardial infarction or stroke 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 kidney disease, 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 where many trials 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 are mentioned briefly, but more interest is placed on trials with hard outcomes.

The original review was limited to information published up to and including December 2003. This update includes literature published from January 2004 through June 2009. A literature search was performed on PubMed/Medline using the search terms candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan through June 30, 2009. Additional outcome trials published after this date and prior to February 2010 have also been included. For the head to head hypertension trials, the search was limited to randomized controlled trials performed in adult humans, with a primary efficacy endpoint of blood pressure reduction, and published in the English language. Results from "hard" outcome trials for the AIIRAs were limited to clinical trials performed in adult humans and published in the English language. The literature was also searched for recent meta-analyses published in the English language. Reference lists of meta-analyses were searched for relevant clinical trials.

Pharmacology and Pharmacokinetics[1-7,39-44]

- 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 AT_1 and AT_2. Effects mediated by the activation of AT_1 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. AT_2 receptors function to oppose the effects of AT_1 receptors. AT_2 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 AT_1 receptor and do not affect bradykinin.
- AIIRA receptor blocking capacity to AT_1 can be described as insurmountable or surmountable. Insurmountable blockade is suppression of agonist response despite escalations in agonist concentration. Surmountable is when there is failure to suppress agonist response with escalation in agonist dose. 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 (trough to peak ratio calculated by dividing the blood pressure reduction at trough by the blood pressure reduction at the peak of the drug's effect) 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.

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 Cr_{Cl}<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/day	80 mg/day	150 mg/day	16 mg/day	40 mg/day	600 mg/day	20 mg/day
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

* Losartan 150 mg daily studied in patients with HF

Dosing and Administration

All the AIIRAs 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 twice daily dosing. Candesartan has been studied for HF in one large clinical trial that used once daily dosing. Losartan once daily was also studied in patients with

heart failure. For diabetic nephropathy, irbesartan and losartan are dosed once daily in doses similar to that used in hypertension.

Table 6: Dosing according to package labeling for HTN, HF, or diabetic nephropathy[1-7]

Generic	Renal/Hepatic Adjustments	Initial Dose (Range)
Losartan	hepatic failure: ↓ initial dose 50%	**HTN:** 50 mg once daily (25 mg to 100 mg once daily or divided twice daily) **HTN with LVH:** 50 mg once daily (50 mg to 100 mg once daily) **Diabetic Nephropathy**: 50 mg once daily (50 mg to 100 mg once daily) **HF:** 12.5 mg to 50 mg once daily; target 150 mg once daily
Valsartan	No	**HTN**: 80 mg to 160 mg once daily (80 mg to 320 mg once daily) **HF:** 40 mg twice daily; target 160 mg twice daily **Post MI**: 20 mg twice daily (20 mg to 160 mg twice daily); target 160 mg twice daily
Irbesartan	No	**HTN**: 150 mg once daily (75 mg to 300 mg once daily) **Diabetic Nephropathy**: 75 mg once daily; target 300 mg once daily
Candesartan	No	**HTN**: 16 mg once daily (8 mg to 32 mg once daily or divided twice daily) **HF:** 4 mg once daily; target 32 mg once daily
Telmisartan	No	**HTN**: 40 mg once daily (20 mg to 80 mg once daily)
Eprosartan	No	**HTN:** 600 mg once daily (400-800 once daily or divided twice daily)
Olmesartan	No	**HTN:** 20mg once daily (5 mg to 40mg once daily)

HTN=Hypertension; HF=Heart Failure; LVH=left ventricular hypertrophy; MI =myocardial infarction

Efficacy

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

Hypertension:

Comparative trials among AIIRAs:[20,29,45-65] (Head-to-head trials of AIIRAs are included in this review; refer to Appendix A) 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 includes labeling that states candesartan 32mg lowered systolic blood pressure (SBP) and diastolic blood pressure (DBP) an average of 2 to 3 mm Hg more than losartan 100mg, comparing once daily 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. In another trial the difference in blood pressure reduction was not significant at the higher dose of olmesartan compared with moderate to high doses of valsartan, or compared to twice daily dosing of losartan at the highest recommended dose. It is unknown if the difference in blood pressure reduction would be apparent with other AIIRAs. A meta-analysis of ten trials comparing telmisartan and losartan in 1,792 patients found telmisartan to be more effective than losartan in reducing clinic-based SBP and DBP (weighted mean difference SBP 2.77 95% CI 1.90 to 3.63; DBP 1.52 95% CI 0.85 to 2.19).[65] Another meta-analysis of candesartan, irbesartan, losartan, and valsartan was performed on 43 trials including 11,281 patients that showed 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.[29]

Hypertension Efficacy Discussion: All AIIRAs are approved for hypertension and appear to be similar in efficacy to the ACEIs.[20] A few trials have shown, at comparable doses, that losartan may be slightly less effective than other AIIRAs.[49,65] However, in a meta-analysis of 43 trials including candesartan, irbesartan,

losartan, and valsartan, blood pressure reduction was similar with all AIIRAs evaluated.[29] 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[63] while another trial reported comparable efficacy with olmesartan and valsartan at the moderate to higher doses.[64] Comparisons trials (all conducted outside the U.S.) showed that telmisartan may be more effective than losartan in reducing SBP and DBP at the recommended doses.[55-58,65] It is unknown if the difference in blood pressure reduction would be apparent with other AIIRAs.

Hypertension Efficacy Conclusion: All AIIRAs are effective in reducing blood pressure and are indicated for treatment of patients with hypertension. The AIIRAs appear to be equally effective for treating hypertension when titrated to blood pressure goals or maximally recommended doses.

Outcomes Trials

AIIRAs have been evaluated in several trials using hard clinical endpoints as well as surrogate endpoints (see table below). There are no known published outcomes trials for olmesartan; although, clinical trials have been completed or are ongoing (clinicaltrials.gov).

Table 7: Summary of Outcome Trials with the AIIRAs

ARB	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
HTN/CV risk	**E-COST** **CASE-J** **HIJ-CREATE** *KCPS (CVD)* *HOPE-3 (w/o HTN)*			**LIFE (LVH)** **LIFE (DM)**	*COLM* *OSCAR*	*KCPS (CVD)*	**VALUE** **Jikei Heart Study** **KYOTO Heart Study**
CVD/DM			*ACTIVE I (Afib)*			**ONTARGET** **TRANSCEND**	
HTN/ elderly	**SCOPE**						*VALISH (ISH)*
Stroke	*ACCOST* *SCAST (Acute)*	**MOSES**		*AMTEC (CAS/CEA)*		**PRoFESS**	*VENTURE (Acute)*
HF	**CHARM (+ ACEI)**		**I-PRESERVE**	**ELITE-II** **HEAAL**	*SUPPORT*	*HF/HD*	**Val-HeFT**
Post-MI				**OPTIMAAL**			**VALIANT**
HTN/DM/ DN/CKD			**IDNT** **IRMA 2**	**RENAAL** *VA NEPHRON-D*	*ORIENT* *ROADMAP*		*VALID* *KVT (CKD)* *V-CARD (CKD)*

italicized = not published/completed

CAS=carotid artery stenosis; CEA=carotid endarterectomy; CKD=chronic kidney disease; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; DN=diabetic nephropathy; HD=hemodialysis; HF=heart failure; HTN=hypertension; LVH=left ventricular hypertrophy; MI=myocardial infarction

Hypertension and/or CV Disease or High CV Risk Outcomes Trials[25,66-89]

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 13% (RRR 13%; CI 2-22).[25] 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).[66] 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 8 below and in Appendix B.

Subgroup analysis of the LIFE trial found a potential interaction between treatment and patient ethnicity (P=0.057). Upon further analysis of the black vs. non-black treatment groups, there was found to be a significant interaction (P=0.005). In a subgroup analysis of the 533 black patients enrolled in the LIFE trial, the primary endpoint of CV death, nonfatal stroke, and nonfatal MI was increased with losartan compared to patients who received atenolol (adjusted HR 1.666 95% CI 1.043-2.661; P=0.033) and was reduced in nonblack patients with losartan compared to atenolol (RR 0.829 95% CI 0.733-0.938; P=0.003). Fatal and nonfatal stroke was higher in black patients in the losartan group compared to atenolol (8.9% vs. 4.6%; adjusted HR 2.179 95% CI 1.079-4.401; P=0.03).[67]

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.[68]

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.[69]

Table 8: 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 CV 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; 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 (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).[70] In a post hoc analysis of data from the SCOPE trial of patients who did not receive add-on antihypertensive therapy (candesartan, n=1253; placebo, n=845), there was a significant reduction in major CV events (RR 0.68 95% CI 0.51-0.92; P=0.013), CV death (RR 0.71 95% CI 0.50-1.00; P=0.049), and total mortality (RR 0.73 95% CI 0.57-0.95; P=0.018). The reduction in fatal or nonfatal stroke was not statistically significant which was felt to be due to the lower rate in this patient cohort .[71]

Candesartan was compared to conventional therapy in a single-blind study of 2,048 Japanese patients with HTN (Efficacy of Candesartan on Outcome in Saitama Trial; E-COST) and was found to reduce the primary outcomes of hospitalizations for stroke (RR 0.61 95% CI 0.41-0.84; P<0.05), and hospitalizations for MI (RR 0.44 95% CI 0.21-0.84; P<0.05), but no difference in the primary endpoint of HF hospitalizations (RR 0.85 95% CI 0.57-1.26). At baseline, SBP and DBP were significantly lower in the candesartan treatment group; with the SBP significantly lower than conventional therapy by the end of the study.[72]

Table 9: Summary Results from the E-COST Trial

Outcomes	Candesartan (n=1053)	Conventional (n=995)	RR (95% CI)	P value	NNT
Hospitalizations for stroke	47 (5.8%)	77 (9.4%)	0.61 (CI 0.41-0.84)	< 0.05	31
Hospitalizations for MI	10 (1.2%)	23 (2.8%)	0.44 (CI 0.21-0.84)	< 0.05	63
HF hospitalizations	35 (4.3%)	41 (5.0%)	0.85 (CI 0.57-1.26)		

The Candesartan Antihypertensive Survival Evaluation in Japan Trial (CASE-J) was a prospective, randomized, open, blinded endpoint trial that compared treatment with candesartan or amlodipine in 4,728 Japanese patients

with HTN and at high CV risk (severe HTN, type 2 DM, previous stroke or TIA, LVH, angina, previous MI, proteinuria or sCr ≥ 1.3 mg/dl, or arteriosclerotic peripheral artery obstruction). The primary endpoint of first fatal or nonfatal CV events occurred in 134 patients in each of the treatment groups (candesartan vs. amlodipine HR 1.01 95% CI 0.79-1.28; P=0.969). There was a reduction in the pre-specified endpoint of new-onset DM with candesartan compared to amlodipine (HR 0.64 95% CI 0.43-0.97; P=0.033).[73]

Table 10: Summary Results from the CASE-J Trial

Outcomes	Candesartan (n=2354)	Amlodipine (n=2349)	HR (95% CI)	P value
CV morbidity and mortality	134 (5.7%)	134 (5.7%)	1.01 (CI 0.79-1.28)	0.969

The Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE) was a prospective, randomized, open, blinded endpoint trial that compared add-on treatment with candesartan or conventional therapy (that could include an ACEI) in 2,049 Japanese patients hospitalized with coronary artery disease (diagnosed by angiography) and HTN. The primary endpoint of time to first major CV event (composite CV death, nonfatal MI, unstable angina, HF, stroke, and other hospitalized CV events) occurred in 264 (25.8%) of patients in the candesartan treatment group compared to 288 (28.1%) of patients treated with conventional therapy (HR 0.89 95% CI 0.76-1.06; P=0.194). There was a reduction in the secondary endpoint of new-onset DM with candesartan compared to conventional therapy (HR 0.37 95% CI 0.16-0.89; P=0.027).[74]

Table 11: Summary Results from the HIJ-CREATE Trial

Outcomes	Candesartan (n=1024)	Conventional (n=1025)	HR (95% CI)	P value
Major adverse CV event	264 (25.8%)	288 (28.1%)	0.89 (CI 0.76-1.06)	0.194

Eprosartan: The Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) study, was a prospective, randomized, open-label, blinded endpoint trial that compared treatment with eprosartan or nitrendipine in 1,352 patients with a history of HTN and cerebrovascular event. The combined primary endpoint of all-cause mortality, cerebrovascular events, and CV events was significantly reduced with eprosartan (13.25%) compared to nitrendipine (16.71%), with an ID ratio (incidence density per 100 person years) of 0.79 (95% CI 0.66-0.96; P=0.014). Fatal and nonfatal cerebrovascular events, an individual component of the primary endpoint, was also reduced with eprosartan (ID ratio 0.75 95% CI 0.58-0.97; P=0.026). The reduction in blood pressure was similar between the treatment groups.[75]

Table 12: Summary Results from the MOSES Trial

Outcomes	Eprosartan (n=681)	Nitrendipine (n=671)	Incidence Density Ratio	P value	NNT
Composite end point all-cause mortality, cerebrovascular events, CV events	206 (13.25%)	255 (16.71%)	0.79 (CI 0.66-0.96)	0.014	13
Fatal and nonfatal cerebrovascular events	102 (6.56)%	134 (8.78%)	0.75 (CI 0.58-0.97)	0.026	

Telmisartan: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated treatment with telmisartan (n=8542), ramipril (n=8576), or the combination (n=8502) in patients with vascular disease (coronary, peripheral, or cerebrovascular) or high-risk DM (with end-organ

damage). The primary composite endpoint of death from CV causes, MI, stroke, or hospitalization for HF was similar between treatment groups [telmisartan 1423 (16.7%), ramipril 1412 (16.5%), combination 1386 (16.3%); telmisartan vs. ramipril RR 1.01 95% CI 0.94-1.09, P=0.83; combination vs. ramipril RR 0.99 95% CI 0.92-1.07, P=0.38), with telmisartan noninferior to ramipril (P=0.004). Combination therapy increased the risk of renal impairment compared to the ramipril treatment group (RR 1.33 95% CI 1.22-1.44; P<0.001).[76]

Table 13: Summary Results from the ONTARGET Trial

Outcomes	Telmisartan (n=8542)	Ramipril (n=8576)	Combination (n=8502)	RR (95% CI)	P value
Composite CV death, MI, stroke, HF hospitalization	1423 (16.7%)	1412 (16.5%)	1386 (16.3%)	Telmisartan vs. Ramipril 1.01 (CI 0.94-1.09)	0.83
				Combination vs. Ramipril 0.99 (CI 0.92-1.07)	0.38

As part of the ONTARGET study, the pre-specified kidney endpoint (composite of dialysis, doubling sCr, and death) was evaluated in the 25,620 patients with vascular disease or high-risk DM randomized to treatment with telmisartan, ramipril, or the combination. The composite endpoint occurred in 1147 (13.4%) of patients treated with telmisartan, in 1150 (13.5%) of patients on ramipril (HR 1.00 95% CI 0.92-1.09; P=0.968), and was increased in patients receiving the combination 1233 (14.5%) compared to treatment with ramipril (HR 1.09 95% CI 1.01-1.18; P=0.037).[77]

The Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) was a multinational, randomized, double-blind, placebo-controlled trial of treatment with telmisartan in 5,926 patients with coronary, peripheral vascular, or cerebrovascular disease, or DM with end-organ damage with documented intolerance to treatment with an ACEI. The primary outcome of composite CV death, MI, stroke, or hospitalization for HF was lower with telmisartan although the difference was not statistically significant [telmisartan 465 (15.7%) vs. placebo 504 (17.0%); HR 0.92 95% CI 0.81-1.05; P=0.216). The secondary outcome of composite CV death, MI, stroke (i.e., the primary outcome of the HOPE trial) was decreased with telmisartan compared to placebo (HR 0.87 95% CI 0.76-1.00; P=0.048).[78]

Table 14: Summary Results from the TRANSCEND Trial

Outcomes	Telmisartan (n=2954)	Placebo (n=2972)	HR (95% CI)	P value
Composite CV death, MI, stroke, HF hospitalization	465 (15.7%)	504 (17.0%)	0.92 (CI 0.81-1.05)	0.216
Composite CV death, MI, stroke	384 (4.8)%	440 (4.1%)	0.87 (CI 0.76-1.00)	0.048

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) evaluated treatment with telmisartan in a multinational, randomized, double-blind, placebo-controlled trial of 20,332 patients with a recent ischemic stroke. There was not a significant difference in the primary outcome of recurrent stroke with telmisartan compared to placebo [telmisartan 880 (8.7%) vs. placebo 934 (9.2%); HR 0.95 95% CI 0.86-1.04; P=0.23). There was also not a difference in the secondary outcomes of major CV events, or new-onset DM.[79]

Table 15: Summary Results from the PRoFESS Trial

Outcomes	Telmisartan (n=10146)	Placebo (n=10186)	HR (95% CI)	P value
Recurrent stroke	880 (8.7%)	934 (9.2%)	0.95 (CI 0.86-1.04)	0.23

Valsartan: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was a multinational, randomized, double-blind, active-controlled, parallel-group study of 15,245 patients with HTN and at high risk for cardiac events. Patients received valsartan or amlodipine with titration and addition of HCTZ, then other antihypertensive agents to achieve goal blood pressure < 140/90 mm Hg. The difference in blood pressure reduction was lower in the amlodipine treatment group at 1 month (4.0/2.1 mm Hg) and at the end of the study or final visit (-15.2/-8.2 mm Hg from baseline with valsartan vs. -17.3/-9.9 mm Hg with amlodipine; P<0.0001). The difference in primary endpoint of time to first cardiac event (composite of cardiac morbidity and mortality) was not statistically significant between valsartan and amlodipine (10.6% vs. 10.4%, respectively; HR 1.04 95% CI 0.94-1.15; P=0.49). The pre-specified endpoint of all-cause mortality was also similar between treatment groups (11% vs. 10.8%, respectively); as were the secondary endpoints of fatal and nonfatal HF or fatal and nonfatal stroke. There was a significant difference in the secondary endpoint of fatal and nonfatal MI between treatment groups (valsartan 4.8% vs. amlodipine 4.1%; HR 1.19 95% CI 1.02-1.38; P=0.02). The pre-specified endpoint of the development of new-onset DM was reduced with valsartan compared to amlodipine (HR 0.77 (95% CI 0.69-0.86; P<0.0001).[80] When employing a more stringent criteria for defining DM that excluded reports of adverse events, the risk of developing new type 2 DM was reduced by 18% (P=0.0015) with valsartan vs. the amlodipine treatment group.[81]

Table 16: Summary Results from the VALUE Trial

Outcomes	Valsartan (n=4605)	Amlodipine (n=4588)	HR (95% CI)	P value
Composite cardiac morbidity and mortality	810 (10.6%)	789 (10.4%)	1.04 (CI 0.94-1.15)	0.49
Fatal and nonfatal MI	369 (4.8)%	313 (4.1%)	1.19 (CI 1.02-1.38)	0.02

In the Jikei Heart Study, a multicenter, randomized, open-label, blinded endpoint trial in 3,081 Japanese patients with HTN and CV disease, additional treatment with valsartan was compared to continued conventional CV therapy. The addition of valsartan was found to reduce the primary endpoint of composite CV morbidity and mortality compared to the control group (CCB 66%, ACEI 34%, beta-blocker 33%, alpha-blocker 6%, thiazide 3%) [valsartan 92 (6.0%) vs. control 149 (9.7%); HR 0.61 95% CI 0.47-0.79; P=0.0002], which was driven by a reduction in the secondary endpoints of stroke or transient ischemic attack (TIA), angina, or HF as shown below. There was no significant difference in all-cause or CV mortality.[82]

Table 17: Summary Results from the Jikei Heart Study

Outcomes	Valsartan (n=1541)	Control (n=1540)	HR (95% CI)	P value	NNT
Composite CV morbidity and mortality	92 (6.0%)	149 (9.7%)	0.61 (CI 0.47-0.79)	0.0002	27
Stroke or TIA	29 (1.9)%	48 (3.1%)	0.60 (CI 0.38-0.95)	0.028	
Angina requiring hospitalization	19 (1.2%)	53 (3.4%)	0.35 (CI 0.20-0.58)	0.0001	
HF requiring hospitalization	19 (1.2)%	36 (2.3%)	0.53 (CI 0.31-0.94)	0.0293	

In the KYOTO HEART Study, a multicenter, randomized, open-label, blinded endpoint trial in 3,031 Japanese patients with HTN and CV disease or CV risk factors, additional treatment with valsartan was compared to continued conventional CV therapy. The addition of valsartan was found to reduce the primary endpoint of composite CV morbidity and mortality compared to the control group (CCB 63%, beta-blocker 21%, alpha-blocker 3%, thiazide 2% at 12 months) [valsartan 83 (5.5%) vs. control 155 (10.2%); HR 0.55 95% CI 0.4-0.7; P=0.00001], which was driven by a reduction in the secondary endpoints of stroke or TIA, or angina as shown below. There was no significant difference in all-cause or CV mortality.[83]

Table 18: Summary Results from the KYOTO HEART Study

Outcomes	Valsartan (n=1517)	Control (n=1514)	HR (95% CI)	P value	NNT
Composite CV morbidity and mortality	83 (5.5%)	155 (10.2%)	0.55 (CI 0.4-0.7)	0.00001	21
Hospitalization for stroke or TIA	25 (1.6)%	46 (3.0%)	0.55 (CI 0.3-0.9)	0.0149	
Hospitalization for angina	22 (1.5%)	44 (2.9%)	0.51 (CI 0.3-0.9)	0.0106	

Meta-analyses: A meta-analysis of 29,375 patients included in the LIFE, SCOPE, and VALUE trials found no difference in all-cause mortality with an AIIRA compared to active controls. There was a significant increase in MI and a decrease in new-onset DM.[84] The potential that an AIIRA increases the risk of MI was evaluated in a systematic review of 19 trials including 31,569 patients comparing treatment with an AIIRA with that of an ACEI or placebo. In the 11 trials that compared an AIIRA to placebo, an MI occurred in 436 of 19,656 (4.06%) patients on an AIIRA vs. 450 of 10,406 (4.32%) of patients on placebo (OR 0.94 95% CI 0.75-1.16; P=0.55). In the 9 trials including 5406 patients on an AIIRA and 5219 patients on an ACEI, 435 MIs (8.05%) were reported with an AIIRA compared to 433 (8.3%) events in patients on an ACEI (OR 1.01 95% CI 0.87-1.16; P=0.91). Data from VALUE were not included since this trial did not have a placebo or ACEI treatment arm. In addition, MI data from VALIANT were not available to be included for the analysis.[85] In a recent meta-analysis including 5 trials comparing an AIIRA to placebo and 16 trials vs. controls, there was a significant reduction in stroke with an AIIRA (overall OR 0.87 95% CI 0.77-0.98; P=0.001) and a nonsignificant reduction in MI with an AIIRA vs. placebo (OR 0.90 95% CI 0.79 to 1.03; P=0.323); however, there was a nonsignificant increase in MI with an AIIRA compared to controls (OR 1.08 95% CI 1.00 to 1.18; P=0.371) and overall (OR 1.03 95% CI 0.96 to 1.10; P=0.172).[86]

A recent meta-analysis pooled data from over 89,000 patients in 37 trials. The data were homogenous except for the HF trials with MI as an endpoint and the trials of patients without HF that included stroke as an outcome. In the non HF trials, there was an increase in MI of borderline significance with an AIIRA compared to controls, and a trend toward a reduction in stroke with an AIIRA. Overall, there was no difference in CV or all-cause mortality with an AIIRA compared to the control groups.[87]

A meta-analysis of ten trials (eight in patients with HTN and two trials of patients with HF; five trials with an ACEI and five with an AIIRA) reported a significant reduction in the risk of developing type 2 DM with an ACEI or AIIRA compared to the control group (placebo, beta-blocker, diuretic, DHP CCB).[88] The effect of an AIIRA in patients with HTN and DM was evaluated in a meta-analysis of three studies that found no difference in all-cause mortality or CV morbidity and mortality between treatment with an AIIRA and placebo or other antihypertensive therapy (significant for heterogeneity of trials vs. active controls), and a reduction in dialysis or transplantation with an AIIRA compared to placebo.[89]

Hypertension and/or CV Disease or High CV Risk Outcomes Trials Discussion: The results of one well-conducted clinical trial support the use of losartan over a beta-blocker 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. One single-blind study with candesartan in Japanese patients was found to reduce hospitalizations for stroke and hospitalizations for MI compared to conventional therapy. In a randomized, open, blinded endpoint trial with candesartan in Japanese patients with HTN and at high CV risk, there was no difference in the primary endpoint of first fatal or nonfatal CV events compared to patients treated with a DHP CCB. An open-label, blinded endpoint trial in Japanese patients with coronary artery disease and HTN found no significant difference in major CV events with candesartan based therapy compared to conventional treatment. In an open-label, blinded endpoint trial, treatment with eprosartan reduced all-cause mortality, cerebrovascular events, and CV events compared to treatment with a DHP CCB in patients with HTN and a history of stroke. Telmisartan was found to be noninferior to treatment with an ACEI in reducing death from CV causes, MI, stroke, or hospitalization for HF in patients with vascular disease or high-risk DM, with no

difference in the pre-specified outcome of composite dialysis, doubling sCr, and death (although this endpoint was increased with combination therapy vs. ACEI alone). Another trial found no difference compared to placebo in a similar patient population intolerant to an ACEI. Treatment with telmisartan was also not found to reduce recurrent stroke compared to placebo in patients with a recent ischemic stroke. Initial therapy with valsartan compared to a DHP CCB did not result in a significant difference in reducing the composite of cardiac morbidity and mortality in patients with HTN at high CV risk. There was an increase in the secondary endpoint of MI with valsartan compared to a DHP CCB, and a decrease in the pre-specified endpoint of new-onset DM. Based on previous meta-analyses, treatment with an AIIRA does not appear to increase MI compared to placebo or compared to treatment with an ACEI. However, another recent meta-analysis reported a nonsignificant increase in MI with an AIIRA compared to controls. Two open-label blinded endpoint trials reported a reduction in the composite CV morbidity and mortality with the addition of valsartan compared to conventional therapy in Japanese patients with HTN and CV disease or CV risk; however, bias may have been introduced due to the components of the primary endpoint that included hospitalizations with the study design (PROBE). Six of the eleven trials in patients with HTN, CV disease, and/or at high CV risk were conducted soley outside the U.S. (where usual and/or maximum doses of the AIIRAs differ from the U.S.) and were of open label design. Published outcome data are currently not available with irbesartan or olmesartan in patients with HTN and/or CV disease or high CV risk.

Hypertension and/or CV Disease or High CV Risk Outcomes Trials Conclusion

Due to the difference in patient populations, comparators, and outcomes evaluated, a conclusion cannot be made regarding the comparative efficacy of the AIIRAs in reducing long-term outcomes in patients with HTN and/or CV disease or high CV risk.

Heart Failure Outcome Trials with AIIRAs[21,26-28,90-105]

Valsartan: Valsartan is FDA approved for use in patients with HF.[7] The indication is based on the results of the Val-HeFT (Valsartan Heart Failure Treatment) study. The trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF on standard therapy (diuretics: 85%; ACEI: 93%; beta-adrenergic blockers: 35%; and digoxin 67%). Baseline left ventricular ejection fraction (LVEF) was 27%. Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily) or placebo. Mean follow-up was 23 months. The two primary endpoints were 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).[26] (See Table 19).

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 beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a statistically significant reduction in mortality (P=0.012).[26] 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).[90] In patients on an ACEI alone (i.e., without a beta-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.[26]

Table 19: 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 IV inotropic agents or vasodilators for > 4 hours

Losartan: In the ELITE[91] pilot trial (Evaluation of Losartan in the Elderly), 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.[91] The favorable mortality rate in the losartan group was not hypothesized *a priori*. Therefore, replication of the results was attempted in ELITE II.[92]

ELITE II[92] 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).[92] Several researchers have speculated that the dose of losartan was sub-optimal in this study.

It was for this reason that the Heart Failure endpoint Evaluation with the Angiotensin II Antagonist Losartan (HEAAL) study[93] was undertaken to determine the effect of losartan 50 mg compared with losartan 150 mg on all-cause mortality and HF hospitalizations in 3846 patients with HF and LVEF $\leq$ 40%, who were intolerant to an ACEI (86% reported intolerance due to cough). Seventy-two percent of patients received concomitant treatment with beta-blockers. After a median of 4.7 years of follow-up, treatment with losartan 150 mg (mean 129$\pm$39 mg) resulted in a 10% decrease in the risk for death or HF hospitalization compared to patients randomized to losartan 50 mg (mean 46$\pm$11 mg) [losartan 150 mg 828 (43.0%) vs. losartan 50 mg 889 (46.3%); HR 0.90 95% CI 0.82-0.99; P=0.027; ARR 3.4%; NNT=30). The secondary endpoint of all-cause mortality did not differ between treatment groups; although, there was a significant reduction in HF hospitalizations in patients treated with the higher dose of losartan (HR 0.87 95% CI 0.76-0.98; P=0.025; ARR 2.9%; NNT=35). Hyperkalemia, hypotension, renal impairment, and angioedema all occurred more frequently in the losartan 150 mg treatment group compared to the 50 mg dose, with no difference in discontinuations due to adverse events.[93]

Table 20: Summary Results of the HEAAL Study

Outcomes	Losartan 150 mg (n=1927)	Losartan 50 mg (n=1919)	HR (95% CI)	P value	NNT
Death or HF hospitalization	828 (43.0%)	889 (46.3%)	0.90 (CI 0.82-0.99)	0.027	30
All-cause mortality	635 (33.0%)	665 (34.7%)	0.94 (CI 0.84-1.04)	0.24	
HF hospitalizations	450 (23.4%)	503 (26.2%)	0.87 (CI 0.76-0.98)	0.025	35

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.[94] 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.[95] 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.

Candesartan is FDA approved for the treatment of patients with HF based on results from the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) program trials. Three separate trials comprised the CHARM program,[96] where candesartan, titrated to 32 mg (median dose 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.[27] See Table 21 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 hospitalization.[21]

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.[28]

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.[97]

The CHARM Overall[27] 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.

When data of patients with low LVEF ($\leq$ 40%) from the CHARM program (i.e., from CHARM Added and CHARM Alternative) were evaluated (n=4576), there was a reduction in the primary endpoint of CV death or HF hospitalization (with a reduction when each endpoint was analyzed separately), as well as a reduction in all-cause mortality (HR 0.88 95% CI 0.79-0.98; P=0.018) with candesartan compared to the placebo group.[98]

The pre-specified secondary endpoint of new onset DM was evaluated in 5436 patients who did not have DM when enrolled in the CHARM program. Treatment with candesartan reduced the development of new DM compared to placebo (HR 0.78 95% CI 0.64-0.96; P=0.020); although the difference was not significant in the patients who received concomitant ACEI at baseline.[99]

Table 21: 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*	1150/3803 (30.2%)	1310/3796 (34.5%)	0.84 (0.77-0.91)	<0.0001
CV death*	693/3803 (18.2%)	796/3796 (20.3%)	0.88 (0.79-0.97)	0.012
CHF hospitalization*	757/3801 (19.9%)	1369/3796 (24.2%)	0.84 (0.72-0.87)	<0.0001(ARR 4.3%; NNT=23)

*Secondary endpoint

Irbesartan: As with CHARM Preserved, the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study was conducted to determine whether treatment with an AIIRA (irbesartan) would improve outcomes in patients with HF and preserved ejection fraction. I-PRESERVE was a multinational, randomized, double-blind trial comparing irbesartan to placebo in 4,128 patients $\geq$ 60 years of age with NYHA class II-IV HF and LVEF $\geq$ 45%. According to the results of the trial, treatment with irbesartan did not differ in the primary composite outcome of all-cause death or CV hospitalization compared to placebo [irbesartan 742 (36%) vs. placebo 763 (37%); HR 0.95 95% CI 0.86-1.05; P=0.35).[100]

Meta-analyses: The AIIRAs have yet to be shown to be equivalent or superior to the ACEIs in patients with HF. A meta-analysis including 30,080 patients from 24 trials found that in the HF trials, there was no difference in all-cause mortality or HF hospitalizations between the ACEIs and AIIRAs, or when the combination of an ACEI and AIIRA was compared to an ACEI alone for all-cause mortality; HF hospitalizations were decreased with combination therapy.[101] Similar results were found in another meta-analysis of 27,495 patients, with no difference in all-cause mortality between treatment with an AIIRA

compared to an ACEI (HR 1.06 95% CI 0.56-1.62), no difference in death between combination with an AIIRA and ACEI compared to an ACEI alone (HR 0.98 95% CI 0.84-1.15), and a 17% reduction in HF hospitalizations with combination therapy compared to an ACEI alone (RR 0.83 95% CI 0.71-0.97).[102] In a previous 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.[103] In an earlier 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 outcome trials with an AIIRA in patients with HF (ELITE II and Val-HeFT).[104] 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.[26]

When considering combination therapy with an AIIRA and ACEI in patients with HF, the risk for increased adverse events should also be taken into account. A meta-analysis evaluated discontinuation data due to adverse events in 18,160 patients with HF or LV dysfunction post MI from 9 trials and reported that patients who were treated with combination therapy experienced an increased risk of any adverse event (RR 1.27 95% CI 1.15-1.40; P<0.00001; NNH 42), hypotension (RR 1.91 95% CI 1.37-2.66; P=0.0002; NNH 89), worsening renal function (RR 2.12 95% CI 1.30-3.46; P=0.003; NNH 100), and hyperkalemia (RR 4.17 95% CI 2.31-7.53; P<0.00001; NNH 149).[105]

HF Outcome 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 HF 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 with a trend toward an increase in combined morbidity and mortality if patients were receiving both an ACEI and beta-blocker. Valsartan is FDA approved for treating HF to reduce HF hospitalizations. The product information also includes a statement that there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI.

The 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 was that losartan is not superior to captopril, and the data showed trends favoring the ACEI. Results from the HEAAL study showed that the benefit of treatment with losartan was dose-dependent, with 150 mg demonstrating a significant reduction in the combined primary endpoint of mortality and HF hospitalizations compared to the 50 mg dose in patients with HF and LVEF $\leq$ 40%.

An early pilot trial of candesartan for heart failure (RESOLVD) was prematurely discontinued. The CHARM program conducted in over 7000 patients found that treatment with candesartan, in addition to standard HF therapies, resulted in a statistically significant reduction in cardiovascular death/HF hospitalization in patients with a LVEF $\leq$ 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 approved by the FDA for reducing CV death and HF hospitalizations in patients with HF; there is also an added effect on these outcomes when used with an ACEI.

Current national guidelines for HF recommend using an ACEI as first line for HF, and reserving AIIRAs for patients unable to take ACEIs. 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 considered if the patient is intolerant to an ACEI or unable to take a beta-adrenergic blocker. Results of the CHARM 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. When data in patients with low LV ejection fraction from the CHARM trials were combined, all-cause mortality was reduced with candesartan.

HF Outcome Trials Conclusion

Candesartan, valsartan, and losartan have data to show benefit in patients with HF, especially in patients who are intolerant of ACEIs. Both valsartan and candesartan have an FDA indication for HF. 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 twice daily. 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, 13 patients would need to be treated with candesartan for 41 months, and 35 patients would need to be treated with losartan 150 mg for 56 months to prevent one hospitalization for HF. The use of losartan for HF is not approved by the FDA; however, the results of the HEAAL study support its use for HF at a dose of 150 mg once daily.

HF/Acute MI Outcome Trials with AIIRAs[22,101,106]

Losartan: Losartan (target dose 50mg once daily) was compared to captopril (target dose 50mg three times daily) in 5477 high-risk (i.e., signs and symptoms of HF or Q-wave MI) patients with acute MI (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.[106] 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)[22] evaluated the effects on mortality of valsartan (target dose of 160 mg twice daily), captopril (target dose of 50 mg three times daily) and the combination of valsartan and captopril (target dose of 80 mg twice daily and 50 mg three times daily, respectively) 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 23).

VALIANT also showed that the combination of an ACEI, 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 23: 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

Meta-analyses: In the meta-analysis of 24 trials previously described in the HF Outcomes section, two of the trials included patients with high risk acute MI and found no difference in all-cause mortality or HF hospitalizations between treatment with an ACEI and an AIIRA.[101]

HF/Acute MI Outcome Conclusion

The results of one large clinical trial support that valsartan was as effective as captopril in reducing overall mortality in patients with acute MI and symptomatic HF; valsartan is FDA approved for this indication. A trial with losartan conducted in similar patients was not able to show benefits above that achieved with captopril.

Diabetic Nephropathy Outcome Trials[23-24,76,107-141]

Irbesartan: The renoprotective effect of irbesartan was evaluated in the IDNT (Irbesartan Type 2 Diabetic Nephropathy Trial), where 1715 patients with type 2 diabetes and nephropathy received either irbesartan 300 mg once daily, 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 end stage kidney disease (defined as kidney transplantation, permanent dialysis, or sCr $\geq$6). Secondary endpoints included cardiovascular, rather than kidney 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). There was no significant difference with irbesartan when only death or end stage kidney disease 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.[23] An FDA Advisory committee questioned the use of doubling of sCr as a marker for kidney disease progression. However, based on the results of this and the IRMA 2 trial (discussed below), 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 24).

Table 24: Summary Results of the IDNT trial

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

Losartan: Losartan was evaluated in 1500 patients with type 2 DM with proteinuria (nephropathy) in the Reduction of Endpoints in Patients with NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. Losartan 50 mg once daily (which could be increased to 100 mg once daily for blood pressure control) was compared to placebo in addition to antihypertensive medications for 3 years. The antihypertensive drugs excluded ACEIs. The primary endpoint was a composite of doubling of sCr, end stage kidney disease (need for chronic dialysis or kidney transplantation), or death. In the losartan group, 71% received a dosage of 100 mg once daily. Losartan reduced the risk of the primary composite endpoint by 16% compared to placebo (P=0.02). Losartan decreased the progression to end stage kidney disease 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).[24] Losartan is labeled for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 DM and HTN. (See Table 25).

Table 25: 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

Table 26: 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) [Results not shown] Placebo (569)	Losartan 50-100 mg (751) Placebo (762)
Mean duration	2.6 yrs	3.4 yrs
1° Endpoint	Composite doubling sCr ESRD Death	Composite doubling sCr ESRD Death
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

Surrogate Renal Endpoint Trials

In the IRMA 2 trial (Irbesartan Microalbuminuria type 2 Diabetes Mellitus in Hypertensive Patients), 590 patients with type 2 DM 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 kidney 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.[107] The Microalbuminuria Reduction with Valsartan (MARVAL) study was a trial in 332 patients with type 2 DM and microalbuminuria (with or without HTN) that compared the percent change in urinary albumin excretion (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 mcg/min) compared to patients on amlodipine (29.9% vs. 14.5%, respectively; 15.4% difference, CI 0.056-0.258; P<0.001).[108] 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.[109]

The AIIRAs have been compared to each other,[110-111] in combination with an ACEI,[112-113] and at higher than the recommended doses[114-117] in their effect on urinary albumin excretion. In general, an AIIRA in combination with an ACEI was more effective in reducing UAE than ACEI monotherapy; and higher than recommended doses of an AIIRA had a greater effect on reducing proteinuria. The trials reported combination therapy or higher doses to be generally safe and well-tolerated; however, the effects on long-term hard outcomes were not evaluated and whether reducing albuminuria is related to improved kidney or cardiovascular outcomes continues to be debated, requiring further study. [76,118-125]

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.[126]

Losartan: The Renoprotection of Optimal Antiproteinuric Doses (ROAD) trial randomized 360 Chinese patients with non-diabetic kidney disease to open-label treatment with losartan 50 mg daily, losartan 50 to 200 mg daily (median 100 mg daily), benazepril 10 mg daily, or benazepril 10 to 40 mg daily (median 20 mg daily). Patients were followed for a median of 3.7 years. The primary endpoint of time to doubling sCr, end stage kidney disease, or death occurred in 15.5% of patients on losartan in the titrated dose group compared to 29.5% of patients on conventional doses (P=0.022). There was also a significant reduction in the primary endpoint in the patients titrated to the higher doses of benazepril compared to conventional doses (P=0.025).[127] 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.[128] 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.[129] 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.[130]

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.[131]

Telmisartan: In a multicenter, randomized, double-blind, comparison study in 250 patients with HTN, type 2 DM, and early nephropathy (UAE rate 11 to 999 mcg/min), treatment with telmisartan was found to be noninferior to ramipril in the primary outcome of change in GFR (telmisartan -17.9 ml/min/1.73m^2 body surface area vs. enalapril -14.9 ml/min/1.73m^2). Secondary endpoints of change in sCr and change in UAE were not statistically different between treatment groups. It was reported that there was no difference in the rates of clinical events (end stage kidney disease, MI, stroke, CHF), or all-cause death.[132]

Meta-analyses: Results of a meta-analysis of 43 trials in patients with DM and microalbuminuria or macroalbuminuria found that all-cause mortality was decreased with an ACEI compared to placebo, but not with an AIIRA vs. placebo. There was a decrease in end stage kidney disease and in doubling sCr with an AIIRA or an ACEI compared to placebo that was statistically significant with an AIIRA and a trend toward significance with an ACEI. Both an AIIRA and an ACEI were beneficial in reducing the progression and increasing the regression of albuminuria. There were not enough data to make a comparison between an ACEI and AIIRA on mortality, end stage kidney disease, or doubling sCr.[133] A systematic review and meta-analysis of 127 trials evaluating an AIIRA or ACEI on kidney outcomes reported a nonsignificant reduction with an ACEI or AIIRA on doubling sCr and a significant decrease in end stage kidney disease when compared with other antihypertensive treatment groups, with no difference in the degree of change in blood pressure. When comparing an ACEI or AIIRA to placebo, there was a benefit in reducing end stage kidney disease and doubling sCr that was associated with a reduction in BP.[134] A systematic review and meta-analysis of 21 trials including 654 patients with proteinuria evaluated the antiproteinuric effect of combination with an AIIRA and an ACEI and reported a further reduction in proteinuria with the addition of an AIIRA compared to an ACEI alone. This was accompanied by a slight increase in potassium (0.11 mEq/L) that was statistically significant. The effect on long-term outcomes was not evaluated.[135] Another meta-analysis evaluated the effect of an AIIRA alone or in combination with an ACEI on proteinuria in 6181 patients from 49 trials and reported that an AIIRA reduced proteinuria compared to placebo, with the combination providing further reduction in proteinuria compared to either agent as monotherapy. The effect of an AIIRA or the combination of an AIIRA with an ACEI on long-term outcomes was also not evaluated in this meta-analysis.[136]

Diabetic Nephropathy Discussion: Nephropathy is characterized by proteinuria and decreasing glomerular filtration rate. In both type 1 and 2 DM, the presence of albuminuria is associated with increased cardiovascular morbidity and mortality. Patients with diabetes 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 kidney transplant, or death due to kidney failure. RENAAL and IDNT were designed to look at kidney outcomes, not cardiovascular outcomes. The composite outcomes in both the RENAAL and IDNT trials, and in the secondary renal outcome of the ONTARGET trial, 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 kidney disease progression. Many of the other trials evaluated a surrogate outcome, albumin excretion rate and were shorter 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.[137-139] 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 $\geq$ 300mg/24hr) with enalapril 10mg compared to placebo ($P<0.001$) after 5 years (NNT=3).[140] This benefit was extended to 7 years in a follow-up evaluation.[141]

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. Losartan and irbesartan received FDA approval in the treatment of nephropathy in patients with type 2 DM and HTN. The secondary endpoint of composite dialysis, doubling sCr, and death was similar with telmisartan compared to an ACEI in a large trial in patients with vascular disease and high-risk DM; with worse outcomes in the combination treatment group. More data are needed to determine whether combination therapy provides any significant benefit over an ACEI alone in patients with diabetic nephropathy. In general, an ACEI is preferred in patients with DM and microalbuminuria or nephropathy (although an AIIRA is appropriate for patients with type 2 DM nephropathy based on outcome data that are not available with the ACEIs in this patient population), and an AIIRA may be considered in patients who are unable to tolerate an ACEI.

Diabetic Nephropathy Conclusion

Losartan and irbesartan have both been studied in patients with type 2 DM 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, end stage kidney disease, and mortality. Over 1500 patients were enrolled in both trials. Losartan was effective in reducing the risk of doubling of sCr and reducing end stage kidney disease 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 patients with type 2 DM with nephropathy. An additional study with irbesartan, IRMA-2 supports that a dose of 300 mg is more effective than 150 mg once daily in patients with DM and microalbuminuria.

Trials with AIIRAs for Other Conditions

Atrial Fibrillation[142-149]

New onset atrial fibrillation: The LIFE trial that enrolled patients with HTN and LVH, evaluated a subgroup of 8851 patients without atrial fibrillation at baseline. After a mean of 4.8 years, the risk of developing new onset atrial fibrillation was decreased with losartan compared to atenolol (HR 0.67 95% CI 0.55-0.83; P<0.001). In addition, there was a reduction in the composite endpoint of CV events, stroke, and MI (HR 0.60 95% CI 0.38-0.94; P=0.03) and the risk for stroke (HR 0.49 95% CI 0.29-0.86; P<0.001) in patients who developed new onset atrial fibrillation who were treated with losartan compared to atenolol.[142] Results from further analysis of the data suggested that treatment of patients with HTN that prevents or contributes to the regression of LVH is beneficial in reducing new onset atrial fibrillation.[143]

In a pre-specified analysis of patients with HTN participating in the VALUE trial, 3.67% of patients treated with valsartan had at least one documented episode of new onset atrial fibrillation compared to 4.34% of patients treated with amlodipine (unadjusted HR 0.843 95% CI 0.713-0.997; P=0.0455).[144] According to a subgroup analysis of Val-HeFT in patients with HF and normal sinus rhythm at baseline, atrial fibrillation occurred in 5.12% of patients treated with valsartan vs. 7.95% of patients on placebo (P=0.0002).[145]

Recurrent atrial fibrillation: Treatment with losartan was compared to amlodipine in preventing the recurrence of atrial fibrillation in 222 patients with HTN and paroxysmal atrial fibrillation (in normal sinus rhythm with document symptomatic atrial fibrillation in the past 6 months). Patients received concomitant therapy with amiodarone. At the end of follow-up (median 299 days), recurrence of atrial fibrillation occurred in 13 patients treated with losartan compared to 39 patients receiving amlodipine (P<0.01).[146] A similar trial of 296 patients with HTN and type 2 DM with paroxysmal atrial fibrillation were treated with valsartan or atenolol, with both groups receiving amlodipine and continued antiarrhythmic therapy. There were 20.3% of patients in the valsartan group who experienced at least one ECG documented episode of atrial fibrillation compared to 34.1% of patients in the atenolol group (P<0.01). The selection of antiarrhythmic agent also influenced the recurrence of atrial fibrillation.[147]

A meta-analysis evaluating the effect of an AIIRA or ACEI on atrial fibrillation found that treatment reduced the risk of new onset atrial fibrillation (OR 0.51 95% CI 0.36-0.72) in 4 trials including an AIIRA (losartan n=8851, valsartan, n=4395) or an ACEI (n=1951); and reduced the failure rate of electrical cardioversion of atrial fibrillation (OR 0.47 95% CI 0.24-0.92) and decreased the rate of recurrence of atrial fibrillation (OR 0.39 95% CI 0.20-0.75) in 4 trials including an AIIRA (irbesartan n=244, losartan n=30) or an ACEI (n=145). The data for new onset atrial fibrillation were found to be heterogeneous and included trials of post hoc analysis of larger clinical trials.[148]

More recently, a large prospective, randomized, placebo-controlled trial enrolling 1442 patients with paroxysmal atrial fibrillation or pharmacologic cardioversion within 2 weeks, and CV disease, DM, or left atrial enlargement reported that treatment with valsartan did not significantly reduce the primary endpoint of time to first recurrence of atrial fibrillation compared to placebo (51.4% vs. 52.1%; adjusted HR 0.97 96% CI 0.83-1.14; P=0.73) or the number of patients with more than one recurrence (26.9% vs. 27.9%; adjusted HR 0.89

99% CI 0.64-1.23; P=0.34). Over 50% of the patients in each group were receiving treatment with an ACEI, less than 10% had LVH, 35% were receiving amiodarone, and 32% were on a class I antiarrhythmic agent.[149]

Further study is needed to determine the role of an AIIRA in preventing the development of or recurrence of atrial fibrillation.

Diabetic Retinopathy[124,150-151]

The Diabetic Retinopathy Candesartan Trials (DIRECT) compared treatment with candesartan 32 mg daily to placebo in 1421 patients with type 1 DM on the prevention of diabetic retinopathy (DIRECT-Prevent 1), and in 1905 patients with type 1 DM on the progression of diabetic retinopathy (DIRECT-Protect 1), defined by at least a 2-step or 3-step increase in the Early Treatment Diabetic Retinopathy Study (ETDRS), respectively. In DIRECT-Prevent 1 (median follow-up 4.7 years), the incidence of retinopathy occurred in 25% of patients receiving candesartan compared to 31% on placebo (HR 0.82 95% CI 0.67-1.00; P=0.0508). In DIRECT-Protect 1 (median follow-up 4.8 years), progression occurred in 13% of patients in the candesartan and placebo treatment groups (HR 1.02 95% CI 0.80-1.31; P=0.85).[150]

DIRECT-Protect 2 (median follow-up 4.7 years) compared treatment with candesartan 32 mg daily to placebo in 1905 patients with type 2 DM on the progression (primary endpoint) and regression (secondary endpoint) of diabetic retinopathy. In this trial, progression of diabetic retinopathy occurred in 17% of patients in the candesartan group compared to 19% on placebo (HR 0.87 95% CI 0.70-1.08; P=0.20), while regression was increased with candesartan compared to placebo (HR 1.34 95% CI 1.08-1.68; P=0.009).[151]

The pre-specified endpoint of progression of diabetic retinopathy was added to the Renin-Angiotensin System Study (RASS) designed to evaluate treatment with an ACEI or AIIRA on the progression of diabetic nephropathy. In 253 patients with type 1DM, progression of retinopathy (defined as at least a 2-step increase in the ETDRS) occurred in 21% of patients treated with losartan compared to 38% on placebo (OR 0.30 95% CI 0.12-0.73; P=0.008), and in 25% of patients treated with enalapril compared to placebo (OR 0.35 95% CI 0.14-0.85; P=0.02).[123]

Further study is needed to determine the role of an AIIRA in the development, progression, or regression of diabetic retinopathy and its place in therapy compared to an ACEI.

Migraine Prophylaxis[152-153]

Two studies evaluated use of an AIIRA for migraine prophylaxis. In a randomized, double-blind, placebo-controlled, crossover trial of 12 weeks in 60 patients with two to six migraine attacks per month, candesartan 16 mg daily decreased the mean number of days with headache compared to placebo (13.6 vs. 18.5 days, respectively; P=0.001).[152] A reduction in the frequency of migraine attacks was also reported in an open-label study with olmesartan in 24 patients with HTN or prehypertension and migraine headaches.[153] Further study is needed to confirm the effectiveness of an AIIRA in migraine prophylaxis and its place in therapy compared to other treatments used for this indication.

Safety / Tolerability [1-8,20-27,35,37,39-41,45,51,54,61,70,78,91,92,94,106,107,154-226]

Serious Side Effects[21,27,78,91,94,169-187]

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.[21] In a large trial of 5926 patients at high CV risk intolerant to an ACEI, 75 (1.3%) of patients were intolerant due to angioedema or anaphylaxis. Of the 2954 patients randomized to telmisartan, angioedema was reported as the reason for discontinuation in 2 patients (0.07%) compared to 3 patients (0.10%) on placebo (P=0.660).[78] A systematic review of 61 trials comparing an AIIRA with an ACEI reported angioedema (in 3 of the studies) in only those patients who were treated with an ACEI.[20] 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. In an evaluation of 54 patients who experienced angioedema while on treatment with an ACEI, 26 were switched to an AIIRA, 14 to a CCB, and 14 to other antihypertensive medications. After review of the 5 patients who did not experience a reduction or resolution of angioedema after switching to an AIIRA, it was reported that 2 of these patients may have had angioedema as a result of the AIIRA.[186] Due to the possibility that angioedema may occur with an AIIRA in patients with reported angioedema on an ACEI, the risk vs. benefit of treatment with an AIIRA should be considered and if prescribed, should be used with caution in patients who have previously experienced angioedema.

Kidney Failure—In patients whose kidney function may depend upon the activity of the renin-angiotensin-aldosterone system, treatment with AIIRAs and ACEIs has been associated with acute kidney failure. These drugs are capable of reducing intraglomerular filtration pressure by causing dilation of the efferent renal arterioles. These agents can cause kidney 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. It is unclear 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 $\geq$ 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 $\geq$ 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.[27] A retrospective analysis of patients with HF found no difference in the incidence of hyperkalemia between concomitant therapy with either losartan 50 mg daily, candesartan 8 mg daily, or enalapril 5 mg daily with spironolactone 25 or 50 mg daily and furosemide 40 mg daily.[187] The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on lisinopril compared to valsartan with kidney insufficiency. In patients with a GFR $\leq$ 60mL/min/1.73 m^2, there was a significant increase of 0.28 mEq/L (P=0.04) above baseline (4.6 mEq/L) with lisinopril. The increase of 0.12 mEq/L seen with valsartan in this subgroup was not significant (P=0.1).[182]

Adverse Event Profile[1-8,20-22,24,26,35,37,45,51,54,61,70,78,91,92,106,107,182-185,189-215]

- 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.
- *Cough*: ACEIs have an incidence of cough ranging from 5 to 39%. Unlike ACEIs, AIIRAs have an incidence of cough comparable to placebo (1.6-4%). In a systematic review of head-to-head comparison trials of an ACEI and AIIRA, cough was reported in 0 to 23% (mean 10%) of patients treated with an ACEI and 0 to 13% (mean 3%) of patients receiving an AIIRA.[20] In a large (n=1100) comparison study of valsartan 160 mg daily and lisinopril 20 mg daily in patients with HTN, dry cough was reported in 1.0% of patients on valsartan and in 7.2% of patients treated with lisinopril (P<0.001).[188] 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.[21] The TRANSCEND trial enrolled patients who were intolerant to an ACEI, with cough as the reported reason for ACEI intolerance in 88.2% (i.e., 5225 patients) enrolled in the trial. Cough was subsequently reported as the reason for discontinuation in 15 (0.51%) of patients treated with telmisartan compared to 18 (0.61%) patients in the placebo group.[78] 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%).[189-194] 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.[195-198] 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. Withdrawals due to adverse events have been reported in 1 to 41% (mean 10%, median 3%) of patients treated with an AIIRA compared to 1 to 41% (mean 19%, median 8%) of patients on an ACEI in a review of head-to-head comparisons.[20] The overall incidence of adverse events is comparable to placebo as shown in Table 23. In addition, the AIIRAs have been studied in large [candesartan (n>8000), eprosartan (n>600), irbesartan (n>2000), losartan (n>9000), telmisartan (n>21,000), and valsartan (n>15000)], 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), HTN and high CV risk (valsartan), vascular disease or high-risk DM (telmisartan), and diabetic nephropathy (irbesartan).[22,24,26,70,78,82,91,92,106,107] 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.[199] 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).[200] 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.[201] 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.[202] Published, post-marketing surveillance data of over 12,000 patients on valsartan identified no unexpected serious adverse events.[203] Candesartan, irbesartan, losartan, telmisartan, and valsartan has been studied most extensively in long-term outcome trials. Eprosartan has also been studied in a long-term outcome trial but with fewer patients. Olmesartan does not have published safety results from long-term outcome trials but have demonstrated safety with collective data from short-term trials and up to 6 months to one year evaluating the safety and efficacy in over 3800 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.[204] 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.[51] 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 tables 27 and 28 below:

Table 27: Overall AIIIRA Adverse Events and Dropout Rates [5,35,37,45,54,61,182-185,200,205-215]

	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.

Table 28: AIIIRA Specific Adverse Events Compared to Placebo[1-7]

	Candesartan		Eprosartan		Irbesartan		Losartan		Olmesartan		Telmisartan		Valsartan	
AIIRA/Placebo W/D due to AE	C	P	E	P	I	P	L	P	O	P	T	P	V	P
%	2.4	3.4	4.0	6.5	3.3	4.5	2.3	3.7	2.4	2.7	2.8	6.1	2.3	2.0
AIIRA/Placebo* %	C	P	E	P	I	P	L	P	O	P	T	P	V	P
n	2350	1027	1202	352	1965	641	1075	334	NR	NR	1455	380	2316	888
Dizziness	4	3					3	2	3	1				
Cough			4	3										
URI	6	4	8	5			8	7			7	6		
Viral infection			2	1									3	2
Sinusitis							1	0			3	2		
Nasal congestion							2	1						
Rhinitis	2	1	4	3										
Pharyngitis	2	1	4	3										
Arthralgia			2	1										
Back pain	3	2					2	1			3	1		
Abdominal pain			2	1									2	1
Dyspepsia/ heartburn					2	1								
Diarrhea					3	2								
Fatigue			2	1	4	3							2	1
Depression			1	0										
Leg pain							1	0						
Muscle cramps							1	0						
Injury			2	1										
↑ Triglycerides			1	0										
UTI			1	0										

W/D due to AE=withdrawals due to adverse events in placebo-controlled trials (exception: olmesartan all trials)
*Adverse events in placebo-controlled trials with an AIIRA occurring in ≥1% of patients and at a greater incidence than placebo
n=number of patients; NR=not reported; P=placebo; URI=upper respiratory tract infection; UTI=urinary tract infection

Drug Interactions[1-8,41,216-226]

- 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 Cmax (30%) and decreased E-174 (the active metabolite of losartan) AUC (43%) and

Cmax (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 Cmax (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[1-8]

- Boxed warning for use in pregnancy; 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.
- Losartan and valsartan are approved for use in pediatric patients ($\geq$ 6 years of age and 6 to 16 years, respectively).
- See Table 6 under the dosing and administration for information on hepatic and kidney 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/Clinical Practice Guidelines [9-19,21-28,40,66,68-70,72,75,76,78-80,82,83,84,90-92,93-97,103,104,106-109,126,128-131,136-141,152,227-229]

Hypertension/CV Disease/High CV Risk

- A systematic review of benefits and harms of first-line antihypertensive therapies concluded that first-line therapy with a thiazide diuretic (lower dose) reduced morbidity and mortality (e.g., mortality, stroke, CHD, CV events), with the ACEIs reducing mortality, stroke, CHD, CV events, and the CCBs decreasing stroke and CV events; with the stronger evidence to support treatment with a thiazide diuretic. No randomized controlled trials with an AIIRA compared to placebo or no treatment were found.[228] In a meta-analysis of first-line therapies for hypertension that included comparison trials, an AIIRA was not significantly more

effective for any of the treatment outcomes (total or CV mortality, CV events, stroke, HF, or CHD) compared to a low-dose thiazide diuretic.[229] Another meta-analysis found no difference in all-cause mortality with an AIIRA vs. active controls.[84] A recent meta-analysis reported a significant reduction in the risk of stroke with an AIIRA; however, there was a nonsignificant increase in MI with an AIIRA compared to controls.[87]

- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, or JNC 7, 2003 guidelines recommend using a thiazide diuretic as initial therapy for most patients with uncomplicated HTN. Other classes (ACEIs, AIIRAs, beta-adrenergic blockers, CCBs) that have demonstrated positive outcomes in randomized controlled trials may be considered in combination or for treatment of patients with compelling indications.[9]
- The VA/DoD 2004 HTN Clinical Practice Guidelines concur with the recommendations of JNC 7. In addition, these guidelines recommend that an AIIRA may be considered in patients with uncomplicated HTN who are intolerant to an ACEI.[10]
- The ESH/ESC 2007 Hypertension guidelines consider a thiazide-type diuretic, ACEI, AIIRA, beta-blocker, or CCB as appropriate first-line therapy for hypertension. In addition, an AIIRA may be considered preferable (along with consideration of other medications listed) in the following conditions: LVH: ACEI, CCB, AIIRA; microalbuminuria: ACEI, AIIRA; kidney dysfunction: ACEI, AIIRA; previous stroke: any agent that lowers BP; previous MI: beta-blocker, ACEI, AIIRA; HF: diuretics, beta-blocker, ACEI, AIIRA, aldosterone antagonist; recurrent atrial fibrillation: AIIRA, ACEI; kidney failure/proteinuria: ACEI, AIIRA, loop diuretics; metabolic syndrome: ACEI, AIIRA, CCB; DM: ACEI, AIIRA; ACEI induced cough: AIIRA.[11]
- The NICE 2006 Hypertension guideline recommends a thiazide-type diuretic or CCB first-line if > 55 years of age or black; and an ACEI (or AIIRA if an ACEI is not tolerated) first-line if < 55 years of age. Combination therapy should include the addition of a thiazide diuretic, CCB, or ACEI (or AIIRA if an ACEI is not tolerated).[12]
- The Canadian Hypertension Education Program 2009 recommends a thiazide diuretic as initial therapy in uncomplicated HTN; an ACEI (not in black patients), long-acting CCB, AIIRA, or beta-blocker (in patients < 60 years of age) are also considered appropriate first-line therapy in patients with HTN.[13]
- According to randomized controlled trials in patients with HTN, treatment with an AIIRA reduced hospitalization for stroke and hospitalization for MI (candesartan) compared to conventional treatment,[72] reduced nonfatal stroke (candesartan) vs. open-label antihypertensive therapy,[70] and decreased combined death, CV and cerebrovascular events (eprosartan) compared to a DHP CCB.[75] In patients at high CV risk or CV disease, treatment with an AIIRA has been shown to reduce the composite death, MI, stroke (losartan) compared to a beta-blocker,[25] and decrease CV morbidity and mortality (valsartan) vs. conventional treatment;[82,83] there was no difference in CV morbidity and mortality (telmisartan) compared to an ACEI,[76] or with telmisartan compared to placebo in patients intolerant to an ACEI,[78] or with valsartan[80] or candesartan[73] compared to a DHP CCB; and no significant difference in reducing major adverse CV events (candesartan) compared to conventional therapy.[74] Although the reduction in CV events appear largely driven from the reduction in stroke, there was no difference in recurrent stroke when treatment with an AIIRA (telmisartan) was compared to placebo.[79]
- In summary, an AIIRA is effective for lowering blood pressure in the treatment of hypertension. There have been mixed results with an AIIRA in patients with HTN and/or CV disease or high CV risk; an AIIRA has been shown to reduce CV morbidity and mortality in patients with high CV risk when compared to treatment with a beta-blocker or conventional treatment, with no difference compared to an ACEI or DHP CCB (per randomized, double-blind clinical trials including patients in the U.S.), and a nonsignificant reduction compared to placebo in patients with CV disease or high risk DM who were ACEI intolerant. At this time, consensus recommendations to consider a thiazide diuretic as initial therapy for the treatment of uncomplicated HTN, with addition of an ACEI or CCB for additional BP control or for compelling indications, and an AIIRA in patients intolerant to an ACEI, are reasonable until additional evidence warrants reevaluation of these recommendations.

Heart Failure/High Risk Acute MI

- The ACEIs have well documented beneficial effects in the treatment and prevention of HF. An AIIRA has been shown to reduce CV mortality and HF hospitalizations in patients intolerant to an ACEI

(candesartan)[21] as well as in addition to standard therapy with an ACEI and beta-blocker (with candesartan),[28] and reduced combined morbidity and mortality, and HF hospitalizations compared to standard therapy in patients with HF (with valsartan).[26] In one trial designed to determine superiority, there was no difference in overall mortality or the secondary endpoint of cardiac events between treatment with an AIIRA (losartan) compared to an ACEI.[92] Another clinical trial that evaluated two different doses of losartan on the morbidity and mortality of patients with HF who have documented intolerance to an ACEI found the higher dose of 150 mg to be more effective in reducing death and HF hospitalizations compared to the lower dose of 50 mg.[93]

- According to the ACC/AHA 2009 HF guideline update, an AIIRA is recommended for patients with HF who are intolerant to an ACEI, and can be considered in patients with persistent symptoms despite standard therapy.[14] In high risk patients with acute MI, an AIIRA has been shown to be similar to (i.e., with valsartan)[22] or no different than (i.e., with losartan)[106] an ACEI in reducing total mortality, with no difference compared to combination with an ACEI; although, discontinuation due to adverse events were higher in patients receiving combination therapy.[22] In conclusion, an AIIRA has not been shown to provide better outcomes in high-risk patients with acute MI compared to treatment with an ACEI; therefore, it is reasonable to consider treatment with an AIIRA in patients intolerant to an ACEI.[230]

Diabetic Nephropathy

- Treatment with an ACEI has been shown to slow the progression of kidney disease in patients with type 1 or 2 DM and microalbuminuria. The ACEIs also decrease the rate of decline in kidney function and reduce the combined risk of death, dialysis, or transplantation in patients with type 1 DM and nephropathy. The AIIRAs have not been adequately studied in patients with type 1 DM and microalbuminuria or macroalbuminuria and are therefore recommended in these patients who are unable to tolerate an ACEI. Outcome trials in patients with type 2 DM and microalbuminuria or nephropathy have shown that an AIIRA can prevent the decline in kidney function (irbesartan),[107] and reduce the composite endpoint of all-cause mortality, kidney failure, and doubling sCr (irbesartan, losartan).[23,24]
- According to clinical practice guidelines, there is strong evidence that an ACEI be used in patients with type 1 DM nephropathy and an AIIRA in patients with type 2 DM nephropathy. In general, if either the ACEI or AIIRA are not tolerated, the other class is recommended as alternate therapy.[16,17] At this time, long-term outcome trials (e.g., with the primary endpoint of mortality, kidney failure, and doubling sCr) comparing an ACEI to an AIIRA are needed to determine if these agents provide similar benefit in treating patients with DM and nephropathy or microalbuminuria.
- Combination therapy with an ACEI and AIIRA should be considered only after evaluation of the risk vs. benefit. It has been recommended that combination therapy with an ACEI and AIIRA may be considered in patients with type 2 DM and persistent high-level macroalbuminuria[17] as it has been shown to further reduce proteinuria.[136] In one trial of patients with vascular disease or high risk DM, combination therapy with an ACEI and AIIRA was shown to increase the secondary endpoint of risk for dialysis, doubling sCr, and death when compared to an ACEI alone.[77] Further study is needed to determine the long-term outcome of combination therapy with an ACEI and AIIRA in patients with DM and nephropathy.

Utilization: Refer to individual VA (data on file) or DoD pre-decisional analysis.

Conclusion

Hypertension/CV Disease/High CV Risk: All seven AIIRAs are labeled for use in hypertension and appear equally effective for lowering blood pressure (refer to Appendix A). There is good evidence from a long-term comparison trial that treatment with losartan reduces the risk of composite CV death, MI, and stroke compared to a beta-blocker; although, losartan has only the additional indication to reduce the risk of stroke in hypertensive patients with left ventricular hypertrophy, although the indication does not apply to black patients. Additional data with the other AIIRAs include fair evidence that candesartan reduces hospitalizations for stroke or MI compared to conventional treatment in patients with hypertension; fair evidence that eprosartan reduces the risk of combined death, cerebrovascular and CV events compared to a DHP CCB in patients with hypertension and previous cerebrovascular event; good evidence that telmisartan is similar to an ACEI in reducing the composite endpoint of CV death, MI, and stroke in patients with vascular disease or high risk DM; and fair evidence from two trials that valsartan decreases CV morbidity and mortality compared to conventional treatment in patients with hypertension with CV

disease or high CV risk. In patients with hypertension and high CV risk or CV disease, there was also no difference with candesartan compared to a DHP CCB in fatal and nonfatal CV events (fair evidence), no difference in major adverse CV events with candesartan compared to conventional therapy (fair evidence), and no difference in CV morbidity and mortality with valsartan compared to a DHP CCB (good evidence). There is also good evidence that there is no significant difference between telmisartan and placebo in the risk for recurrent stroke. (Refer to Appendix F) Due to the difference in patient populations (difference in inclusion criteria as well as majority of outcome trials conducted outside the U.S.), comparators, study design, and outcomes evaluated, a conclusion cannot be made as to the comparative efficacy of the AIIRAs in reducing long-term outcomes in patients with HTN and/or CV disease or high CV risk.

Heart Failure/AMI w/HF or LVD: Valsartan is indicated for use in patients with HF (NYHA class II-IV) based on good evidence from one long-term outcome trial with a target dose of 160 mg twice daily. For hypertension, valsartan is dosed once daily (usual dosage is 80 mg once daily). Candesartan is also approved for use in HF (NYHA class II-IV in patients with systolic dysfunction LVEF $\leq$ 40%), based on good evidence from the results of one large trial supporting its use for this indication. The candesartan dose used in the CHARM trials was 32 mg once daily. Candesartan may be dosed once or twice daily in hypertension, but once daily dosing is more common (usual dose is 16 mg once daily). Losartan is not approved for use in HF patients; although, good evidence from one long-term clinical outcome trial showed losartan 150 mg to be effective in reducing death or HF hospitalizations compared to a dose of 50 mg. Valsartan is approved for use in high-risk patients after an acute MI and its use is supported by a long-term outcome trial. Losartan is not approved for use in patients post-MI and the data from one long-term outcome trial are not as strong to support its use for this indication.

Diabetic Nephropathy: Both irbesartan (dose 300 mg once daily) and losartan (dose 50-100 mg once daily) 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 once daily and losartan 50 mg once daily. None of the other AIIRAs is 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.

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Appendix A: Summary of comparative trials of AIIRAs vs. AIIRAs[45-64]

1. Candesartan vs. Losartan: Compared candesartan 8 mg once daily, candesartan 16 mg once daily, losartan 50 mg once daily, 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.[45]
2. Candesartan vs. Losartan: Compared candesartan 16 mg once daily and losartan 50 mg once daily 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.[46]
3. Candesartan vs. Losartan: Compared candesartan 32 mg once daily and losartan 100 mg once daily 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).[47]
4. Candesartan vs. Losartan: Compared candesartan 8 to 16 mg once daily, losartan 50 to 100mg once daily, and losartan/HCTZ once daily 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.[48]
5. Candesartan vs. Losartan: Compared candesartan 8 mg once daily, losartan 50 mg once daily, and placebo in a 6-week trial of 256 patients. At week 6, treatment with candesartan significantly reduced mean DBP by 0-24 hour ABPM compared with losartan (-7.3 ± 6.9 mm Hg vs. -5.1 ± 4.9 mm Hg, respectively; P<0.05). There was no significant difference in the reduction of mean SBP by 0-24 hour ABPM between treatment with candesartan and losartan.[49]
6. Candesartan vs. Olmesartan: Compared olmesartan 20 mg once daily and candesartan 8 mg once daily in an 8-week trial of 643 patients. At 8 weeks, olmesartan resulted in a significantly greater reduction in mean daytime DBP by ABPM compared with candesartan (-9.3 ± 0.5 mm Hg vs. -7.8 ± 0.5 mm Hg, respectively, P≤0.0126). There was also a significant difference in the reduction of mean daytime SBP by ABPM in favor of olmesartan compared to candesartan (numbers not reported).[50]
7. Eprosartan vs. Losartan: Compared eprosartan 600 mg once daily and losartan 50 mg once daily 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 (SBP -12.7 mm Hg, DBP -12.4 mm Hg) and losartan (SBP -10.9 mm Hg, DBP -9.6 mm Hg).[51]
8. Eprosartan vs. Telmisartan: Compared eprosartan 600 mg once daily, telmisartan 40 mg once daily, and placebo in a 12-month study of 119 patients with hypertension and type 2 DM. At 12 months, treatment with telmisartan significantly reduced mean DBP from baseline compared with eprosartan (-8 ± 2 mm Hg vs. -4 ± 1 mm Hg, respectively; P<0.05). There was no significant difference in the reduction of mean SBP between treatment with telmisartan and eprosartan.[52]
9. Irbesartan vs. Losartan: Compared irbesartan 150 mg once daily and losartan 50 mg once daily 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.[53]
10. Irbesartan vs. Losartan: Compared irbesartan 150 mg once daily, irbesartan 300 mg once daily, losartan 100 mg once daily, 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).[54]
11. Telmisartan vs. Losartan: Compared telmisartan 40 mg once daily, telmisartan 80mg once daily, losartan 50 mg once daily, 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.[55]
12. Telmisartan vs. Losartan: Compared telmisartan 40 mg once daily and losartan 50 mg once daily in an 8-week trial of 330 patients. After 4 weeks, if DBP was ≥90 mm Hg, patients were titrated to telmisartan 80 mg or losartan 100 mg. At week 8, telmisartan resulted in a significantly greater reduction in both SBP and DBP compared with losartan (SBP -12.5 mm Hg vs. -9.4 mm Hg, respectively, P=0.037; DBP -10.9 mm Hg vs. -9.3 mm Hg, respectively, P=0.030).[56]
13. Telmisartan vs. Losartan: Compared telmisartan 40 mg once daily and losartan 50 mg once daily in an 8-week trial of 180 patients. After 4 weeks, if DBP was ≥90 mm Hg or < 10 mm Hg reduction in blood pressure, patients were titrated to telmisartan 80 mg or losartan 100 mg. At week 8, telmisartan resulted in a significantly greater reduction in SeSBP compared with losartan (-22.1 mm Hg vs. -16.5 mm Hg, respectively, P=0.032). There was no significant difference in the reduction of DBP between treatment with telmisartan and losartan.[57]
14. Telmisartan vs. Losartan: Compared telmisartan 40 mg once daily and losartan 50 mg once daily in a 6-week trial of 61 patients. At 6 weeks, telmisartan resulted in a significantly greater reduction in mean DBP 18-24 hour ABPM compared with losartan (-12.1 ± 1.6 mm Hg vs. -7.0 ± 1.8 mm Hg, respectively, P=0.036). There was no significant difference in the reduction of mean SBP 18-24 hour ABPM between treatment with telmisartan and losartan.[58]
15. Telmisartan vs. Valsartan: Compared telmisartan 80 mg once daily and valsartan 160 mg once daily in an 8-week trial of 930 patients. At 6 to 8 weeks, telmisartan resulted in a significantly greater reduction in mean SBP 18-24 hour ABPM compared with valsartan (-11.1 mm Hg vs. -9.1 mm Hg, respectively, P=0.0066) and in mean DBP 18-24 hour ABPM compared with valsartan (-7.6 ± 7.9 mm Hg vs. -5.8 ± 7.8 mm Hg, respectively, P=0.0044).[59]
16. Telmisartan vs. Valsartan: Compared telmisartan 80 mg once daily and valsartan 160 mg once daily in an 8-week trial of 490 patients. At 6 to 8 weeks, telmisartan resulted in a significantly greater reduction in mean SBP 18-24 hour ABPM compared with valsartan (-

11.0 ± 0.8 mm Hg vs. -8.7 ± 0.8 mm Hg, respectively, P=0.02) and in mean DBP 18-24 hour ABPM compared with valsartan (-7.6 ± 0.6 mm Hg vs. -5.8 ± 0.6 mm Hg, respectively, P=0.01).[60]

17. Valsartan vs. Losartan: Compared valsartan 80 mg once daily, losartan 50 mg once daily, 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).[61]
18. Valsartan vs. Losartan: Compared losartan 50mg once daily to valsartan 80mg once daily 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≤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.[62]
19. Olmesartan vs. Losartan, Valsartan, Irbesartan: Compared olmesartan 20 mg once daily (n=147), losartan 50 mg once daily (n=150), valsartan 80 mg once daily (n=145), irbesartan 150 mg once daily (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).[63]
20. Olmesartan vs. Losartan, Valsartan: Compared olmesartan 40 mg once daily (n=189), losartan 100 mg once daily (n=192), valsartan 160 mg once daily (n=189), and placebo (n=94) at week 8 where there was a significantly greater decrease in the primary efficacy variable of SeDBP with olmesartan (-12.9 mm Hg) compared with losartan (-9.4 mm Hg, P<0.001). There was no significant difference in SeDBP between olmesartan and valsartan at these doses. The decrease in SeSBP was also lower in patients on olmesartan (-15.2 mm Hg) compared to losartan (-10.9 mm Hg, P<0.001), without a difference compared to valsartan. At week 12, the dose of losartan was 50 mg twice daily and valsartan 320 mg once daily, while the dose of olmesartan was continued at 40 mg once daily. The change in SeDBP and SeSBP were not significantly different between treatment groups at this point of evaluation. [64]

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

Appendix A (continued): Summary of comparative trials of AIIRAs vs. AIIRAs[45-64]

RCT	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan	Results
1. Andersson 1998	C 8 C 16			L 50 L 50				NS (DBP) C > L (↓ 3.7 DBP)
2. Gradman 1999	C 16-32			L 50-100				C > L (↓ 2.1 DBP)
3. Bakris 2001	C 32			L 100				C > L (↓ 3.5 SBP/ ↓ 2.2 DBP)
4. Manolis 2000	C 8-16			L 50-100				NS (SBP/DBP)
5. Baguet 2006	C 8			L 50				C > L (NS mean ABPM SBP/ ↓ 2.2 DBP)
6. Brunner 2006	C 8				O 20			O > C (↓ 1.5 mean daytime ABPM DBP)
7. Puig 1999		E 600		L 50				NS (SBP/DBP)
8. Derosa 2004		E 600				T 40		T > E (NS SBP/ ↓ 4 DBP)
9. Oparil 1998			I 150-300	L 50-100				I > L (↓ 2.3 DBP)
10. Kassler-Taub 1998			I 150 I 300	L 100 L 100				NS (DBP) I > L (↓ 3 DBP)
11. Mallion 1999				L 50 L 50 L 50 L 50		T 40 T 80 T 40 T 80		NS (DBP) T > L (↓ 3.7 DBP) T > L (↓ 2.5 mean ABPM DBP) T > L (↓ 3.5 mean ABPM DBP)
12. Zhu 2004				L 50-100		T 40-80		T > L (↓ 3.1 SBP/ ↓ 1.6 DBP)
13. Lee 2004				L 50-100		T 40-80		T > L (↓ 5.6 SBP/ NS DBP)
14. Ding 2004				L 50		T 40		T > L (↓ 5.1 mean ABPM DBP)
15. Lacourciere 2004						T 80	V 160	T > V (↓ 2.0 mean ABPM SBP/ ↓ 1.8 DBP)
16. White 2004						T 80	V 160	T > V (↓ 2.3 mean ABPM SBP/ ↓ 1.8 DBP)
17. Hedner 1999				L 100			V 160	NS (SBP/DBP)
18. Monterroso 2000				L 50			V 80	?NS (mean ABPM DBP)
19. Oparil 2001			 I 150	L 50 	O 20 O 20 O 20		 V 80 	O > L (NS SBP/ ↓ 3.3 DBP; ↓ 3.5 mean ABPM SBP/ ↓ 2.3 DBP) O > V (NS SBP/ ↓ 3.6 DBP; ↓ 4.4 mean ABPM SBP/ ↓ 2.9 DBP) O > I (NS SBP/ ↓ 1.6 DBP; NS mean ABPM SBP/DBP)
20. Giles 2007				L100 L 50 BID	O 40 O 40 O 40		 V 160 V 320	O > L (↓ 4.3 SBP/↓ 3.5 DBP) NS (SBP/DBP) NS (SBP/DBP)

Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
	600		50*			
8*					40	80
16		150	100*	20	80*	160*
32		300	50 BID	40		320

Approximate equivalencies of doses included in comparison hypertension trials evaluating BP reduction

*Exceptions:

C 8mg NS L 50mg DBP (1 RCT)

T 40-80 mg > L 50-100 mg SBP/DBP (1 RCT)

T 40-80 mg > L 50-100 mg SBP (1 RCT)

T 80 mg > V 160 mg ABPM SBP/DBP (2 RCT)

V 160 mg NS O 40 mg SBP/DBP (1 RCT)

Appendix B: Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>LIFE

R, dm, DD, PG

N=9193 (92% Caucasian)

Supported by Merck and Co.</td>
<td>Losartan (LOS) vs. atenolol (ATEN)</td>
<td>Inclusion: 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</td>
<td><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

NNT for PEP: 56
NNT for stroke: 59

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<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>
</table>
</td>
<td>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)</td>
</tr>
<tr>
<td>LIFE
(Diabetes)
R, dm, DD, PG

N=1195

Supported by Merck and Co.</td>
<td></td>
<td>Inclusion: 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</td>
<td><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
NNT for PEP: 19.1

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<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>
</table>
</td>
<td>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</td>
</tr>
</table>

AHR=adjusted hazard ratio; ARR=absolute risk reduction; ATEN=atenolol; dm=double masked; DD=double dummy; ECG=electrocardiogram; LOS=losartan; NNT=number needed to treat; PEP=primary endpoint; PG=parallel group; R=randomized; RRR=relative risk reduction

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

Trial	Comparison	Methods	Outcomes	Additional Results
VALUE R, DB, PG, MC N=15,245 U.S., Canada, Europe, S. America, Asia, Australia, S. Africa Supported by Novartis Pharma AG	Valsartan (VAL) vs. Amlodipine (AML)	**Inclusion: ≥ 50 years, HTN, CV RF (male, > 50 years, DM, TOB, ↑ TC, LVH) and CVD (CHD, PAD, stroke or TIA, LVH w/strain)** Exclusion: RAS, pregnancy, acute MI, PTCA or CABG w/in 3 months, valvular disease, hepatic disease, CRF, HF on ACEI, CAD and HTN on BB VAL (80mg): N=7649 AML (5mg): N=7596 Titrated then add HCTZ (12.5 to 25mg) BP < 140/90 mm Hg Mean age: 67 years; Mean F/U: 4.2 years **PEP: Time to first cardiac event (composite SCD, fatal MI, death during or after PCI or CABG, HF death, death due to MI, HF hosp, nonfatal MI, ER to prevent M)I**	**VAL 810 (10.6%) vs. AML 789 (10.4%); (HR 1.04, CI 0.94-1.15)** Tx / N / PEP / P VAL / 7649 / 810 (10.6%) / NS AML / 7596 / 789 (10.4%) / Additional outcome measures Fatal/nonfatal MI: ↑ VAL 369 (4.8%) vs. AML 313 (4.1%), (HR 1.19 CI 1.02-1.38; P=0.02) Fata/nonfatal HF, Fatal/nonfatal stroke: VAL vs. AML (NS) New-onset DM: ↓ VAL 690 (13.1%) vs. AML 845 (16.4%), (OR 0.77 CI 0.69-0.86; P<0.0001)	Mean BP VAL: 139.3±17.6/79.2±9.8 mm Hg AML: 137.5±15.0/77.7±9.0 mm Hg ↓ from BL VAL 15.2/8.2 vs. AML 17.3/9.9 mm Hg; P<0.0001 VAL: 73.7% on study drug at end; mean dose 151.7mg AML: 74.9%% on study drug at end; mean dose 8.5mg VAL 80mg + HCTZ (2.1%); VAL 160mg + HCTZ (11.1%) AML 5mg + HCTZ (4.3%); AML 10mg + HCTZ (10.5%) AEs: VAL vs. AML: ↓ peripheral edema (14.93% vs.32.9%; P<0.0001); ↑ dizziness 16.5% vs. 14.3%; P<0.0001); ↑ HA (14.7% vs. 12.5%; P<0.0001; also SS ↑ diarrhea, angina, syncope; ↓ hypokalemia
PRoFESS R, DB, PC, MC N=20,332 U.S., Canada, Europe, S. America, Asia, Australia, S. Africa Supported by BI , Bayer Schering Pharma, GSK	Telmisartan (TEL) vs. Placebo (PL) (Pts R to ASA/DP vs. clopidogrel)	**Inclusion: ≥ 55 years, ischemic stroke w/in 90 days (after N=6000, 50 to 54 years, stroke w/in 90 to 120 days) w/ ≥ 2 additional RF** Exclusion: primary hemorrhagic stroke, severe disability post stroke, contraindication to study antiplatelet agent TEL (80mg): N=10,146 PL: N=10,186 Mean age: 66 years Mean F/U: 2.5 years **PEP: Recurrent stroke (any)**	**PEP: TEL 880 (8.7%) vs. PL 934 (9.2%); (HR 0.95, CI 0.86-1.04)** Tx / N / PEP / P TEL / 10146 / 880 (8.7%) / NS PL / 10186 / 934 (9.2%) / Additional outcome measures Major CV events (CV death, MI, recurrent stroke, worsening or new HF): TEL vs. PL (NS) New-onset DM: TEL vs. PL (NS)	Mean BP TEL ↓ 3.8/2.0 mm Hg vs. PL TEL: 68.3% on study drug at 3 years PL: 70.8% on study drug at 3 years Concomitant Rx (TEL vs. PL): Diuretic (22.6% vs. 28.2%); ACEI (28.4% vs. 33.9%); CCB (26.5% vs. 30.9%); BB (22.3% vs. 25.4%) DC due to AE: TEL vs. PL: ↑ total AE (14.3% vs.11.1%; P<0.001); ↑ hypotensive sx (3.9% vs. 1.8%; P<0.001); ↑ syncope (0.2% vs. 0.1%; P=0.004); ↑ diarrhea (0.7% vs. 0.4%; P=0.02); ↑ nausea (1.0% vs. 0.7%; P=0.01); ↑ AF (0.8% vs. 0.5%; P=0.006)

ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; AF=atrial fibrillation; AML=amlodipine; ARR=absolute risk reduction; ASA/DP=aspirin/dipyridamole; BI=Boehringer Ingelheim; BB=beta-blocker; BL=baseline; CABG=coronary artery bypass graft; CCB=calcium channel blocker; CHD=coronary heart disease; CRF=chronic renal failure; CV=cardiovascular; CVD=CV disease; DC=discontinuations; DM=diabetes mellitus; ER=emergency room procedure; GSK=Glaxo Smith Kline; HA=headache; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; LVH=left ventricular hypertrophy; MC=multicenter; MI=myocardial infarction; NNT=number needed to treat; NS=not statistically significant; OR=odds ratio; PAD=peripheral arterial disease; PC=placebo-controlled; PCI=percutaneous coronary intervention, PEP=primary endpoint; PL=placebo; PTCA=percutaneous transluminal coronary angioplasty; R=randomized; RAS=renal artery stenosis; RF=risk factors; SCD=sudden cardiac death; SS=statistically significant; sx=symptoms; TC=total cholesterol; TEL=telmisartan; TIA=transient ischemic attack; TOB=tobacco smoking; TOD=target organ damage; VAL=valsartan

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>E-COST

R, OL, PG, MC

N=2048

Japan</td>
<td>Candesartan (CAN) vs. conventional therapy (CTx)</td>
<td>Inclusion: HTN (BP 140-180/90-110 mm Hg)
Exclusion: DM or FBG > 126 mg/dl or PPG > 200 mg/dl; secondary HTN, MI or stroke w/in 6 months; angina requiring tx w/BB or CCB; HF, LVEF ≤ 40%; condition requiring tx w/AIIRA or ACEI

CAN (2-12mg): n=1053
Initial dose: 4mg (25%); 8mg (69%)
CTx: n=995
Rx titrated to BP < 140/90 mm Hg
ACEI use prohibited

Age: > 65 (CAN 50%; CTx 53%)
Mean F/U: 3.1 years

PEP: Hosp for stroke, hosp for MI, HF hosp</td>
<td>PEP: (Hosp stroke): ↓ w/CAN 47 (5.8%) vs. CTx 77 (9.4%); (RR 0.61, CI 0.41-0.84, P<0.05); ARR: 3.28%; NNT: 31

(Hosp MI): ↓ w/CAN 10 (1.2%) vs. CTx 23 (2.8%); (RR 0.44, CI 0.21-0.84, P<0.05); ARR: 1.6%; NNT: 63

(HF hosp): CAN 35 (4.3%) vs. CTx 41 (5.0%); (RR 0.85, CI 0.57-1.26)

<table>
<tr><th>PEP</th><th>CAN</th><th>CTx</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<tr><td>Stroke</td><td>47 (5.8%)</td><td>77 (9.4%)</td><td><0.05</td><td>3.28%</td><td>31</td></tr>
<tr><td>MI</td><td>10 (1.2%)</td><td>23 (2.8%)</td><td><0.05</td><td>1.6%</td><td>63</td></tr>
<tr><td>HF</td><td>35 (4.3%)</td><td>41 (5.0%)</td><td>NS</td><td>NA</td><td>NA</td></tr>
</table>
Additional outcome measures
Hosp stroke: w/hx CVD: CAN vs. CTx (↓ 61%; P<0.01); w/o hx CVD: CTx vs. CAN (↓ 66%; P<0.05)
Hosp MI: w/hx: CAN vs. CTx (NS); w/o hx: CAN vs. CTx (NS)
Hosp HF: w/hx: CAN vs. CTx (↓ 49%; P<0.05); w/o hx: CAN vs. CTx (NS)</td>
<td><u>Mean BP</u>
CAN 162.1±9.2/91.1±6.1 to 140.1±7.6/78.9±5.4 mm Hg
CTx 165.9±5.8/95.9±5.6 to 138.4±7.9/81.1±7.5 mm Hg
(Difference SBP at study end P<0.001)
Dose CAN: 4mg (24%); 8mg (71%)

<u>Concomitant Tx</u>
CAN: diuretic (5.4%); BB (15.5%); CCB (48.1%); other (7.8%)
CTx: diuretic (3.9%); BB (34.0%); CCB (90.5%); other (16.8%)
77.3% CAN and 81.9% CTx were taking Rx at study end
22.6% CAN and 18.1% CTx dropped out or withdrew</td>
</tr>
<tr>
<td>MOSES

PROBE, MC

N=1405

Germany, Austria

Supported by Solvay Pharmaceut and Aventis Pharma Germany</td>
<td>Eprosartan (EPR) vs. nitrendipine (NIT)</td>
<td>Inclusion: HTN (requiring tx), cerebrovascular event (TIA, ischemic stroke, cerebral hemorrhage) w/in past 24 months
Exclusion: ICA occlusion or stenosis > 70%; HF NYHA III-IV; > 85 years; anticoag for arrhythmia; high grade AV or MV stenosis; unstable angina

EPR (600mg): n=681 (ITT)
NIT (10mg): n=671 (ITT)
Rx titrated or additional tx to BP < 140/90 mm Hg; additional AIIRA, CCB, ACEI avoided

Mean age: 68 years; Mean F/U: 2.5 years

PEP: Composite total death, CV events, cerebrovascular events</td>
<td>PEP: ↓ w/EPR 206 (13.3/100 pt yrs) vs. NIT 255 (16.7/100 pt yrs); (IDR 0.79, CI 0.66-0.96, P=0.014); ARR: 7.75%; NNT: 13

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>ARR</th><th>NNT</th></tr>
<tr><td>EPR</td><td>681</td><td>206 (30.3%)</td><td>7.75%</td><td>13</td></tr>
<tr><td>NIT</td><td>671</td><td>255 (38.0%)</td><td></td><td></td></tr>
</table>
Additional outcome measures
Total mortality: EPR vs. NIT (NS)
CV events: EPR vs. NIT (NS); first occurrence ↓ w/EPR vs. NIT (P=0.03)
Cerebrovascular events: ↓ w/EPR 102 vs. NIT 134 (IDR 0.75 CI 0.58-0.97, P=0.026); first occurrence (NS)</td>
<td><u>Mean BP (NS)</u>
EPR 137.5/80.8 mm Hg
NIT 136.0/80.2 mm Hg

<u>Mean Dose</u>
EPR 623±129.3mg
NIT 16.2±7.9mg
<u>Combination tx</u>
EPR (65.6%); NIT (66.9%); more pts on EPR received CCBs and more pts on NIT received ACEIs

Similar reports of relevant AEs</td>
</tr>
</table>

AE=adverse event; AHR=adjusted hazard ratio; ARR=absolute risk reduction; AV=aortic valve; BB=beta-blocker; CAN=candesartan; CCB=calcium channel blocker; CTx=conventional therapy; CVD=cardiovascular disease; ECG=electrocardiogram; EPR=eprosartan; FBG=fasting blood glucose; hosp=hospitalizations; hx=history; ICA=internal carotid artery; IDR=incidence density ratio; MC=multicenter; MV=mitral valve; NA=not applicable; NIT=nitrendipine; NNT=number needed to treat; NS=not statistically significant; OL=open-label; PEP=primary endpoint; PG=parallel group; PPG=postprandial glucose; PROBE=prospective, randomized, open, blinded endpoint; pts=patients; R=randomized; RRR=relative risk reduction; TIA=transient ischemic attack; tx=treatment

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>ONTARGET

R, DB, MC

N=25,620

U.S., Canada, Europe, S. America, Asia, Australia, S. Africa

Supported by Boehringer Ingelheim, Heart and Stroke Foundation of Canada, Canada Institute of Health Research Award</td>
<td>Telmisartan (TEL) vs. ramipril (RAM) vs. combination (COM)
TEL + RAM</td>
<td>Inclusion: coronary, peripheral, or cerebrovascular disease or DM w/TOD
Exclusion: inability to DC AIIRA, known hypersensitivity or intolerance to AIIRA; HF, valvular or cardiac outflow tract obstruction, constrictive pericarditis, congenital heart disease, unexplained syncope, cardiac surgery or revascularization w/in 3 months, SBP > 160 mm Hg, heart transplantation, subarachnoid hemorrhage, renal artery stenosis, sCr > 265 micromoles/L, proteinuria, hepatic dysfunction

TEL (80mg): N=8542
RAM (10mg): N=8576
COM: N=8502

Mean age: 66 yrs; Median F/U: 4.7 yrs

PEP: Composite CV death, MI, stroke, HF hosp</td>
<td>PEP: TEL 1423 (16.7%) vs. RAM 1412 (16.5%), (RR 1.01 CI 0.94-1.09)
COM 1386 (16.3%) vs. RAM, (RR 0.99, CI 0.92-1.07)

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th></tr>
<tr><td>TEL</td><td>8542</td><td>1423 (16.7%)</td><td>TEL vs. RAM (NS)</td></tr>
<tr><td>RAM</td><td>8576</td><td>1412 (16.5%)</td><td></td></tr>
<tr><td>COM</td><td>8502</td><td>1386 (16.3%)</td><td>COM vs. RAM (NS)</td></tr>
</table>
Additional outcome measures
Death from CV cause, MI, stroke (PEP HOPE):
TEL vs. RAM (NS); COM vs.RAM (NS)
Other secondary endpoints:
new HF, DM, AF, dementia or cognitive decline, revascularization:
TEL vs. RAM (NS); COM vs.RAM (NS)
RI: TEL vs. RAM (NS); ↑ COM 1148 (13.5%) vs. RAM 871 (10.2%), (RR 1.33 CI 1.22-1.44; P<0.001)</td>
<td><u>Mean BP</u>
TEL ↓ 0.9/0.6 mm Hg vs. RAM
COM ↓ 2.4/1.4 mm Hg vs. RAM

TEL: 93.9% on AIIRA at study end
RAM: 84.7% on ACEI at end of study
COM: 73.6% on AIIRA + ACEI at study end
DC: TEL: 21.0%; RAM: 23.7%; COM: 22.7% both
DC due to AE: TEL vs. RAM: ↓ cough (1.1% vs. 4.2%; P<0.001); ↓ angioedema (0.1% vs. 0.3%; P=0.01)
RAM vs. TEL: ↓ hypotensive sx (1.7% vs. 2.7%; P<0.001)
COM vs. RAM: ↑ syncope (0.3% vs. 0.2%; P=0.03); ↑ hypotensive sx (4.8% vs. 1.7%; P<0.001); ↑ diarrhea (0.1% vs.0.5%; P<0.001); ↑ RI (1.1% vs. 0.7%; P<0.001); ↑ K+ > 5.5 mmom/L (5.7% vs. 3.3%; P<0.001)</td>
</tr>
<tr>
<td>TRANSCEND

R, DB, PC, MC

N=5926 parallel trial of ONTARGET in pts intolerant to ACEI

U.S., Canada, Europe, S. America, Asia, Australia, S. Africa

Supported by Boehringer Ingelheim (and as above ONTARGET)</td>
<td>Telmisartan (TEL) vs. Placebo (PL)</td>
<td>Inclusion: coronary, peripheral, or cerebrovascular disease or DM w/end-organ damage; intolerance to ACEI

Exclusion: see ONTARGET above

TEL (80mg): N=2954
PL: N=2972

Mean age: 67 years; Median F/U: 4.7 years

PEP: Composite CV death, MI, stroke, HF hosp</td>
<td>PEP: TEL 465 (15.7%) vs.PL 504 (17.0%), (RR 0.92 CI 0.81-1.05)

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th></tr>
<tr><td>TEL</td><td>2954</td><td>465 (15.7%)</td><td>NS</td></tr>
<tr><td>PL</td><td>2972</td><td>504 (17.0%)</td><td></td></tr>
</table>
Additional outcome measures
Death from CV cause, MI, stroke (PEP HOPE):
↓ TEL 384 (13.0%) vs. PL 440 (14.8%), (RR 0.87 CI 0.76-1.00; P=0.048)
Other secondary endpoints reported:
new DM, AF, revascularization: TEL vs. PL (NS)</td>
<td><u>Mean BP</u>
TEL ↓ 3.2/1.3 mm Hg vs. PL

More pts on PL received diuretics, CCBs, and alpha-blockers vs. TEL

DC: TEL: 36.9%; PL: 38.5%
DC due to AE: TEL vs. PL: ↑ hypotensive sx (0.98% vs. 0.54%; P=0.049)
Angioedema: TEL (n=2, 0.07%); PL (n=3, 0.10%)</td>
</tr>
</table>

AE=adverse event; AF=atrial fibrillation; CCBs=calcium channel blockers; COM=combination telmisartan plus ramipril; CV=cardiovascular; DC=discontinuations; DM=diabetes mellitus; HF=heart failure; hosp=hospitalizations; MC=multicenter; MI=myocardial infarction; NS=not statistically significant; PC=placebo-controlled; PL=placebo; PEP=primary endpoint; pts=patients; R=randomized; RAM=ramipril; RI=renal impairment; RR=relative risk; sx=symptoms; TEL=telmisartan; TOD=target organ damage; tx=treatment; yrs=years

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>ONTARGET (Renal)

R, DB, MC

N=25,620

U.S., Canada, Europe, S. America, Asia, Australia, S. Africa

Supported by Boehringer Ingelheim</td>
<td>Telmisartan (TEL) vs. ramipril (RAM) vs. combination (COM)
TEL + RAM</td>
<td>Inclusion: > 55 years, coronary, peripheral, or cerebrovascular disease or DM w/TOD
Exclusion: major renal artery stenosis, uncorrected volume or sodium depletion, sCr > 265 micromoles/L, SBP > 160 mm Hg or DBP > 100 mm Hg

TEL (80mg): N=8542
RAM (10mg): N=8576
COM: N=8502

Mean age: 66 years
Median F/U: 4.7 years

Pre-specified secondary renal endpoint of ONTARGET: Composite first occurrence dialysis, renal transplant, doubling sCr, or death</td>
<td>Renal endpoint: TEL 1147 (13.4%) vs. RAM 1150 (13.5%), (HR 1.00 CI 0.92-1.09)
↑ w/COM 1233 (14.5%) vs. RAM, (HR 1.09, CI 1.01-1.18; P=0.037)

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARI</th><th>NNH</th></tr>
<tr><td>TEL</td><td>8542</td><td>1147 (13.4%)</td><td>TEL vs. RAM (NS)</td><td></td><td>NA</td></tr>
<tr><td>RAM</td><td>8576</td><td>1150 (13.5%)</td><td></td><td></td><td>NA</td></tr>
<tr><td>COM</td><td>8502</td><td>1233 (14.5%)</td><td>COM vs. RAM (0.037)</td><td>1.1%</td><td>91</td></tr>
</table>

Additional renal outcome measures
Composite total dialysis and doubling sCr: TEL vs. RAM (NS); ↑ COM (2.49%) vs.RAM (2.03%) HR 1.24 CI 1.01-1.51; P=0.038
eGFR decreased less w/RAM vs. TEL (P<0.0001) or vs. COM (P<0.0001)
Increase in UAE rate was less w/TEL vs. RAM (P=0.004) or vs. COM (P=0.001)
Dialysis; doubling sCr; death: TEL vs. RAM (NS); COM vs. RAM (NS)</td>
<td>DC due to hypotensive sx: TEL (N=229); RAM (N=149); COM (406)
DC due to renal abnormalities: TEL (N=68); RAM (N=60); COM (N=94)' COM vs. RAM (P<0.005)</td>
</tr>
</table>

ARI=absolute risk increase; COM=combination telmisartan plus ramipril; DB=double-blind; DC=discontinuations; DM=diabetes mellitus; HR hazard ratio; MC=multicenter; NA=not applicable; NNH=number needed to harm; NS=not statistically significant; R=randomized; RAM=ramipril; sx=symptoms; TEL=telmisartan; TOD=target organ damage

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

Trial	Comparison	Methods	Outcomes	Additional Results
Jikei Heart Study PROBE N=3081 Japan Supported by Novartis Pharma KK	Valsartan (VAL) vs. conventional therapy (CTx)	**Inclusion: HTN, CHD, HF, or combination** Exclusion: ACS or MI w/in 6 months, cerebrovascular event w/in 3 months, sCr > 265 micromoles/L, potassium > 5 mmol/L, AIIRA w/in 4 weeks VAL(40 to 160mg): N=1541 CTx: N=1540 Titrated to BP < 130/80 mm Hg Mean age: 65 years Median F/U: 3.1 years **PEP: Composite CV morbidity and mortality (hosp for stroke/TIA; MI; HF hosp; hosp angina; dissecting AA; doubling sCr; dialysis)**	**PEP: ↓ w/VAL 92 (6.0%) vs. CTx 149 (9.7%); (HR 0.61, CI 0.47-0.79, P=0.0002); ARR: 3.71%; NNT: 27** Tx / N / PEP / P / ARR / NNT VAL / 1541 / 92 (6.0%) / 0.0002 / 3.71% / 27 CTx / 1540 / 149 (9.7%) Additional outcome measures Hosp stroke/TIA: ↓ VAL 29 (1.9%) vs. CTx 48 (3.1%), (HR 0.60 CI 0.38-0.95; P=0.028) Hosp angina: ↓ VAL 19 (1.2%) vs. CTx 53 (3.4%), (HR 0.35 CI 0.20-0.58; P=0.0001) HF hosp: ↓ VAL 19 (1.2%) vs. CTx 36 (2.3%), (HR 0.53 CI 0.31-0.94; P=0.0293) Dissecting AA: ↓ VAL 2 (0.1%) vs. CTx 10 (0.6%), (HR 0.19 CI 0.04-0.88; P=0.034) MI; doubling sCr, dialysis; all-cause mortality: VAL vs. CTx (NS)	Mean BP VAL: 131±12/77±8 mm Hg (↓ 8.2/4.7) CTx: 132±11/78±8 mm Hg (↓ 7.2/3.7) VAL: mean dose 75mg Main added tx in both groups: CCB, ACEI, BB Any AE: VAL (2.7%) vs. CTx (2.3%) Dizziness: VAL (N=9) vs. CTx (N=3)
CASE-J PROBE N=4728 Japan Supported by Takeda	Candesartan (CAN) vs. Amlodipine (AML)	**Inclusion: HTN, high risk (severe HTN w/SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg; type 2 DM; stroke or TIA > 6 months; LVH, angina, or MI > 6 months; proteinuria or sCr ≥ 1.3 mg/dl; or PA arteriosclerotic occlusion)** CAN (4 to 12 mg): N=2354 AML(2.5 to 10 mg): N=2349 Titrated to SBP/DBP targets: < 60 years: < 130/85 mm Hg; 60 to 69 years: < 140/90 mm Hg; 70 to 79 years: < 150/90 mm Hg; ≥ 80 years: < 160/90 mm Hg Mean age: 63.8 years; Median F/U: 3.2 years **PEP: Composite CV morbidity and mortality (sudden death; stroke or TIA; HF, angina, AMI; sCr ≥ 4.0 mg/dl, doubling sCr, ESRD; dissecting AA, PA arteriosclerotic occlusion)**	**PEP: CAN 134 (5.7%) vs. AML 134 (5.7%); (HR 1.01, CI 0.79-1.28)** Tx / N / PEP / P CAN / 2354 / 134 (5.7%) / NS AML / 2349 / 134 (5.7%) Additional outcome measures All-cause death: CAN vs. AML (NS) New-onset DM: ↓ CAN vs. AML (HR 0.64 CI 0.43-0.97; P=0.033)	Mean BP CAN: 136.1±12.9/77.3±9.6 mm Hg AML: 134.4±12.1/76.7±9.3 mm Hg AML vs. CAN: SBP (↓ 1.7 mm Hg; P<0.001); DBP (↓ 0.6 mm Hg; P=0.028) CAN (54.5%) vs. AML (42.7%) were tx w/additional antiHTN medications (P<0.001) DC due to AE: CAN (5.4%) vs. AML (5.8%) Hyperkalemia: CAN (1.0%), AML (0.3%); flushing: CAN (0%), AML (0.2%)

AA=aortic aneurysm; ACEI=angiotensin-converting enzyme inhibitor; ACS=acute coronary syndrome; AMI=acute myocardial infarction; ARR=absolute risk reduction; BB=beta-blocker; CAN=candesartan; CCB=calcium channel blocker; CHD=coronary heart disease; CTx=conventional therapy; CV=cardiovascular; DBP=diastolic blood pressure; DC=discontinued; DM=diabetes mellitus; ESRD=end-stage renal disease; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; MI=myocardial infarction; NNT=number needed to treat; PA=peripheral artery; PEP=primary endpoint; PROBE=prospective, randomized, open, blinded endpoint; SBP=systolic blood pressure; TIA=transient ischemic attack; tx=treated; VAL=valsartan

Appendix B (continued): Hypertension/CV Disease/High CV Risk Outcome Trials with AIIRAs

Trial	Comparison	Methods	Outcomes	Additional Results
KYOTO Heart Study PROBE N=3031 Japan Supported by Kyoto Prefectural University School of Medicine	Valsartan (VAL) vs. conventional therapy (CTx)	**Inclusion: uncontrolled HTN (BP > 140/90 mm Hg) with CAD, PAD, or CV RF** Exclusion: previous tx w/AIIRA, worsening HF, angina, PCI or CABG w/iin 6 months VAL(80 to 160mg): N=1517 CTx: N=1514 Titrated then addition of other classes to BP < 140/90 mm Hg (< 130/80 mm Hg DM or CKD) Mean age: 66 years Median F/U: 3.3 years **PEP: Composite fatal and nonfatal CV events (hosp stroke/TIA; hosp AMI; hosp angina; HF hosp; hosp dissecting AA; lower limb arterial obstruction; ER thrombosis; doubling sCr; dialysis)**	**PEP: ↓ w/VAL 83 (5.5%) vs. CTx 155 (10.2%); (HR 0.55, CI 0.4-0.7, P=0.00001); ARR: 4.77%; NNT: 21** Tx / N / PEP / P / ARR / NNT VAL / 1517 / 83 (5.5%) / 0.00001 / 4.77% / 21 CTx / 1514 / 155 (10.2%) / / / Additional outcome measures Hosp stroke/TIA: ↓ VAL 25 (1.6%) vs. CTx 46 (3.0%), (HR 0.55 CI 0.3-0.9; P=0.0149) Hosp angina: ↓ VAL 22 (1.5%) vs. CTx 44 (2.9%), (HR 0.51 CI 0.3-0.9; P=0.0106) Other components of the PEP (NS) New onset DM: ↓ VAL 58 (5.2%) vs. CTx 86 (7.7%), (HR 0.67 CI 0.5-0.9; P=0.0282)	Mean BP VAL: baseline 157±14/88±11 vs. end 133±14/76±11 mm Hg) CTx: baseline 157±14/88±11 vs. end 133±14/76±10 mm Hg) VAL: mean dose 88mg CTx (month 12): CCB (63%), BB (21%) Any AE (n ≥ 2): VAL (2.7%) vs. CTx (2.6%)
HIJ-CREATE PROBE N=2049 Japan Supported by Japan Research Promotion Society for CV Diseases	Candesartan (CAN) vs. CTx	**Inclusion: Hosp w/CAD (by angiography) and HTN** Exclusion: secondary HTN, AMI w/in 1 week, CVA w/in 3 months, in addition to other major exclusion criteria[74] CAN (4 to 12 mg): N=1024 CTx (could include ACEI): N=1025 Titration and addition to BP < 130/85 mm Hg Mean age: 65 years Median F/U: 4.2 years **PEP: time to first major CV event (MACE; composite CV death, nonfatal MI, unstable angina, HF, stroke, other CV events during hosp)**	**PEP: CAN 264 (25.8%) vs. CTx 288 (28.1%); (HR 0.89, CI 0.76-1.06)** Tx / N / PEP / P CAN / 1024 / 264 (25.8%) / NS CTx / 1025 / 288 (28.1%) / Additional outcome measures All-cause death, components of PEP (NS) New-onset DM: ↓ CAN vs. CTx (HR 0.37 CI 0.16-0.89; P=0.027)	Mean BP CAN: 135.0/76 mm Hg (↓ 4.3/2.7 mm Hg) CTx: 135.5/75.8 mm Hg (↓ 3.3/1.1 mm Hg) CAN vs. CTx (NS) Baseline(prior to hosp discharge) CAN: ACEI (0.8%), CCB (44.6%), BB (45.3%), diuretic (10.1%) CTx: ACEI (70.5%), CCB (56.0%), BB (49.4%), diuretics (8.0%) End of Study CAN: 73.9% on < 8 mg; 2.5% on ACEI CTx: 23.0% on ACEI DC due to AE: CAN (5.7%) vs. CTx (12.2%); P<0.001 Cough: CAN (3.1%) vs. CTx (16.2%); P<0.001 Anemia: CAN (0.7%) vs. CTx (2.6%); P<0.001 Hyperkalemia: CAN vs. CTx (NS) Dizziness: CAN vs. CTx (NS)

AA=aortic aneurysm; ACEI=angiotensin-converting enzyme inhibitor; AMI=acute myocardial infarction; ARR=absolute risk reduction; BB=beta-blocker; BP=blood pressure; CABG=coronary artery bypass graft; CAD=coronary artery disease; CAN=candesartan; CCB=calcium channel blocker; CTx=conventional therapy; CV=cardiovascular; DC=discontinued; DM=diabetes mellitus; ER=emergency; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; MI=myocardial infarction; NNT=number needed to treat; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; PEP=primary endpoint; PROBE=prospective, randomized, open, blinded endpoint; TIA=transient ischemic attack; tx=treated; VAL=valsartan

Appendix C: Heart Failure Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>VALHefFT[30]

R, D B, PC, MC

N=5010

Supported by Novartis</td>
<td>Valsartan (VAL) + standard care vs. Placebo (PL)+ standard care

Standard care could include ACEI, diuretics, digoxin and beta blockers</td>
<td>5010 pts; mean age 62 yrs
LVEF <40%
Mean duration 23 months

VAL dose: initial was40 mg twice daily titrated to 160 mg twice daily
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)</td>
<td>
<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<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>PL</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>PL</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>2511</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>PL</td><td>2488</td><td>455 (18.2%)</td></tr>
</table>
</td>
<td>All-cause mortality(NS)
VAL was sig better than placebo in the combined endpoint
Benefit of VAL 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 AIIRA 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</td>
</tr>
<tr>
<td>HEAAL[93]

R, DB, MC

N=3846

Supported by Merck</td>
<td>Losartan (LOS) 150 mg vs. LOS 50 mg</td>
<td>Inclusion: > 18 years, NYHA class II-IV HF, LVEF <u><</u> 40% on stable CV tx <u>></u> 2 weeks, ACEI intolerance

Exclusion: pregnancy or lactation; AIIRA intolerance; SBP < 90 mm Hg; sig stenotic valvular heart disease; active myocarditis; active pericarditis; scheduled heart transplant w/in 6 months; coronary angioplasty, CABG, AMI, unstable angina, CVA, or TIA w/in previous 12 wks; renal artery stenosis; sCr > 220 micromol/L; potassium < 3.5 mmol/L or > 5.7 mmol/L; liver enzymes > 3 X normal; Hgb < 6.2 mmol/L

LOS 150 mg: N=1921
LOS 50 mg: N=1913
<u>LOS titration</u>
Previous AIIRA: 25 mg X 1 wk then 50 mg (titrated to 150 mg over 3 wks if 150 mg tx group)
No previous AIIRA: 12.5 mg to 25 mg over 2 wks; then 50 mg (or titration to 150 mg)

Mean age: 66 years; Median F/U: 4.7 years

PEP: Composite death or HF hosp</td>
<td>PEP: LOS 150 mg 828 (43.0%) vs. LOS 50 mg 889 (46.3%); (HR 0.90, CI 0.82-0.99)

<table>
<tr><th>LOS</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<tr><td>150 mg</td><td>1921</td><td>828 (43.0%)</td><td rowspan="2">0.027</td><td rowspan="2">3.4%</td><td rowspan="2">30</td></tr>
<tr><td>50 mg</td><td>1913</td><td>889 (46.3%)</td></tr>
</table>
</td>
<td>All-cause mortality (NS)
HF hosp: ↓ LOS 150 mg vs. 50 mg (HR 0.87 CI 0.76-0.98; P=0.025)

<u>Baseline Medications</u>
LOS 150 mg vs. 50 mg: BB (both 72%), diuretics (77% vs. 76%); cardiac glycosides (both 42%), aldosterone blockers (both 38%)

<u>Mean Dose</u>
LOS 150 mg: 129<u>+</u>39 mg
LOS 50 mg: 46<u>+</u>11 mg

<u>Adverse Events (LOS 150 mg vs. 50 mg)</u>
Potassium
Mean ↑ (12 months): 0.02 vs. 0.01 mmol/L; P=0.03
<u>></u> 6.0 mmol/L: 20 vs. 14; 1% each; NS
Hyperkalemia or ↑ potassium: 195 vs. 131; P=0.0004
Kidney function
Change in eGFR (12 months): ↓ 6.1vs. ↓ 1.9 ml/min/1.73 m^2; P<0.0001
RI or ↑ sCr: 454 vs. 317; P<0.0001
Blood Pressure
Mean change SBP/DBP (6 months):↓ 2.2/2.1 mm Hg vs. 0.8/0.9 mm Hg; SBP P=0.008, DBP P<0.0001
Angioedema: 6 vs. 0; P=0.03
DC due to AE: 148 vs. 133; P=0.44</td>
</tr>
</table>

ACEI=angiotensin-converting enzyme inhibitor; AIIRA=angiotensin II receptor antagonist; AMI=acute myocardial infarction; ARR=absolute risk reduction; BB=beta-blockers; BP=blood pressure; CABG=coronary artery bypass graft; CV=cardiovascular; CVA=cerebrovascular accident; DB=double-blind; DBP=diastolic blood pressure; dig=digoxin; eGFR=estimated glomerular filtration rate; F/U=follow-up; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; LOS=losartan; LVEF= left ventricular ejection fraction; NNT=number needed to treat; NS=no significant difference; PL=placebo; PC=placebo-controlled; PEP=primary endpoint; R=randomized; RI=renal insufficiency; SBP=systolic blood pressure; sCr=serum creatinine; Sig=significant; TIA=transient ischemic attack; Tx=treatment

Appendix C (continued): Heart Failure Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>CHARM Overall[39]

R, DB, PC, PG, MC

N=7601

Supported by AstraZeneca</td>
<td>Candesartan (CAN) vs. placebo (PL)</td>
<td>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
CAN (mean 24mg at 6 months)
41% ACEI, 55% BB, 83% diuretics, 43% dig, 17% SPL

PEP: all-cause mortality</td>
<td>
<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<tr><td>CAN</td><td>3803</td><td>886 (23%)</td><td>0.055</td><td>1.6%</td><td>63</td></tr>
<tr><td>PL</td><td>3796</td><td>945 (25%)</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>CAN 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%</td>
</tr>
<tr>
<td>CHARM Alternative[40]

R, DB, PC

N=2028

Supported by AstraZeneca</td>
<td>CAN vs. PL</td>
<td>2028 pts; mean age 66yrs
NYHA class: 48% II, 48% III, 4% IV
Mean EF: 30%
F/U: median 33.7 months
CAN (mean 23mg at 6 months)
55% BB (64% at 6 months), 85% diuretics, 45% dig, 25% SPL

PEP: CV death or HF hosp</td>
<td>
<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<tr><td>CAN</td><td>1013</td><td>334 (33%)</td><td>0.0004</td><td>7.0%</td><td>14</td></tr>
<tr><td>PL</td><td>1015</td><td>406 (40%)</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>CAN DC'd in 24%
3 pts w/angioedema (previous angioedema w/ACEI)
59% at target dose (32mg) at 6 months</td>
</tr>
<tr>
<td>CHARM Added[41]

R, DB, PC

N=2548

Supported by AstraZeneca</td>
<td>CAN vs. PL</td>
<td>2548 pts; mean age 64yrs
NYHA class: 24% II, 73% III, 3% IV
Mean EF: 28%
F/U: median 41 months
CAN (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</td>
<td>
<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>ARR</th><th>NNT</th></tr>
<tr><td>CAN</td><td>1276</td><td>483 (38%)</td><td>0.011</td><td>4.4%</td><td>23</td></tr>
<tr><td>PL</td><td>1272</td><td>538 (42%)</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>CAN 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</td>
</tr>
</table>

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

Appendix C (continued): Heart Failure Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Outcomes</th><th>Additional Results</th></tr>
<tr>
<td>CHARM Preserved[42]

R, DB, PC

N=3023

Supported by AstraZeneca</td>
<td>CAN vs. PL</td>
<td>3023 pts; mean age 67 yrs
NYHA class: 61% II, 37% III, 2% IV
EF >40%
F/U: mean 36.6 months
CAN (mean 25mg at 6 months)
20% ACEI, 56% BB, 75% diuretics, 29% dig, 11% SPL, 31% CCB

PEP: CV death or HF hosp</td>
<td><table><tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th></tr><tr><td>CAN</td><td>1514</td><td>333 (22%)</td><td>NS</td></tr><tr><td>PL</td><td>1509</td><td>366 (24%)</td><td></td></tr></table></td>
<td>CAN DC'd in 22%
67% at target dose (32mg) at 6 months</td>
</tr>
<tr>
<td>I-PRESERVE

R, DB, PC, MC

N=4128

U.S., Canada, Europe, S. America, Australia, S. Africa

Supported by Bristol-Myers Squibb and Sanofi Aventis</td>
<td>Irbesartan (IRB) vs. Placebo (PL)</td>
<td>Inclusion: ≥ 60 years, NYHA II, III, or IV HF, EF ≥ 45%

Exclusion: AIIRA intolerance; alternate cause for HF sx; hx EF < 40%; ACS, coronary revascularization, or stroke w/in 3 months; valvular disease; CM; pericardial disease; cor pulmonale or right HF; SBP < 100 or > 160 mm Hg; DBP > 95 mm Hg; disease w/life expectancy < 3 years; lab abnormalities (e.g., sCr > 2.5 mg/dL)

IRB (300mg): N=2067
PL: N=2061

Mean age: 72 years
Mean F/U: 4.125 years

PEP: Composite all-cause death or CV hosp (HF, MI, unstable angina, arrhythmia, stroke)</td>
<td>PEP: IRB 742 (36%) vs. PL 763 (37%); (HR 0.95, CI 0.86-1.05)

<table><tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th></tr><tr><td>IRB</td><td>2067</td><td>742 (36%)</td><td>NS</td></tr><tr><td>PL</td><td>2061</td><td>763 (37%)</td><td></td></tr></table>
Additional outcome measures
All-cause death; HF death or hosp; CV death, nonfatal MI, or stroke; CV death; CV hosp; Hosp worsening HF; All-cause hosp; QOL: IRB vs. PL (NS)</td>
<td>IRB: mean dose 275mg
Concomitant tx IRB vs. PL: ACEI (39% vs. 40%); SPL (28% vs. 29%); BB (both 73%)

DC: IRB 34% vs. PL 33% at study end</td>
</tr>
</table>

ACEI=angiotensin-converting enzyme inhibitor; AIIRA=angiotensin II receptor antagonist; ACS=acute coronary syndrome; BB=beta-blockers; CAN=candesartan; CCB=calcium channel blocker; CM=cardiomyopathy; CV=cardiovascular; DB=double-blind; DC=discontinued; dig=digoxin; EF=ejection fraction; F/U=follow-up; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; hx=history; IRB = irbesartan; MC=multicenter; MI=myocardial infarction; NS=not statistically significant; PL=placebo; PC=placebo-controlled; PEP=primary endpoint; QOL=quality of life; R=randomized; SPL=spironolactone; sx=symptoms; tx=treatment

Appendix D: Acute Myocardial Infarction Outcome Trials with AIIRAs

<table>
<tr><th>Trial</th><th>Comparison</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>VALIANT

R, DB, AC, PG

N=14,808

Supported by Novartis</td>
<td>Valsartan (VAL) vs. Captopril (CAP) vs. VAL + CAP

VAL: dose titrated to 160 mg twice daily

VAL + CAP: VAL dose titrated to 80 mg twice daily; CAP titrated to 50 mg three times daily

CAP: dose titrated to 50 mg three times daily</td>
<td>14,808 patients hospitalized with acute MI who were at high risk (LV systolic dysfunction and/or signs of HF, including rales/dyspnea)

LVSD was defined as an EF <35% via echo

Randomization occurred within 12 hours to 10 days post-MI.

Other ACEs or ARBs were DC'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

Mean duration: 24.7 months

Mean age: 64.8 years; 69.9% male; 93.5% Caucasian

PEP: all-cause mortality</td>
<td>PEP: VAL 979 (19.0%); CAP 958 (19.5%); VAL + CAP 941 (19.3%)

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P value (vs. CAP)</th><th>ARR</th><th>NNT</th></tr>
<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>
</table>

Since VAL was not superior to CAP, a non-inferiority analysis was done which showed VAL to be noninferior to CAP

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 CAP alone (P=0.41).

Mean blood pressure at 1 yr:
VAL 127/75 mmHg
CAP 127/76 mmHg
VAL + CAP 125/75 mmHg</td>
<td>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

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.

Val-HeFT and CHARM-added were conducted in chronic heart failure patients, a different patient population (↓ LVEF, dyspnea, ankle edema, fatigue) than VALIANT.

Mean doses:
CAP: 117 mg; VAL: 247 mg; VAL+CAP: 116 mg valsartan and 107 mg captopril.

Target doses were reached in approximately 55% of patients in the monotherapy groups, but 47% in the combination group.

DC due to AE: CAP:7.7%; VAL: 5.8% (P<0.05 vs. CAP); CAP+VAL 9% (P<0.05 vs. CAP)
Hypotension and renal dysfunction were the most common AEs in the VAL group; cough, rash and taste disturbance were the most common AEs in the CAP group.</td>
</tr>
<tr>
<td>OPTIMAAL

DB, R, PG (European study)

N=5477

Supported by Merck and Co.</td>
<td>Losartan (LOS) target dose 50 mg once daily vs.
Captopril (CAP) target dose 50 mg three times daily</td>
<td>5477 patients ≥50 years

Confirmed acute MI and signs/symptoms of HF during the acute phase or a new Q-wave anterior MI or reinfarction

Mean follow-up: 2.7 yrs

Mean age: 67 years; 70% male; 98% Caucasian

PEP: all-cause mortality</td>
<td>PEP: LOS 499 (18%) vs. CAP 447 (16%); (RR 1.13 (95% CI 0.99-1.28; P=0.07)

<table>
<tr><th>Tx</th><th>N</th><th>PEP</th><th>P</th><th>RRI</th><th>NNH</th></tr>
<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">NS</td></tr>
<tr><td>CAP</td><td>2733</td><td>447 (16%)</td></tr>
</table>

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).

For the non-primary endpoint of CV death, captopril had significantly fewer CV deaths than losartan (CAP 363 (13.3%) vs. LOS 420 (15.3%), RR 1.17 (1.01-1.34; P=0.03).</td>
<td>LOS did not satisfy criteria for non-inferiority, since the RR exceeded the pre-set boundary of 1.10.

Fewer LOS patients DC'd therapy due to AEs compared to CAP (LOS 202 (7%) vs. CAP 387 (14%); P<0.0001

At study end, 83% of LOS reached target dose; 81% of CAP reached target dose
Mean LOS dose: 45 mg once daily
Mean CAP dose: 44 mg three times daily

Author conclusion: losartan did not show superiority or non-inferiority relative to captopril.</td>
</tr>
</table>

ARR=absolute risk reduction; CAP=captopril; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; LOS=losartan; MI=myocardial infarction; NNH=number needed to harm; NNT=number needed to treat; NS=not statistically significant; PG=parallel group, PEP=primary endpoint; R=randomized; RR=relative risk; RRI=relative risk increase; VAL=valsartan

Appendix E: Diabetic Nephropathy Outcome Trials with AIIRAs

Trial	Comparison	Methods	Outcomes	Additional Results
IRMA 2 R, DB, PC N=590 Supported by BMS and Sanofi-Synthelabo	IRB 300mg vs. IRB 150mg vs. PL	**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%) NNT for PEP: 10 IRB 300mg; 19 IRB 150mg	Secondary Endpoints UAE rate 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 Average trough BP IRB 300mg 141/83 mm Hg IRB 150mg 143/83 mm Hg PL 144/83 mm Hg (P=0.004 vs. IRB)
IDNT R, DB, PC N=1715 Supported by BMS and Sanofi-Synthelabo	IRB 300mg vs. AML 10mg vs. PL	**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% NNT for PEP: 16 IRB 300mg	Secondary Endpoints Doubling sCr IRB ↓ 33% vs. PL (P=0.003) IRB ↓ 36% vs. AML (P<0.001) ESRD IRB ↓ 23% vs. PL and AML (P=0.07) Death from any cause IRB ↓ 8% vs. PL; AML ↓ 12% vs. PL Not stat sig between groups BP: not stat sig IRB vs. AML
RENAAL R, DB, PC N=1513 Supported by Merck and Co.	LOS 50-100mg vs. PL	**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% NNT for PEP: 28 LOS 50-100mg	Secondary Endpoints CV morbidity and mortality LOS ↓ 10% vs. PL (P=0.26) UAC ratio LOS ↓ 35% (P<0.001) Rate of decline in renal function LOS ↓ 18% vs. PL (P=0.01) Doubling sCr LOS ↓ 25% vs. PL (P=0.006) ESRD: 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; 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

Appendix F: Summary Results of Primary Endpoints of AIIRA Outcome Trials [Level of Evidence]

AIIRA	HTN	CV Disease/High CV Risk	Hx Cerebrovascular Event	Recent MI w/HF/LVD	HF	Type 2 Diabetic Nephropathy
Candesartan	[Fair] No difference major CV events (vs. placebo + open-label antiHTN tx) [Fair] ↓ hosp stroke, ↓ hosp MI, no difference HF hosp (vs. conventional tx)	[Fair] No difference fatal or nonfatal CV events (vs. DHP CCB) [Fair] No difference major adverse CV events [vs. conventional tx)			[Good] ↓ CV death and HF hosp (in addition to standard therapy; and in patients ACEI intolerant)	
Eprosartan			[Fair] ↓ combined death, cerebrovascular and CV events (vs. DHP CCB)			
Irbesartan						[Good] ↓ composite doubling sCr, ESRD, all-cause mortality (vs. placebo and vs. DHP CCB)
Losartan		[Good] ↓ composite CV death, MI, stroke (vs. beta-blocker)		[Good] No difference (not superior or noninferior) in all-cause mortality (vs. ACEI)	[Good] No difference (not superior) in mortality or CV endpoints (vs. ACEI) [Good] ↓death and HF hosp (150 mg vs. 50 mg)	[Good] ↓ composite doubling sCr, ESRD, all-cause mortality (vs. placebo)
Olmesartan						
Telmisartan		[Good] Composite CV death, MI, stroke, HF hosp similar (noninferior) vs. ACEI (and w/AIIRA + ACEI vs. ACEI) [Good] No difference composite CV death, MI, stroke, HF hosp (vs. placebo) (ACEI intolerant)	[Good] No difference recurrent stroke (vs. placebo)			
Valsartan		[Good] No difference (not superior) CV morbidity and mortality (vs. DHP CCB) [Fair; 2 trials] ↓ CV morbidity and mortality (vs. conventional therapy)		[Good] Total mortality similar (noninferior) vs. ACEI	[Good] ↓ combined morbidity and mortality (in addition to standard therapy)	