Oregon Health Resources Commission

Angiotensin II Receptor Antagonists (AIIRA)

Subcommittee Report

March 2006

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

In the winter of 2003 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Angiotensin II Receptor Antagonists (AIIRA), formerly AIIRA, drugs. Members of the subcommittee consisted of physicians, a pharmacist, an adult Nurse Practitioner, a PhD, and other health care professionals. The subcommittee had three meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the Southern California Evidence-based Practice Center (RAND) reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The RAND EPC's report, "Drug Class Review on Angiotensin II Receptor Antagonists" was completed in September 2004, circulated to subcommittee members and posted on the web. The subcommittee met on September 20, 2004 to review the document and by consensus agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. The subcommittee's final meeting was held on November 2, 2004. All available sources of information including the RAND EPC report, information submitted by pharmaceutical manufacturers, and public testimony were considered. The conclusions drawn by the AIIRA Subcommittee comprise the body of this report.

The RAND EPC's report, "Drug Class Review on Angiotensin II Receptor Antagonists update 1" was completed in September 2005, circulated to Standing Update Committee members and posted on the web. The Standing Update Committee met on March 7, 2006 to review the document and by consensus agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. All available sources of information including the RAND EPC report, information submitted by pharmaceutical manufacturers, and public testimony were

considered. The conclusions drawn by the Standing Update Committee comprise the body of this report.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the RAND EPC, the AIIRA Subcommittee, the Standing Update Committee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the Health Resources Commission in providing recommendations to the Department of Human Services.

The Standing Update Committee of the Health Resources Commission, working together with the EPCs, Center, OMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. At least once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The AIIRA report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or involve at least two members of the original AIIRA subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on Angiotensin II Receptor Antagonists update #1*, is available on the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: www.ohpr.state.or.us. You may request more information including copies of the draft report, minutes and tapes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents both from the Office of Oregon Health Policy & Research and from the Center.

Critical Policy:

- *Senate Bill 819*
  - "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."
- *Health Resources Commission*
  - "Clinical outcomes are the most important indicators of comparative effectiveness";
  - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Definition of Angiotensin II Receptor Antagonists (AIIRA)

The AIIRAs, also referred to as angiotensin receptor blockers (ARBs) selectively inhibit angiotensin II from activating the angiotensin type 1 receptor (AT_1). This action blocks the vasoconstriction, sodium and water retention, activation of the sympathetic nervous system, constriction of efferent arterioles in the kidney, and stimulation of vascular and myocardial fibrosis, that are all mediated by the activation of AT_1 receptors.

The first agent in this class to be approved by the US Food and Drug Administration (FDA) for the treatment of hypertension was losartan in 1995. All the AIIRAs are effective in lowering blood pressure and are approved by the FDA for the treatment of hypertension. This review covers the seven AIIRAs currently marketed in the United States:

- ***AIIRA Drugs:***

Generic	Brand(s)
-Candesartan	-Atacand
-Eprosartan	-Tevetan
-Irbesartan	-Avapro
-Losartan	-Cozaar
-Olmesartan	-Benicar
-Telmisartan	-Micardis
-Valsartan	-Diovan

Quality of the Evidence

For quality of evidence the Standing Update Committee took into account the number of studies, the total number of patients in each study, the length of the study period, and the end points of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency and power of the body of evidence relevant to that question.

The Standing Update Committee's task was to identify AIIRAs that would offer the greatest likelihood of success for the treatment of hypertension, especially with high cardiovascular

risk, recent MI, and/or heart failure (HF). Additionally, it was their task to identify AIIRAs that are used to treat nephropathy.

While all of these agents have demonstrated efficacy in the management of hypertension, some have demonstrated additional benefits independent of blood pressure lowering such as end-organ protection and have obtained FDA approval for these conditions. (See Table 1.)

Table 1

FDA Approved Indications for AIIRAs

AIIRA	HTN	HTN/LVH*	HF**	POST MI***	DIABETES NEPHROPATHY****
Candesartan	X		X		
Eprosartan	X				
Irbesartan	X				X
Losartan	X	X			X
Olmesartan	X				
Telmisartan	X				
Valsartan	X		X	X	

* Reduction in the risk of stroke in patients with HTN and LVH (the manufacturer's product information also states that there is evidence that this benefit does not apply to black patients.)

** Candesartan : Treatment of HF (NYHA Class II-IV) in patients with left ventricular systolic dysfunction (EF ≤40%) to reduce CV death and to reduce HF hospitalizations; candesartan has an additive effect on those outcomes in patients already taking an ACEI. Valsartan: Treatment of HF (NYHA class II-IV). HF hospitalizations were significantly reduced with valsartan. Manufacturer's production information states that there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACEI.

*** Demonstrated reduced CV mortality in clinically stable patients with LV failure or LV dysfunction following MI

**** Treatment of diabetic nephropathy with an elevated Cr. and proteinuria (≥300 mg/day for irbesartan; urninary albumin to Cr ratio ≥ 300 mg/day for irbesartan; urinary albuin to Cr ration ≥ 300 mg/g for losartan) in patients with type 2 DM and HTN

Scope and Key Questions

1. For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, heart failure, or nephropathy, do AIIRAs differ in efficacy as seen in results from head-to head trials, active controlled trials, placebo-controlled trials or systematic reviews?

   The selected indications/patient populations are further defined with the outcomes of interest listed below:

   a. Essential hypertension (>140/90 mmHg) with and without compelling indications: history of coronary heart disease (CHD); other cardiovascular diseases (CVD), such as cerebrovascular (carotid)

disease, peripheral vascular disease, or a history of stroke; other risk factors for CAD/CVD, such as diabetes, smoking or hyperlipidemia; or renal insufficiency. The outcomes of interest for this indication are:

i. All-cause and cardiovascular mortality
ii. Cardiovascular (CV) events (stroke, MI, or development of HF)
iii. End-stage renal disease (including dialysis or need for transplantation) or clinically significant or permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance.)

b. High cardiovascular risk. This group includes patients who have a history of CHD/CVD, or a combination of other risk factors for CHD/CVD, such as diabetes, smoking, microalbuminuria, left ventricular hypertrophy and hyperlipidemia. These patients may or may not have hypertension as well. The outcomes of interest for this indication are:
    i. All-cause and cardiovascular mortality
    ii. Cardiovascular events (stroke, MI, or development of HF)
    iii. Quality of life.

c. Recent myocardial infarction. This group includes patients who have had a recent myocardial infarction and who have normal left ventricular function or asymptomatic left ventricular dysfunction. The outcomes of interest for this indication are:
    i. All-cause and cardiovascular mortality
    ii. Cardiovascular events (stroke, MI, or development of HF)
    iii. Quality of life.

d. Heart failure including patients who have symptomatic heart failure due to left ventricular systolic dysfunction (LV ejection fraction < 45%), with or without hypertension; or with sustained left ventricular function (LV ejection fraction > 45%), with or without hypertension. The outcomes of interest for this indication are:
    i. All-cause and cardiovascular mortality
    ii. Symptomatic improvement (heart failure class, functional status, visual analogue scores, exercise intolerance)
    iii. Hospitalizations for HF
    iv. Quality of life

e. Nephropathy including patients who have laboratory evidence of nephropathy, such as albuminuria or decreased creatinine clearance due to diabetes or non-diabetic causes. The outcomes of interest for this indication are:
    i. End-stage renal disease (including dialysis or need for transplantation)

ii. Clinically significant or permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)
iii. Quality of life

2. For adult patients with essential hypertension, high cardiovascular risk factors, recent MI, HF, diabetic or non-diabetic nephropathy, do AIIRAs differ in safety or adverse events? The outcomes of interest with regard to safety include:
    a) Overall adverse effect reports
    b) Withdrawals due to adverse effects
    c) Serious adverse events reported (including mortality)
    d) Specific adverse effects or withdrawals due to specific adverse events (e.g., renal impairment, cough, and angioedema)
    e) Specific adverse effects or withdrawals due to specific adverse events, for example, renal impairment, cough, and angioedema

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one angiotensin receptor blocker is more effective or associated with fewer adverse events, e.g. renal insufficiency? Evidence unique to minority and ethnic groups are of particular interest.

New Findings March 2006

- Using the same search strategy up to June 2005 as was used in the original AIIRAs, the EPC found 684 new citations since the original report. Of these, only 27 new articles met inclusion criteria - 7 active-controlled trials, 14 placebo-controlled trials, 3 sub-group analyses of previously reviewed trials, 1 systematic review and 2 observational studies were also included.
- There were still no head-to-head trials of AIIRA drugs.
- The FDA has revised it's labeling of existing AIIRAs since the original report:
    - Atacand (candesartan) has been approved for its use for the treatment of heart failure (NYHA Class II-IV and EF ≤40%) to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for HF. Atacand also has an added effect on these outcomes when used with an ACEI.
    - Cozaar (losartan) added under **ADVERSE REACTIONS** *Post-Marketing Experience*
      Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving AIIRA blockers.
    - Benicar (olmesartan) added under **ADVERSE REACTIONS** *Post-Marketing experiences*

Musculoskeletal: Rare cases of angioedema and rhabdomyolysis have been reported in patients receiving olmesartan.

- Micardis (telemisartan) added under **Special Populations,** *Renal Insufficiency:* No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration.
- Diovan (valsartan) added this drug may be used in the treatment of patients' post-myocardial infarction in clinically stable patients with LVF or LVD following MI to reduce cardiovascular mortality.

Amended Summary of Results

Key Question 1a. For adult patients with essential hypertension, do AIIRAs differ in efficacy?

There were no head-to-head that addressed the specified outcomes comparing the effects of AIIRAs on all-cause or CV mortality, or CV events. One placebo controlled trial of fair quality found all-cause mortality, CV mortality, or the primary endpoint of first major CV event to be not statistically significant with candesartan when compared to control. Only non-fatal stroke was decreased significantly with candesartan. (relative risk reduction 27.8%, P=0.04 or 2.8% candesartan vs. 3.8% placebo.) None of the trials were designed to compare one AIIRA to another. As a group, these studies do not provide useful information to compare the effectiveness of different AIIRAs in patients who have high blood pressure and no other compelling indications.

Six active controlled trials of fair quality evaluated an AIIRA for QOL and reported: losartan improved quality of life compared to baseline and active control; candesartan in patients with previous ACEI-induced cough showed significant improvement in contentment compared to placebo, but not compared to treatment with an ACEI; losartan compared to enalapril showed decreased bother due to cough; but no significant differences in quality of life were seen with eprosartan monotherapy compared to enalapril or placebo. The interpretation of active-controlled trials and sub-analysis of one placebo-controlled trial is limited by the use of different QOL scales and comparator agents.

The Standing Update Committee agreed by consensus that in patients with essential hypertension there are no data to suggest that one AIIRA is superior to another.

Key Question 1b. For patients with high cardiovascular risk factors do AIIRAs differ in efficacy?

There were no head-to-head or placebo-controlled trials that evaluated the effects of an AIIRA on all-cause or CV mortality, or CV events in patients with high CV risk.

The only available randomized active-controlled trial Losartan Intervention for Endpoint reduction **(LIFE**) showed that treatment with losartan reduced CV morbidity and mortality (primary composite endpoint) compared with atenolol in patients with high CV risk (11% losartan vs. 13% atenolol). The benefit was largely due to the reduction in stroke (losartan 5% vs. 7%).

In the substudy of patients without vascular disease, losartan reduced the primary composite endpoint of CV morbidity and mortality as well as stroke (HR 0.18, p=0.008). In the substudy of patients with isolated systolic hypertension (ISH), losartan reduced all cause mortality (HR 0.72, p=0.05) but failed to significantly reduce the primary composite endpoint of CV morbidity CV mortality, and stroke compared to atenolol. In the sub-study of patients with diabetes, losartan reduced the primary composite endpoint of CV morbidity and mortality, CV mortality, and HF hospitalizations compared to atenolol (HR 0.77, P=0.031); as well as mortality (HR 0.62, P=0.002).

One active-controlled trial **MOSES**[1] compared morbidity and mortality in treatment with eprosartan treatment and dihydropyridine calcium channel blockers. The combined primary endpoint of all-cause mortality, and cardiovascular and cerebrovascular events in patients with HTN and a history of cerebrovascular events compared to control therapy. The combined primary endpoint was significantly reduced with eprosartan compared to nitrendipine, with an incidence density per 100 person years (ID) of 13.25% vs. 16.71% respectively; and an ID ratio of 0.79 (95% CI 0.66-0.96; P=0.014). The individual components of the primary endpoint were also significantly reduced with eprosartan for fatal and nonfatal cerebrovascular events (IDR 0.75 95% CI 0,55-0.97; P=0.025), but were not significant for fatal and non-fatal cardiovascular events. The reduction in BP was similar between the treatment groups.

The **VALUE** trial[2] evaluated treatment with valsartan compared to the dihydropyridine calcium channel blocker amlodipine on reducing cardiac morbidity and mortality in patients with HTN and high cardiovascular risk. This large,

[1] Schrader J, Luders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principle results of a prospective randomized controlled study (MOSES); *Stroke*2005;36(6):2328-26.

[2] Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regiments based on valsartan or amlopdipine: the VALUE randomized trial. *Lancet* 2004;363(9426):2022-31

multicenter, randomized, double-blind, active-controlled, parallel-group study of good quality enrolled 15245 patients with treated or untreated HTN and at high risk for cardiac events with a mean follow-up of 4.2 years. Patients were upwardly titrated; if needed HCTZ was added to achieve a target BP <140/90.

There failed to be a statistically significant difference in all-cause mortality in patients treated with valsartan compared to amlodipine (11.0% vs. 10.8%; HR 1.04 95% CI 0.94-1.14; P=0.45%.) Cardiac mortality was similar (i.e. 4% each) with fatal and not fatal HF non-significant; fatal and non-fatal stroke non-significant; but fatal and non-fatal MI reached significance (4.8% vs. 4.1%, adjusted HR 1.19 95% CI 1.02-1.38, P=0.02.)

Quality of life with the AIIRAs was not assessed in these trials with high CV risk factors.

The Standing Update Committee agrees by consensus that in patients with high cardiovascular risk there is no comparative data to suggest that one AIIRA is superior to another.

Key Question 1c. For patients with recent myocardial infarction do AIIRAs differ in efficacy?

In patients who have had a recent MI, AIIRAs are given to prevent the development or progression of heart failure and to reduce mortality irrespective of the presence of heart failure. No head-to-head or placebo-controlled trials evaluated the effects of an AIIRA on all-cause or CV mortality, or CV events.

There is insufficient evidence from active-controlled trials to determine whether valsartan or losartan are equivalent or superior to one another for this indication. In one multicenter, randomized, active-controlled trial of good quality (**VALIANT**), valsartan was shown to be as effective as captopril in reducing all-cause mortality, CV mortality, and CV events in patients with recent MI and at high risk for further coronary events (P=0.004).

Another multicenter, randomized, active-controlled trial of good quality (**OPTIMAAL**) failed to show that losartan was equivalent or superior to captopril in reducing all-cause mortality in patients with recent MI and signs or symptoms of HF. The quality of life results with AIIRAs from these trials were not reported.

The Standing Update Committee agrees by consensus that in patients with recent MI there is no comparative data to suggest that one AIIRA is superior to another.

Key Question 1d. For patients with HF do AIIRAs differ in efficacy?

There were no head-to-head trials to compare all-cause mortality, CV endpoints, HF hospitalizations, symptomatic improvement, or quality of life among the AIIRAs in patients with HF.

There is good evidence that candesartan and valsartan are beneficial in patients with HF who are unable to tolerate therapy with an ACEI. In a placebo controlled trial of good quality, treatment with candesartan **(CHARM)** reduced CV death or HF hospitalizations in patients, where it was added to standard therapy and in patients intolerant to an ACEI, but not in patients with LVEF>40%. In another good quality placebo-controlled trial **Val-HeFT),** valsartan reduced the combined morbidity and mortality in patients with HF who were receiving standard therapy for HF, but did not reduce all-cause mortality.

For patients with HF, it is not so clear that the addition of an AIIRA to ACEI and beta-adrenergic blocker is beneficial. One trial suggested an increased mortality with the addition of valsartan, whereas the addition of candesartan did not change mortality, but did show a reduction in CV death or HF hospitalization.

Three placebo-controlled trials and five active-controlled trials all of fair quality, evaluated symptomatic improvement in patients with HF. Symptoms of HF were improved with candesartan and losartan compared to placebo, and were similar with losartan, telmisartan, and valsartan compared to an ACEI.

Three placebo-controlled trials and three active-controlled trials of fair quality evaluated quality of life parameters in patients with HF. Losartan and valsartan improved quality of life compared to placebo and were similar to ACEIs. Quality of life was reported to be unchanged with candesartan in one placebo-controlled trial. Not enough data were available to assess the results with telmisartan compared to an ACEI.

Long-term outcome data was available for candesartan, losartan, and valsartan; however it is difficult to compare the effect on morbidity and mortality due to different trial designs, outcomes, and patient characteristics.

The Standing Update Committee agrees by consensus that for patients with HF there is no comparative data to suggest that one AIIRA is superior to another.

Key Question 1e. For patients with diabetic or non-diabetic nephropathy, do AIIRAs differ in efficacy?

AIIRAs reduce or eliminate microabluminuria, an early sign of renal damage in diabetics (and non-diabetics). They have also been used in patients with frank proteinuria (>3 gm/d) and/or in patients with decreased renal function.

No head-to-head trials were identified that compared the effects of AIIRAs on end-stage renal disease or clinical deterioration of renal function or quality of life with nephropathy. There were 7 active-controlled trials that met acceptance criteria: candesartan (1), losartan (3), telemisartan (1), and valsartan (2). There were 3 placebo-controlled trials with 1 each for irbesartan, losartan, and valsartan and two new subgroup analyses for irbesartan and losartan. There were no trials with eprosartan or olmesartan.

Non-diabetic Nephropathy

In patients with non-diabetic nephropathy, one good quality active-controlled trial found the combination of losartan and an ACEI (**COOPERATE**) significantly (p=0.018) reduced composite doubling of the serum creatinine (sCr) or ESRD compared to either treatment alone. However in another active-controlled trial of fair quality, the combination of candesartan plus an ACEI (lisonopril) compared to either monotherapy did not differ significantly. In one small trial of fair quality the combination of valsartan and benazepril at half doses significantly (p=0.024) decreased the urinary protein excretion rate more than either drug alone at higher doses.

Diabetic Nephropathy

Two large, good quality placebo-controlled trials demonstrated a reduction in composite doubling sCr, onset of ESRD, or all-cause mortality compared to placebo in patients with type 2 diabetic nephropathy. In one, Irbesartan Type 2 Diabetic Nephropathy Trial (**IDNT**), irbesartan significantly reduced the risk of the composite doubling sCr, onset of ESRD, or all-cause mortality when compared to placebo (RR 0.80, P=0.02, NNT=16), but there was no significant difference with irbesartan compared to amlodipine when only death or ESRD were analyzed. In the other, Reduction of Endpoints in patients with NIDDM with the AIIRA trial (**RENAAL**), losartan reduced the risk of the composite doubling of sCr, onset of ESRD, or all-cause mortality compared to placebo (RR 0.84, P=0.02, NNT=28). A new sub-group analyses of most CV outcomes showed no significant differences, but favored irbesartan over placebo for HF (p=0.048.)

In patients with diabetic nephropathy, one fair quality active-controlled trial found a significant decrease in albumin excretion rate with valsartan and an ACEI compared to placebo, but no significant difference with a higher dose of valsartan. Another active control trial found albuminuria to be reduced with losartan and an ACEI compared to placebo, but no significant difference was found when the higher doses of the losartan and the ACEI

were compared to each other. When analyzed separately, only doubling baseline sCr and ESRD were decreased significantly with losartan compared to placebo.

The Standing Update Committee agrees by consensus that in patients with non-diabetic or diabetic nephropathy there is no comparative data to suggest that one AIIRA is superior to another.

Key Question 2

For adult patients with essential hypertension, high cardiovascular risk factors, recent myocardial infarction, and heart failure, diabetic or nondiabetic nephropathy do AIIRAs differ in safety or adverse events?

There were no head-to-head trials in adult patients with essential hypertension, high CV risk factors, recent MI, HF, or diabetic or non-diabetic nephropathy.

The AIIRAs appear to be well tolerated. Depending on the adverse effect, patient population, and agent evaluated, reports of adverse effects were similar to increased or decreased compared to placebo. Withdrawal rates were generally less than placebo, except for studies in patients with HF. Withdrawals due to adverse events were also generally less than ACEIs, especially regarding cough. Reports of angioedema are rare with the angiotensin II receptor antagonists, but have been reported to occur in patients previously experiencing angioedema on an ACEI.

The Standing Update Committee agrees by consensus that in patients with hypertension, HF, or MI there is no evidence that any AIIRA is associated with a higher risk of serious complications than any other AIIRA.

Key Question 3.

Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one AIIRA is more effective or associated with fewer adverse events, e.g. renal insufficiency? Evidence unique to minority and ethnic groups are of particular interest.

In 3 trials with HF or HTN, age did not appear to have a significant impact on the results of the AIIRAs studies. Up to 22% of patients enrolled in the trials were black. Evaluation of the subgroup of black patients in one trial showed an increased risk of morbidity and mortality with losartan as compared to atenolol in patients with HF or HTN and LVH.

In four trials with high CV risk or HTN, anywhere from 11-54% of patients enrolled were women. It appears that women derive similar benefit from AIIRAs as men. The subgroup of patients with DM (with HTN and LVH) on losartan had a reduction in CV mortality but not a significant decrease in stroke as compared to the larger patient population. There is not enough evidence with other AIIRAs to determine whether comorbidities influence results.

Conflicting results are available regarding the effects of AIIRAs in combination with an ACEI or beta-blocker in patients with HF. Data with a subgroup analysis with valsartan found an increase in mortality; whereas, data with candesartan showed no difference in mortality, but a significant decrease in the combined endpoint of CV mortality and HF hospitalizations. The role of combination therapy in reducing CV events or hospitalization is unclear because the evaluation of subgroups had different endpoints for different AIIRAs. There are inadequate data to determine whether there is a difference between the AIIRAs.

Although there were no trials designed to compare AIIRAs according to race, a subgroup analysis of the **LIFE** (LVH) losartan vs. atenolol revealed that there was actually an increased risk of stroke 8.9% vs 4.6% for black patients (adjusted HR 2.18 P=0.03).[3]

The Standing Update Committee agrees by consensus that in subgroups of patients:

- **There is inadequate data to determine whether one AIIRA is superior based on demographics (age, racial groups, or gender.)**
- **There is inadequate data to determine whether there is a difference between AIIRAs when combined with other medications.**
- **There is inadequate data to determine whether there is a difference between AIIRAs when treating hypertensive patients with other comorbidities.**

[3] Julius S, Alderman MH, Beevers G., et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J. of the American College of Cardiology 2004;43(6):1047-55

Conclusion

In a series of public meetings with the opportunity for public questions, comment and testimony, the AIIRA Subcommittee of the Health Resources Commission reviewed the medical evidence comparing AIIRA. The OHSU EPC's report, "Drug Class Review on AIIRA Drugs," which included appropriate information presented in pharmaceutical manufacturer dossiers, was reviewed and public testimony considered.

Using all of these sources of information, the subcommittee arrived at the following conclusions about the comparative effectiveness and safety of AIIRA drugs as supported by analysis of the medical literature. A summary of the evidence is found in Table 2.

It is the decision of the Standing Update Committee that:

1. **In patients with essential hypertension, high cardiovascular risk factors, recent MI, heart failure or nephropathy there is no data to suggest that one AIIRA is superior to another for efficacy or safety.**

2. **There is inadequate data to determine whether there is a difference between the AIIRAs with respect to demographics (age, racial groups, or sex), in combination with other medications, or in hypertensive patients with other comorbidities**.

Table 2. Summary of the Evidence for Efficacy by Drug and Indication

DRUG	HTN	High CV Risk	Recent MI	HF	Nephropathy
Candesartan	Reduced non-fatal stroke; some improvement in QOL vs. placebo; Reduced first stroke seen in subgroup analysis ISH; decrease first CV event in subgroup pts with stroke	NA	NA	Reduced CV death, HF hospitalization (in patients on ACEI and beta-blocker and those ACEI intolerant); no significant effect on mortality; improved HF symptoms vs. placebo; Reduced all-cause mortality in pts with low LVEF	Decrease in CrCl not significant vs. ACEI or combination
Eprosartan	No improvement in QOL vs. placebo; Reduced combined primary endpoint cerebrovascular events in pts with previous event vs. nitrendipine.	NA	NA	NA	NA
Irbesartan	Reduced onset diabetic nephropathy (300mg)	NA	NA	NA	Type 2 DM nephropathy: Reduced composite doubling sCr, ESRD, all-cause mortality; only doubling baseline sCr significant vs. placebo when analyzed separately
Losartan	Improved QOL	Reduced CV morbidity and mortality; reduced stroke vs. atenolol. Sub-group analysis LIFE Black pts. Showed increased stroke vs. atenolol.	Unable to determine effect on mortality compared to ACEI vs. captopril	No reduction in mortality or CV endpoints compared with ACEI; improved HF symptoms and QOL vs. captopril	Type 2 DM nephropathy: Reduced composite doubling sCr, ESRD, all-cause mortality (only doubling baseline sCr and ESRD significant when analyzed separately); reduced albuminuria vs. placebo Non-DM nephropathy:Reduced doubling sCr, ESRD in combination w/ACEI
Olmesartan	NA	NA	NA	NA	NA
Telmisartan	NA	NA	NA	Improved symptoms	Type II DM pts non-inferior to enalapril for change in GFR
Valsartan	One PCT did not result in significant change in GFR vs. placebo	No difference in CV morbidity & mortality compared to amlodipine	Reduced total mortality, CV mortality and CV events not inferior to ACEI vs. captopril	Reduced combined morbidity and mortality and hospitalizations in subgroup analysis, increased mortality in combination with ACEI and beta-blocker); improved HF symptoms vs. placebo and QOL	DM nephropathy: Reduced AER; Non-DM nephropathy: Reduced albuminuria vs. placebo

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Chair, Health Resources Commission

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Vice Chair, Health Resources Commission

David Labby, MD
Chair, Standing Update Committee

Jeanene Smith, MD, MPH
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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.