

# Drug Class Review

## Angiotensin Converting Enzyme Inhibitors, Angiotensin II Receptor Antagonists, and Direct Renin Inhibitors

Preliminary Update Scan 3

August 2014

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## OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged since the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations voted in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews of relevant trials, and actions taken by the US Food and Drug Administration since the last report. Other important studies could exist.

### Date of Last Report

January 2010 (searches through June 2009)

### Date of Last Preliminary Update Scan Report

February 2014

### Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The Participating Organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what is the effectiveness and efficacy and what are the harms of aliskiren compared with placebo?
  - 1a. When used as monotherapy?
  - 1b. When used in combination with angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (AIIRA) drugs?
2. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in effectiveness and efficacy between direct renin inhibitor (DRI), ACE-I and AIIRA drugs?
  - 2a. When used as monotherapy?
  - 2b. When used in combination with one another?

3. For adults with diagnosed coronary heart disease, hypertension, left ventricular dysfunction, heart failure, nondiabetic chronic kidney disease, or diabetic nephropathy, what are the inter-class differences in harms between DRI, ACE-I and AIIRA drugs?
4. Are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which there are inter-class differences between DRI, ACE-I and AIIRA drugs?

**Inclusion Criteria**

**Populations**

Adults with any of the following indications:

- Diagnosed coronary heart disease (including post-myocardial infarction)
- Hypertension
- Left ventricular dysfunction
- Heart failure
- Nondiabetic chronic kidney disease, with or without proteinuria
- Diabetic nephropathy, defined as documented diabetes, with either microalbuminuria or macroalbuminuria, and any level of renal function. Trials of diabetics with normo albuminuria will be excluded.

Excluded:

- Renal transplantation

**Interventions**

**Table 1. Included interventions**

Drug type	Active ingredient	Trade name
Angiotensin-converting enzyme inhibitor (ACE-I)	Benazepril	Lotensin
	Captopril	Capoten
	Enalapril	Vasotec
	Fosinopril	Monopril
	Lisinopril	Prinivil, Zestril
	Moexipril	Univasc
	Perindopril	Aceon
	Quinapril	Accupril
	Ramipril	Altace
	Trandolapril	Mavik
Angiotensin II receptor antagonist (AIIRA) <sup>a</sup>	Azilsartan	Edarbi
	Candesartan	Atacand
	Eprosartan	Teveten
	Irbesartan	Avapro
	Losartan	Cozaar
	Olmesartan	Benicar

Drug type	Active ingredient	Trade name
	Telmisartan	Micardis
	Valsartan	Diovan
Direct renin inhibitor (DRI)	Aliskiren	Tekturna
DRI + AIIRA	Aliskiren Valsartan	Valturna <sup>b</sup>

<sup>a</sup> Also called angiotensin receptor blockers (ARBs)

<sup>b</sup> Manufacturer decided to stop marketing Valturna in the U.S. in July 2012, citing ALTITUDE trial.

### Comparators:

- Individual DRIs, ACE-Is, AIIRAs
- Placebo compared with aliskiren

### Effectiveness outcomes

- All-cause mortality, cardiovascular mortality, sudden death
- Cardiovascular events (stroke, myocardial infarction, or death or hospitalization due to heart failure)
- Chronic kidney disease, end-stage renal disease, dialysis, transplantation
- Changes in renal function, including serum creatinine, estimated glomerular filtration rate, proteinuria and albuminuria (total amount over a 24-hour period, but not solely short-term excretion rates per minute or per hour), creatinine clearance
- Quality of life
- Symptomatic improvement in heart failure symptoms (heart failure class, functional status, visual analogue scores, exercise tolerance tests with symptom outcomes)
- Cardiovascular hospitalizations
- Overall withdrawals

### Harms outcomes

- Numbers of adults who experienced the following:
  - One or more adverse event
  - One or more serious adverse event (life threatening or requiring medical intervention, including hospitalization)
- Total withdrawals due to any adverse event
- Specific harms (including, but not limited to hypotension, hyperkalemia, acute kidney injury, cough, angioedema, gastrointestinal effects) or withdrawals due to specific harms
- Harms considered to be major are defined as those that required unanticipated and/or urgent medical treatment (including, but not limited to hypotension, hyperkalemia, acute kidney injury, angioedema)

### Study designs

- Randomized controlled trials (RCTs):
  - Head-to-head and placebo-controlled trials for aliskiren
  - Inter-class head-to-head trials only for ACE-I and AIIRA
- Good quality systematic reviews

## METHODS

### Literature Search

To identify relevant trials, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2009 through July 30, 2014 using terms for included drugs and populations. In addition, we searched the US Food and Drug Administration website (<http://www.fda.gov/> and <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) to identify new drugs and indications and changes in safety labeling (boxed warnings). To identify new drugs we also searched CenterWatch (<http://centerwatch.com>), a privately-owned database of clinical trials information. We excluded new fixed-dose combination products of drugs already approved. To identify relevant systematic reviews, we searched the websites for the Agency for Healthcare Research and Quality (AHRQ) (<http://www.ahrq.gov/> and <http://www.effectivehealthcare.ahrq.gov>), the Canadian Agency for Drugs & Technologies in Health (CADTH) (<http://www.cadth.ca/>), the VA's Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp>), and the Health Technology Assessment (HTA) database from the University of York's Centre for Reviews and Dissemination (CRD). All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

### Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### New Drugs

#### ***New drugs identified in this Preliminary Update Scan***

No new drugs Identified.

#### ***New drugs identified in previous Preliminary Update Scan(s)***

New angiotensin II receptor antagonist:  
Azilsartan was approved on 2/25/2011.

No new ACE-Inhibitors or Direct Renin Antagonists

### New Formulations

#### ***New formulations identified in this Preliminary Update Scan***

Epaned™ Kit (enalapril maleate) (8/13/13): oral solution (1 mg/ml) for the treatment of hypertension.

## **New Indications**

### ***New indications identified in this Preliminary Update Scan***

None

### ***New indications identified in previous Preliminary Update Scan(s)***

Telmisartan (Micardis®) (10/16/2009): Reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

## **Comparative Effectiveness Reviews**

### ***Reviews identified in this Preliminary Update Scan***

None

### ***Reviews identified in previous Preliminary Update Scan(s)***

We identified 13 potentially relevant comparative effectiveness reviews that address the key questions in this report (see Appendix A for abstracts). These include two AHRQ CERs: one compared ACE-I to AIIRA drugs in patients with chronic kidney disease (Fink 2012), and the other ACE-I, AIIRA, and DRI drugs in patient with hypertension (Sanders 2011).

## **Randomized Controlled Trials**

### ***Trials identified since the most recent Full Report***

Medline searches resulted in 453 citations, 39 of these new for this scan. Of the 453 citations, we identified 18 potentially relevant, head-to-head trials published since the 2010 report, one new for this scan (see Appendix B for abstracts). Characteristics of these trials are shown in Table 2 below. Most trials compared ACE-I to AIIRA drugs in patients with renal disease, but there were also 6 trials (one new this scan) comparing aliskiren (DRI) to ACE-I or to AIIRA drugs in patients with cardiovascular disease, renal disease, or both. About half of the head-to-head trials compared dual therapy with drugs from two included classes to monotherapy. One trial of azilsartan (an AIIRA approved since the last review) met inclusion criteria (Bonner 2013).

We also identified 9 placebo-controlled trials of aliskiren (also in Appendix B; one new this scan), primarily in populations with cardiovascular disease but also including some in patients with renal disease. These included the ALTITUDE trial (Parving 2012), which randomized subjects with diabetes and chronic kidney disease, cardiovascular disease, or both to aliskiren or placebo. Eligibility criteria also included treatment with an ACE-I or AIIRA, but not both, according to local guidelines. The trial was stopped early because of higher rates of adverse events (hyperkalemia and hypotension) with aliskiren, as well as a trend toward increased risk of the composite primary endpoint, which included cardiovascular or renal mortality, myocardial infarction, and stroke.

**Table 2. Characteristics of new head-to-head trials**

Author, Year Trial Name	N	Drugs	Population
Bakris, 2013	1,143	Valsartan vs. Aliskiren/ valsartan	Hypertensive with T2DM and stage 1 or stage 2 CKD
Bonner, 2013	884	Azilsartan vs. Ramipril	Hypertension: SBP 150-180mmHg
Fernandez-Juarez, 2013	133	Irbesartan vs. Lisinopril vs. Irbesartan + Lisinopril	Type 2 diabetic nephropathy
Fogari, 2013	138	Aliskiren vs. Ramipril	Hypertensive with T2DM and microalbuminuria
Fried, 2013	1,448	Losartan vs. Lisinopril + Losartan	Type 2 diabetic nephropathy
Lizakowski, 2012	14	Aliskiren vs. Perindopril	Non-diabetic CKD
Mann, 2013 ONTARGET	9,628	Ramipril vs. Telmisartan vs. Ramipril + Telmisartan	Diabetes ± nephropathy
Meier, 2011	20	Losartan vs. Losartan + Lisinopril	Hypertensive patients with proteinuric nephropathy
Nakamura, 2010	30	Telmisartan vs. Enalapril	CKD - mild to moderate
Nakamura, 2012	36	Aliskiren vs. Olmesartan vs. Aliskiren+olmesartan	Stage 1 and 2 CKD
Reyes-Marin, 2012	60	Enalapril vs. Losartan	Patients on automated peritoneal dialysis
Slagman, 2011	52	Lisinopril vs. Lisinopril + Valsartan	Non-diabetic nephropathy
Suzuki, 2013	40	Aliskiren vs. Valsartan	Hypertensive nephrosclerosis
Titan, 2011	55	Enalapril vs. Enalapril + Losartan	Diabetic nephropathy with macroalbuminuria
Tylicki, 2012	18	Telmisartan vs. Aliskiren + Telmisartan	Non-diabetic proteinuric CKD
Woo, 2009	207	Losartan vs. Enalapril	IgA nephritis
Xie, 2011 ROAD	339	Benazepril vs. Losartan	Chinese nondiabetic CKD patients
Yu, 2011 ONTARGET	1,159	Telmisartan vs. Ramipril vs. Telmisartan + ramipril	Chinese patients at high risk of cardiovascular events

Abbreviations: CKD, chronic kidney disease, SBP systolic blood pressure, T2DM, type 2 diabetes mellitus

## New Safety Alerts

See Appendix C for details.

## Identified in this Preliminary Update Scan

None

**Identified in previous Preliminary Update Scan (s)****Warning About Fetal Toxicity – January 2012**

All drugs in this report now carry a warning about potential fetal toxicity if used during pregnancy. The warning states that these drugs are contraindicated in pregnancy and should be discontinued as soon as the pregnancy is known.

**Warning Against Dual Blockade of the Renin-Angiotensin System – September 2012**

All drugs in this report now carry a warning about dual blockade of the renin-angiotensin system by combining a DRI with an ACE-I or and ARB, citing increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

**Warning against co-administration of Non-steroidal anti-inflammatory drugs (NSAIDs) – August 2011**

ACE-Inhibitors and ARBs now have a warning or precaution statement about co-administration of NSAIDs, particularly in the elderly, volume depleted or those with compromised renal function and deterioration of renal function.

**Summary**

This scan identified 18 new head-to-head trials with comparisons across all three drug classes, including one of the new AIIRA azilsartan. Since the 2012 scan, more evidence has emerged on the direct renin inhibitor aliskiren, with a total now of 6 new head-to-head trials comparing this drug to ACE-I or AIIRA drugs, and 9 new placebo-controlled trials. The 2010 report included two trials of aliskiren, one in combination with losartan and one a placebo-controlled trial of aliskiren alone. We also identified 13 systematic reviews with comparisons across the three drug classes.

## **Appendix A. Abstracts of potentially relevant new comparative effectiveness reviews of angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and direct renin inhibitors**

Bangalore S, Kumar S, Messerli FH. When conventional heart failure therapy is not enough: angiotensin receptor blocker, direct renin inhibitor, or aldosterone antagonist? *Congestive Heart Failure* 2013;19:107-15.

In patients on conventional heart failure therapy including angiotensin-converting enzyme (ACE) inhibitors, the addition of angiotensin receptor blockers (ARBs), direct renin inhibitors (DRIs), or aldosterone antagonists are therapeutic options to further reduce the risk of cardiovascular events. However, whether one is preferable over the other is not known. PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched for randomized clinical trials (RCTs), until March 2011, of trials testing either an ARB, DRI, or an aldosterone antagonist in patients with heart failure who were on conventional heart failure therapy with follow-up of at least 3 months. Efficacy (death, cardiovascular death, nonfatal myocardial infarction, heart failure hospitalization and composite of cardiovascular death or heart failure hospitalization) and safety (hyperkalemia, hypotension, renal failure) outcomes were compared. The authors identified 16 RCTs involving 31,429 participants that satisfied the inclusion criteria. When compared with placebo (reference rate ratio [RR] of 1), aldosterone antagonists reduced the rate of death (RR, 0.79; 95% credibility interval [CrI], 0.66-0.98), cardiovascular death (RR, 0.78; 95% CrI, 0.65-0.93), heart failure hospitalization (RR, 0.74; 95% CrI, 0.55-0.94), and the composite of cardiovascular death or heart failure hospitalization (RR, 0.73; 95% CrI, 0.55-0.90) with no difference for other efficacy outcomes. However, ARBs and DRIs did not result in any significant reduction in the rate of any of the efficacy outcomes when compared with placebo. When compared with placebo (RR=1), ARBs increased the rate of hyperkalemia (138% increase), renal failure (126% increase), and hypotension (63% increase). Similarly, aldosterone antagonists resulted in a 110% increase in hyperkalemia and DRIs with a 98% increase in hypotension. In patients with heart failure and reduced systolic function on conventional heart failure medications, the risk benefit ratio favors the addition of aldosterone antagonists over ARBs or DRIs. 2012 Wiley Periodicals, Inc.

Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. *American Journal of Cardiovascular Drugs* 2012;12:263-77.

Background: Between 5% and 20% of patients treated with angiotensin-converting enzyme inhibitors (ACE inhibitors) develop intolerance. Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) can be used as an alternative treatment. Objective: In this study we aimed to evaluate the tolerability of ARBs in patients with intolerance to ACE inhibitors. Data Sources: The electronic databases PubMed, MEDLINE/EMBASE via Dialog, CENTRAL, and ISI Web of Knowledge were searched. Study Selection: Randomized controlled trials (RCTs) evaluating ARBs in patients with intolerance to ACE inhibitors were selected. Data Synthesis: Risk ratio (RR) and 95% confidence intervals (CIs) were estimated assuming the random effects method. We found 11 RCTs comparing ARBs with ACE inhibitors, diuretics, or placebo,

and one RCT comparing high-dose versus low-dose ARB. Results: ARBs had fewer cough events versus ACE inhibitors (RR 0.37; 95% CI 0.28, 0.48). ARBs had drug discontinuation (RR 0.99; 95% CI 0.84, 1.17) and cough risk (RR 1.01; 95% CI 0.74, 1.39) rates similar to placebo. Angioedema risk with ARBs was also similar to placebo (RR 1.62; 95% CI 0.17, 15.79). Compared with placebo, hypotension (RR 2.63; 95% CI 1.77, 3.92), renal dysfunction (RR 2.07; 95% CI 1.45, 2.95) and hyperkalemia (RR 3.37; 95% CI 1.60, 7.11) were more frequent with ARBs. Conclusions: ACE inhibitor rechallenge should be discouraged in patients with previous intolerance to ACE inhibitors due to a higher risk of cough. ARBs had cough and angioedema incidences similar to placebo. Despite a significantly higher incidence of hypotension, renal dysfunction and hyperkalemia, discontinuation of ARBs was similar to placebo.

Chen Y, Meng L, Shao H, Yu F. Aliskiren vs. other antihypertensive drugs in the treatment of hypertension: a meta-analysis. *Hypertension Research - Clinical & Experimental* 2013;36:252-61.

To investigate the antihypertensive effects and tolerability of aliskiren in comparison with other antihypertensive drugs and placebo in patients with hypertension, a meta-analysis was performed of studies published between 1950 and 2012. A systematic literature search of MEDLINE and the Cochrane Library was conducted for randomized controlled trials. Weighted mean differences and relative risk with 95% confidence intervals were calculated for continuous and dichotomous data, respectively. In all, 14 studies with 6741 participants were included in the present meta-analysis. Nine studies included trial arms with placebo, four included angiotensin (Ang) AT1 receptor blockers (ARBs), three included Ang-converting enzyme inhibitors (ACEIs), two included calcium channel blockers (CCBs), one included a beta-blocker, and one included hydrochlorothiazide (HCTZ). We found that aliskiren, which lowered blood pressure (BP) effectively in patients with mild-to-moderate hypertension, was similar to HCTZ but inferior to CCBs in BP reduction, response rates and control rates. Furthermore, aliskiren was superior to ACEIs in lowering diastolic BP (DBP), while it had similar effects to ACEIs on systolic BP (SBP) reduction, response rates and control rates. Additionally, the present meta-analysis showed the superiority of atenolol over aliskiren in DBP reduction and BP response but showed that atenolol was inferior in SBP reduction and BP control. No difference was found in the rates of therapeutic response between aliskiren and ARBs, while more patients achieved BP control with aliskiren. Further studies will be needed to determine the antihypertensive effects and tolerability of aliskiren in comparison with other antihypertensive drugs.

Cheng J, Zhang X, Tian J, Li Q, Chen J. Combination therapy an ACE inhibitor and an angiotensin receptor blocker for IgA nephropathy: a meta-analysis. *International Journal of Clinical Practice* 2012;66:917-23.

**OBJECTIVE:** The pathogenesis of IgA nephropathy (IgAN) is still unknown. Combination therapy with angiotensin-converting enzyme inhibitors (ACEIs) plus angiotensin receptor blockers (ARBs) might provide more benefits to IgAN patients. We conducted a systematic review to assess the efficacy of combination therapy for IgAN. **METHODS:** The MEDLINE, EMBASE, the Cochrane Library and article reference lists were searched for randomised clinical trials (RCTs) which involved combination therapy

ACEI plus ARB in only one arm. A meta-analysis was performed on the outcomes of proteinuria and renal function in IgAN patients.

**RESULTS:** Six RCTs involving 109 patients were included in the review. Combined treatment with ACEI plus ARB was more effective than with ACEI/ARB alone for reducing daily proteinuria. This did not translate into an improvement in GFR. Patients receiving ACEI plus ARB therapy did not have an increased risk of hyperkalemia.

**CONCLUSIONS:** The current cumulative evidence suggests that combination therapy ACEI plus ARB may provide more benefits to IgAN patients for reducing daily proteinuria. Long-term effects of these agents on renal outcomes, and safety need to be established. 2012 Blackwell Publishing Ltd.

Fink HA, Ishani A, Taylor BC, et al. Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment. Comparative Effectiveness Review No. 37. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHS 290-2007-10064-I.) AHRQ Publication No. 11(12)-EHC075-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2012.

**Objective.** The objective was to systematically review and synthesize evidence regarding benefits and harms of screening for and monitoring and treatment of chronic kidney disease (CKD) stages 1–3.

**Data Sources.** The data sources were MEDLINE® and Cochrane Database of Systematic Reviews electronic databases, hand searches of references from relevant systematic reviews and eligible trials, and references from expert consultants.

**Review Methods.** We screened abstracts and full text articles of identified references for eligibility and reviewed randomized controlled trials (RCTs) for evidence on benefits and harms of CKD treatments. We reviewed RCTs and observational studies for evidence regarding possible benefits and harms of CKD screening or monitoring. For all included RCTs, data were extracted, quality was rated, and strength of evidence was graded. Evidence on the benefits and harms of CKD treatments was quantitatively synthesized when possible. Additional evidence on CKD screening and monitoring was qualitatively described.

**Results.** We found no RCTs of CKD screening or monitoring. In treatment RCTs, several interventions significantly reduced clinical events. In patients with proteinuria, nearly all with diabetes and hypertension, angiotensin converting enzyme inhibitors (ACEIs) (relative risk [RR], 0.60, 95 percent confidence interval [CI], 0.43 to 0.83) and angiotensin receptor blockers (ARBs) (RR 0.77, 95 percent CI, 0.66 to 0.90) significantly reduced risk of end-stage renal disease (ESRD) versus placebo. In patients with microalbuminuria who had cardiovascular disease or diabetes with other cardiovascular risk factors, ACEI treatment reduced mortality risk (RR 0.79, 95 percent CI, 0.66 to 0.96) versus placebo. In individuals with hyperlipidemia and impaired estimated glomerular filtration rate (eGFR) or creatinine clearance, HMG CoA-reductase inhibitors (statins) reduced risk of mortality (RR 0.80, 95 percent CI, 0.68 to 0.95), myocardial infarction (MI), and stroke compared with placebo. However, limited data addressed whether these effects differed between patients with and without CKD or as a function of CKD severity. In RCTs that directly compared different treatments, including high dose versus low dose, combination versus monotherapy, and strict versus standard control, it was unclear whether intensification of treatment improves clinical outcomes. Reporting of study

withdrawals and adverse events was limited. Based on treatment RCT findings and additional indirect data, including high CKD prevalence, low CKD recognition and limited CKD monitoring in usual care, uncertain sensitivity of screening and monitoring measures for CKD, and insufficient evidence on CKD screening and monitoring harms, the overall benefits of CKD screening and monitoring are unclear. The likelihood of benefit, if present, appears to be greater in specific subgroups. For example, individuals not being treated with ACEIs or ARBs who have cardiovascular disease or diabetes combined with other cardiovascular risk factors may benefit from screening for albuminuria. Individuals not being treated with a statin who have hyperlipidemia and no cardiovascular disease may benefit from screening for impaired eGFR. Younger patients, and those without diabetes, hypertension, cardiovascular disease, or obesity, are the least likely to benefit from CKD screening. Individuals with impaired eGFR and at high risk for cardiovascular complications who are not being treated with ACEIs or ARBs may benefit from monitoring for incident albuminuria.

Conclusions. No trials directly show a benefit for CKD screening or monitoring. The likelihood of benefit, if present, appears to be greater in specific subgroups. Screening and monitoring harms are poorly described. In selected CKD patients, ACEI or ARB treatment reduces ESRD risk, ACEI treatment reduces mortality risk, and statin treatment reduces risk of mortality, MI, and stroke. Many of these patients may already warrant treatment with these therapies regardless of CKD status. Many knowledge gaps remain, and additional research should increase understanding regarding optimal approaches to CKD screening, monitoring, and treatment.

Gao D, Ning N, Niu X, Wei J, Sun P, Hao G. Aliskiren vs. angiotensin receptor blockers in hypertension: meta-analysis of randomized controlled trials. *American Journal of Hypertension* 2011;24:613-21.

**BACKGROUND:** Aliskiren, a newly discovered renin inhibitor, blocks the renin-angiotensin system (RAS) from the top of the enzyme cascade and therefore, might provide comparable or even superior clinical efficacy of blood pressure (BP) control than angiotensin receptor blockers (ARBs). With this meta-analysis, we aimed to compare the efficacy and tolerability of aliskiren and ARBs in the treatment of hypertension in the short-term treatment period.

**METHODS:** Reports of randomized controlled trials (RCTs) comparing aliskiren and ARBs in patients with hypertension were selected by a search of the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE. The main outcome measures were reduction in diastolic BP (DBP) and systolic BP (SBP) and rates of therapeutic response and BP control. We also compared the tolerability of aliskiren and ARBs. Revman v5.0 was used to obtain the pooled estimates.

**RESULTS:** We analyzed data from 10 reports of trials involving 3,732 participants. DBP and SBP reduction did not differ between aliskiren and ARBs (weighted mean difference (WMD), -0.18; 95% confidence interval (CI), -1.07 to 0.71, and WMD, 0.15; 95% CI, -1.38 to 1.69, respectively). Aliskiren and ARB treatment did not differ in rates of BP control or therapeutic response. Moreover, aliskiren and ARB treatment led to a similar number of adverse events, severe adverse events, and withdrawal due to adverse events. **CONCLUSION:** Aliskiren is as effective as ARBs (losartan, valsartan, and irbesartan) in controlling BP and does not differ from ARBs in risk of adverse events.

Harel Z, Gilbert C, Wald R, et al. The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis. *Bmj* 2012;344:e42.

**OBJECTIVE:** To examine the safety of using aliskiren combined with agents used to block the renin-angiotensin system.

**DESIGN:** Systematic review and meta-analysis of randomised controlled trials.

**DATA SOURCES:** Medline, Embase, the Cochrane Library, and two trial registries, published up to 7 May 2011.

**STUDY SELECTION:** Published and unpublished randomised controlled trials that compared combined treatment using aliskiren and angiotensin converting enzyme inhibitors or angiotensin receptor blockers with monotherapy using these agents for at least four weeks and that provided numerical data on the adverse event outcomes of hyperkalaemia and acute kidney injury. A random effects model was used to calculate pooled risk ratios and 95% confidence intervals for these outcomes.

**RESULTS:** 10 randomised controlled studies (4814 participants) were included in the analysis. Combination therapy with aliskiren and angiotensin converting enzyme inhibitors or angiotensin receptor blockers significantly increased the risk of hyperkalaemia compared with monotherapy using angiotensin converting enzymes or angiotensin receptor blockers (relative risk 1.58, 95% confidence interval 1.24 to 2.02) or aliskiren alone (1.67, 1.01 to 2.79). The risk of acute kidney injury did not differ significantly between the combined therapy and monotherapy groups (1.14, 0.68 to 1.89).

**CONCLUSION:** Use of aliskiren in combination with angiotensin converting enzyme inhibitors or angiotensin receptor blockers is associated with an increased risk for hyperkalaemia. The combined use of these agents warrants careful monitoring of serum potassium levels.

He Y, Feng L, Huo D, Yang Z, Liao Y. Enalapril versus losartan for adults with chronic kidney disease: A systematic review and meta-analysis. *Nephrology* 2013;18 605–14.

**Aim:** Both enalapril and losartan are effective and widely used in patients with chronic kidney disease (CKD). This review aimed to evaluate the benefits of enalapril and losartan in adults with CKD.

**Methods:** PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov were searched, without language limitations, for randomized controlled trials (RCT), in which enalapril and losartan were compared in adults with CKD. Standard methods, consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, were used. Reviewer Manager software, ver. 5.2, was used for meta-analysis.

**Results:** Of 318 citations retrieved, 17 RCT (14 parallel-group and three cross-over) met our inclusion criteria. The pooled analysis for parallel RCT showed that the effects of enalapril and losartan on blood pressure, renal function and serum uric acid (UA) were similar. Meta-analysis indicated that patients taking enalapril had a higher risk of dry cough (risk ratio, 2.88; 95% CI, 1.11–7.48; P = 0.03). Sensitivity analysis showed good robustness of these findings.

**Conclusion:** Enalapril has similar effects to losartan on systemic blood pressure, renal function and serum UA in patients with CKD, but carries a higher risk of dry cough.

Larger trials are required to evaluate the effects of these medications on clinical outcomes.

Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *Bmj* 2013;346:f360.

**OBJECTIVE:** To compare the long term efficacy and adverse events of dual blockade of the renin-angiotensin system with monotherapy.

**DESIGN:** Systematic review and meta-analysis.

**DATA SOURCES:** PubMed, Embase, and the Cochrane central register of controlled trials, January 1990 to August 2012.

**STUDY SELECTION:** Randomised controlled trials comparing dual blockers of the renin-angiotensin system with monotherapy, reporting data on either long term efficacy (> 1 year) or safety events (> 4 weeks), and with a sample size of at least 50. Analysis was stratified by trials with patients with heart failure versus patients without heart failure.

**RESULTS:** 33 randomised controlled trials with 68,405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks were included. Dual blockade of the renin-angiotensin system was not associated with any significant benefit for all cause mortality (relative risk 0.97, 95% confidence interval 0.89 to 1.06) and cardiovascular mortality (0.96, 0.88 to 1.05) compared with monotherapy. Compared with monotherapy, dual therapy was associated with an 18% reduction in admissions to hospital for heart failure (0.82, 0.74 to 0.92). However, compared with monotherapy, dual therapy was associated with a 55% increase in the risk of hyperkalaemia ( $P<0.001$ ), a 66% increase in the risk of hypotension ( $P<0.001$ ), a 41% increase in the risk of renal failure ( $P=0.01$ ), and a 27% increase in the risk of withdrawal owing to adverse events ( $P<0.001$ ). Efficacy and safety results were consistent in cohorts with and without heart failure when dual therapy was compared with monotherapy except for all cause mortality, which was higher in the cohort without heart failure ( $P=0.04$  v  $P=0.15$ ), and renal failure was significantly higher in the cohort with heart failure ( $P<0.001$  v  $P=0.79$ ).

**CONCLUSION:** Although dual blockade of the renin-angiotensin system may have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalaemia, hypotension, and renal failure compared with monotherapy. The risk to benefit ratio argues against the use of dual therapy.

Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. *Am J Cardiol* 2012;110:383-91.

Angioedema is a rare, potentially life-threatening adverse event of renin-angiotensin system inhibitors. The objective of the present study was to determine the risk of angioedema from randomized clinical trials. A PubMed/CENTRAL/EMBASE search was made for randomized clinical trials from 1980 to October 2011 in patients on angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or direct renin inhibitor (DRI). Trials with a total number of patients  $\geq 100$  and a duration of  $\geq 8$  weeks were included for analysis. Incidence of angioedema was pooled by weighing the incident rate of each trial by the inverse of the variance. Twenty-six

trials with 74,857 patients in the ACE inhibitor arm with 232,523 person-years of follow-up, 19 trials with 35,479 patients on ARB with 122,293 person-years of follow-up, and 2 trials with 5,141 patients on DRI with 1,735 person-years of follow-up met the inclusion criteria and were included in the analysis. In head-to-head comparison in 7 trials, risk of angioedema with ACE inhibitors was 2.2 times higher than with ARBs (95% confidence interval [CI] 1.5 to 3.3). With ACE inhibitors and ARBs, incidence of angioedema was higher in heart failure trials compared to hypertension or coronary artery disease trials without heart failure ( $p < 0.0001$ ). Weighted incidence of angioedema with ACE inhibitors was 0.30% (95% CI 0.28 to 0.32) compared to 0.11% (95% CI 0.09 to 0.13) with ARBs, 0.13% (95% CI 0.08 to 0.19) with DRIs, and 0.07% with placebo (95% CI 0.05 to 0.09). In conclusion, incidence of angioedema with ARBs and DRI was  $< 1/2$  than that with ACE inhibitors and not significantly different from placebo. Incidence of angioedema was higher in patients with heart failure compared to those without heart failure with ACE inhibitors and ARBs.

Morgado MP, Rolo SA, Castelo-Branco M. Efficacy of Aliskiren/Hydrochlorothiazide Combination for the Treatment of Hypertension: A Meta-Analytical Approach. *Open Cardiovasc Med J*. 2011; 5: 6–14

**Background:** Single-pill combinations of aliskiren/hydrochlorothiazide have recently been approved by the European Medicines Agency for the treatment of hypertension.

**Objective:** This study aimed to assess the antihypertensive efficacy of aliskiren/hydrochlorothiazide combination in reducing systolic and diastolic blood pressure in hypertensive patients.

**Methods:** A search in International Pharmaceutical Abstracts, MEDLINE, The Cochrane Library and ISI Web of Knowledge was performed from 2000 to November 2009, to identify randomized, double-blind, clinical trials using aliskiren/hydrochlorothiazide for the treatment of hypertension. Studies were included if they evaluated the antihypertensive efficacy of aliskiren/hydrochlorothiazide in patients with mild or moderate essential hypertension and age  $\geq 18$  years. The meta-analytical approach calculated the weighted average reductions of systolic and diastolic blood pressure for each daily dosage combination.

**Results:** We included 5 clinical trials testing several combinations of aliskiren/hydrochlorothiazide and containing data on 5448 patients. In all studies blood pressure was assessed at inclusion (baseline) and after 8 weeks of therapy. Blood pressure reductions and control rates were significantly ( $p < 0.05$ ) higher with the aliskiren/hydrochlorothiazide combinations than with placebo and the same doses of aliskiren or hydrochlorothiazide alone. The weighted mean reductions (mm Hg) from baseline of systolic and diastolic blood pressure for each aliskiren/hydrochlorothiazide combination were: -15.8/-10.3 (150/25 mg); -15.9/-11.8 (300/12.5 mg); -16.9/-11.6 (300/25 mg). Blood pressure control rates (%) for the above combinations were, at least, respectively: 43.8, 50.1 and 51.9.

**Conclusions:** Aliskiren/hydrochlorothiazide provided clinically significant additional blood pressure reductions and improved blood pressure control rates over aliskiren or hydrochlorothiazide monotherapy.

Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011.

**Objectives.** A 2007 comparative effectiveness review (CER) evaluated the long-term benefits and harms of angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin II receptor blockers/antagonists (ARBs) for treating essential hypertension in adults. Since then, significant additional research has been published comparing these agents, and direct renin inhibitors (DRIs) have been introduced to the market. We sought to update 2007 CER on ACEIs versus ARBs and expand this to include comparisons with DRIs.

**Data Sources.** We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, a list of systematic reviews underway in the Cochrane Hypertension Review Group, and selected gray literature sources.

**Review Methods.** We included studies that directly compared ACEIs, ARBs, and/or DRIs in at least 20 total adults with essential hypertension; had at least 12 weeks of followup; and reported at least one outcome of interest. Two investigators reviewed each article, and a standard protocol was used to extract data on study design, interventions, population characteristics, and outcomes; evaluate study quality; and summarize the evidence. When appropriate, quantitative metaanalysis was performed.

**Results.** We included 97 studies (36 new since 2007) directly comparing ACEIs versus ARBs and 3 studies directly comparing DRIs to ACEIs or ARBs. The strength of evidence remains high for equivalence between ACEIs and ARBs for blood pressure lowering and use of a single antihypertensive agent, and for superiority of ARBs over ACEIs for short-term adverse events (primarily due to cough). The new evidence did not strengthen our conclusions regarding longterm cardiovascular outcomes, quality of life, progression of renal disease, medication adherence or persistence, rates of angioedema, or differences in key patient subgroups: the strength of evidence for these outcomes remained low to moderate. For DRIs, we were not able to reach definitive conclusions for any of the outcomes of interest. Few studies involved a representative sample treated in a typical clinical setting over a long duration; treatment protocols had marked heterogeneity; and significant amounts of data about important outcomes and patient subgroups were missing.

**Conclusions.** Evidence does not support a meaningful difference between ACEIs and ARBs for any outcome except short-term adverse events. Few, if any, of the questions that were not answered in the 2007 CER have been addressed by the 39 new studies. Future research in this area should consider areas of uncertainty and be prioritized accordingly.

Zhenfeng Z, Huilan S, Junya J, Dong L, Shan L. A systematic review and meta-analysis of aliskiren and angiotension receptor blockers in the management of essential hypertension. *Journal of the Renin-Angiotensin-Aldosterone System* 2011;12:102-12.

Aliskiren is a novel antihypertensive agent and the first direct renin inhibitor (DRI) in clinical use. Several clinical trials have compared DRI with angiotensin receptor blockers (ARBs) in the management of essential hypertension. However, systematic comparison

of efficacy and safety between DRIs and ARBs is still lacking. We reviewed randomized controlled trials (RCTs) comparing aliskiren with ARBs for net reduction of blood pressure from baseline, achieved rate of control, and incidences of common and serious adverse events. Weighted mean differences (WMD) and relative risk (RR) with 95% confidence intervals (CI) were calculated for continuous and dichotomous data, respectively. Seven RCTs with 5488 patients were included in this meta-analysis. We compared the efficacy of aliskiren and ARBs in reducing systolic blood pressure (SBP) and diastolic blood pressure (DBP). No differences were found between the two groups. Aliskiren combined with ARBs was superior to aliskiren monotherapy at the maximum recommended dose on SBP and DBP reduction. (WMD -4.80, 95% CI -6.22-- -3.39,  $p < 0.0001$ ; WMD -2.96, 95% CI -4.63-- -1.28,  $p = 0.0001$ ; respectively). Similar results were found with aliskiren combined with ARBs versus ARB monotherapy (WMD -4.43, 95% CI -5.91-- -2.96,  $p < 0.0001$ ; WMD -2.40; 95% CI -3.41-- -1.39,  $p < 0.0001$ ; respectively). No differences were found in adverse events between the aliskiren and ARB groups. Similar results were found with aliskiren and ARB combination therapy and its respective monotherapy. We conclude that aliskiren's BP-lowering capabilities were comparable to those of ARBs. Aliskiren and ARB combination therapy provided more effective BP reduction than each respective monotherapy without increasing adverse events.

## Appendix B. Abstracts of potentially relevant new trials of angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and direct renin inhibitors

### Head-to-head trials

Bakris GL, Oparil S, Purkayastha D, Yadao AM, Alessi T, Sowers JR. Randomized study of antihypertensive efficacy and safety of combination aliskiren/valsartan vs valsartan monotherapy in hypertensive participants with type 2 diabetes mellitus. *Journal of Clinical Hypertension* 2013;15:92-100.

In this double-blind study, 1143 hypertensive participants with type 2 diabetes and stage 1 or 2 chronic kidney disease (CKD) were randomized to receive combination aliskiren/valsartan 150/160 mg or valsartan 160 mg monotherapy for 2 weeks, with force-titration to 300/320 mg and 320 mg, respectively, for another 6 weeks. Ambulatory blood pressure (ABP), the primary outcome, was available for 665 participants. Reductions from baseline to week 8 in 24-hour ABP were -14.1/-8.7 mm Hg with aliskiren/valsartan vs -10.2/-6.3 mm Hg with valsartan ( $P<.001$ ). Adverse events were reported in 202 participants (35.2%) taking aliskiren/valsartan and 182 participants (32.2%) taking valsartan. No participant had blood urea nitrogen values  $>40$  mg/dL or serum creatinine values  $>2.0$  mg/dL. There were no confirmed cases of serum potassium values  $>6.0$  mEq/L. Combination aliskiren/valsartan has additive effects on blood pressure reduction and tolerability similar to valsartan in hypertensive/diabetic participants with early-stage (stages 1 and 2) CKD. 2012 Wiley Periodicals, Inc.

Bonner G, Bakris GL, Sica D, et al. Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor ramipril. *Journal of Human Hypertension* 2013;27:479-86.

Drug therapy often fails to control hypertension. Azilsartan medoxomil (AZL-M) is a newly developed angiotensin II receptor blocker with high efficacy and good tolerability. This double-blind, controlled, randomised trial compared its antihypertensive efficacy and safety vs the angiotensin-converting enzyme inhibitor ramipril (RAM) in patients with clinic systolic blood pressure (SBP) 150-180mmHg. Patients were randomised (n=884) to 20mg AZL-M or 2.5mg RAM once daily for 2 weeks, then force-titrated to 40 or 80mg AZL-M or 10mg RAM for 22 weeks. The primary endpoint was change in trough, seated, clinic SBP. Mean patient age was 57+11 years, 52.4% were male, 99.5% were Caucasian. Mean baseline BP was 161.1+7.9/94.9+9.0mmHg. Clinic SBP decreased by 20.6+0.95 and 21.2+0.95mmHg with AZL-M 40 and 80mg vs 12.2+0.95mmHg with RAM ( $P<0.001$  for both AZL-M doses). Adverse events leading to discontinuation were less frequent with AZL-M 40 and 80mg (2.4% and 3.1%, respectively) than with RAM (4.8%). These data demonstrated that treatment of stage 1-2 hypertension with AZL-M was more effective than RAM and better tolerated.

Fernandez Juarez G, Luno J, Barrio V, et al. Effect of dual blockade of the renin-angiotensin system on the progression of type 2 diabetic nephropathy: a randomized trial. *American Journal of Kidney Diseases* 2013;61:211-8.

**BACKGROUND:** Blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers has been shown to lessen the rate of decrease in glomerular filtration rate in patients with diabetic nephropathy.

**STUDY DESIGN:** A multicenter open-label randomized controlled trial to compare the efficacy of combining the angiotensin-converting enzyme inhibitor lisinopril and the angiotensin II receptor blocker irbesartan with that of each drug in monotherapy (at both high and equipotent doses) in slowing the progression of type 2 diabetic nephropathy.

**SETTING & POPULATION:** 133 patients with type 2 diabetic nephropathy (age, 66 + 8 years; 76% men) from 17 centers in Spain.

**INTERVENTION:** Patients were randomly assigned (1:1:2) to lisinopril (n = 35), irbesartan (n = 28), or the combination of both (n = 70).

**OUTCOMES:** The primary composite outcome was a >50% increase in baseline serum creatinine level, end-stage renal disease, or death.

**RESULTS:** Baseline values for mean estimated glomerular filtration rate and blood pressure were 49 + 21 mL/min/1.73 m<sup>2</sup> and 153 + 19/81 + 11 mm Hg. Mean geometric baseline proteinuria was protein excretion of 1.32 (95% CI, 1.10-1.62) g/g creatinine. After a median follow-up of 32 months, 21 (30%) patients in the combination group, 10 (29%) in the lisinopril group, and 8 (29%) in the irbesartan group reached the primary outcome. HRs were 0.96 (95% CI, 0.44-2.05; P = 0.9) and 0.90 (95% CI, 0.39-2.02; P = 0.8) for the combination versus the lisinopril and irbesartan groups, respectively. There were no significant differences in proteinuria reduction or blood pressure control between groups. The number of adverse events, including hyperkalemia, was similar in all 3 groups.

**LIMITATIONS:** The study was not double blind. The sample size studied was small.

**CONCLUSIONS:** We were unable to show a benefit of the combination of lisinopril and irbesartan compared to either agent alone at optimal high doses on the risk of progression of type 2 diabetic nephropathy. Copyright 2013 National Kidney Foundation, Inc.

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Fogari R, Mugellini A, Zoppi A, et al. Time course of antiproteinuric effect of aliskiren in arterial hypertension associated with type 2 diabetes and microalbuminuria. *Expert Opin Pharmacother* 2013;14:371-84.

**OBJECTIVE:** The aim was to compare the antiproteinuric effect of aliskiren and ramipril in hypertensive patients with type 2 diabetes and microalbuminuria.

**RESEARCH DESIGN AND METHODS:** A total of 138 patients were treated with aliskiren 300 mg/day or ramipril 10 mg/day for 12 weeks and checked after 1, 2, 4, 8 and 12 weeks and 2 and 4 weeks after treatment withdrawal.

**MAIN OUTCOME MEASURES:** Clinic and ambulatory BP, urinary albumin excretion rate (UAER) and plasma aldosterone were measured.

**RESULTS:** Both aliskiren and ramipril induced a similar lowering in clinic and ambulatory BP (p < 0.001 vs baseline). However, such a lowering persisted longer after stopping aliskiren than after stopping ramipril regimen. Both treatments reduced UAER, but the decrease in UAER associated with aliskiren was more pronounced, the difference vs ramipril being maximal at week 12 (-42 vs -15%, p < 0.01). Two weeks after stopping

therapy, UAER remained below baseline values with aliskiren, but not in the ramipril group. Plasma aldosterone decreased in the aliskiren group, whereas in the ramipril group it decreased until week 8 and thereafter increased toward baseline values.

**CONCLUSIONS:** Aliskiren has a greater and more prolonged antiproteinuric effect than R; it might partly be related to a higher degree of intrarenal renin-angiotensin-aldosterone system blockade. Publication Type: Journal Article. Randomized Controlled Trial.

Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *New England Journal of Medicine* 2013;369:1892-903.

**BACKGROUND:** Combination therapy with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain. **Methods** We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m<sup>2</sup> of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of > 30 ml per minute per 1.73 m<sup>2</sup> if the initial estimated GFR was > 60 ml per minute per 1.73 m<sup>2</sup> or a decline of > 50% if the initial estimated GFR was <60 ml per minute per 1.73 m<sup>2</sup>), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury. **Results** The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001). **Conclusions** Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.).

Lizakowski S, Tylicki L, Renke M, et al. Effect of aliskiren on proteinuria in non-diabetic chronic kidney disease: a double-blind, crossover, randomised, controlled trial. *International Urology & Nephrology* 2012;44:1763-70.

**AIM:** To evaluate the proteinuria-lowering effect of a renin inhibitor (aliskiren), compared to placebo and to an angiotensin-converting enzyme inhibitor (perindopril), in patients with non-diabetic chronic kidney disease.

**METHODS:** A randomised, double-blind, crossover trial was performed in 14 patients with nondiabetic chronic kidney disease with 24-h mean proteinuria of 2.01 g (95% CI,

1.36-2.66) and estimated creatinine clearance of  $93 \pm 6.8$  ml/min. The study consisted of five treatment periods. The patients were randomly assigned to receive aliskiren (150 mg), aliskiren (300 mg), perindopril (5 mg), perindopril (10 mg) or placebo.

**RESULTS:** Aliskiren and perindopril reduced proteinuria. These effects were dose-dependent. Furthermore, 24-h proteinuria was reduced by 23% (mean 95% CI; 2-44) by treatment with aliskiren (150 mg), by 36% (95% CI, 17-55;  $P < 0.001$ ) with aliskiren (300 mg), by 7.1% (95% CI, 11-26) with perindopril (5 mg) and by 25% (95% CI, 11-39;  $P < 0.05$ ) with perindopril (10 mg), compared to placebo. No significant difference was found between the effects of aliskiren and perindopril.

**CONCLUSIONS:** Aliskiren significantly reduced proteinuria. The antiproteinuric effect is probably similar to that of perindopril, for equivalent hypotensive dosages. The renin inhibitor provides a promising alternative approach for the treatment of patients with chronic proteinuric non-diabetic kidney disease.

Mann JFE, Anderson C, Gao P, et al. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial. *Journal of Hypertension* 2013;31:414-21.

**BACKGROUND:** A recent study suggested that addition of a direct renin inhibitor to either an angiotensin-converting enzyme (ACE) inhibitor (ACEi) or an angiotensin receptor blocker (ARB) may increase stroke risk in people with diabetes and renal disease.

**METHODS:** We examined the effects of addition of an ACE inhibitor (ramipril) to an ARB (telmisartan) for a mean follow-up of 56 months in people with diabetes [ $n = 9628$ , mean age 66 years, baseline blood pressure 144/82 mmHg, BMI 29 kg/m<sup>2</sup>, estimated glomerular filtration rate (eGFR) 73 ml/min, and urine albumin 11 mg/mmol] who participated in the ONTARGET trial, divided by those with ( $n = 3163$ ) and without ( $n = 6465$ ) nephropathy. We compared participants on monotherapy with either ramipril or telmisartan with those on dual therapy.

**RESULTS:** SBP decreased more with dual over monotherapy (-7.1 vs. -5.3 mmHg,  $P < 0.0001$ ) and the same number of strokes occurred (1.19 vs. 1.22 per 100 patient-years; hazard ratio 0.99, 95% confidence interval 0.82-1.20). Stroke rate was higher in participants with than those without diabetic nephropathy (1.5 vs. 1.0 per 100 patient-years), but effects of dual-therapy vs. monotherapy were not different in either subgroup (1.59 vs. 1.55 and 1.01 vs. 1.08 per 100 patient-years;  $P$  value for interaction = 0.60). Other cardiovascular and kidney outcomes (dialysis or doubling of serum creatinine) did not differ between dual-therapy and monotherapy in subgroups, but adverse events, namely acute dialysis, hyperkalemia and hypotension, tended to be more frequent with dual therapy.

**CONCLUSION:** A combination of ACEi and ARB does not increase strokes or alter other major cardiovascular or renal events in patients with diabetes, irrespective of the presence of nephropathy.

Meier, P., M. P. Maillard, et al. (2011). "Combining blockers of the renin-angiotensin system or increasing the dose of an angiotensin II receptor antagonist in proteinuric patients: a randomized triple-crossover study." *Journal of Hypertension* 29(6): 1228-1235.

**OBJECTIVE:** The goal of this study was to investigate whether increasing the dose of an angiotensin II receptor blocker (ARB) provides as much benefits as combining the ARB with

an angiotensin-converting enzyme inhibitor (ACEI) in terms of blood pressure (BP) control and urinary albumin excretion (UAE) in hypertensive patients with a proteinuria. **METHODS:** We enrolled 20 hypertensive patients with proteinuric nephropathies and a reduced renal function in a randomized, 12-month, triple-crossover, prospective, open-label study to compare the effects of a regular dose of losartan (Los 100 mg q.d., LOS100) vs. a high dose of losartan (Los 100 mg b.i.d., LOS200) vs. losartan 100 mg q.d. associated with lisinopril 20 mg q.d. (LOS100 + LIS20). Each treatment was given for 8 weeks with a 4-week initial run-in period and 2 weeks of washout between each treatment phases. 24 h UAE and ambulatory BP were measured during the running phase and at the end of each treatment period. **RESULTS:** Compared to pretreatment, 24 h SBP and DBP were reduced by 10/5 +/- 7/4 mmHg with LOS100 (P = 0.023 vs. baseline) and, respectively, 13/6 +/- 12/5 mmHg with LOS200 (P = 0.011) and 19/9 +/- 15/8 mmHg with LOS100 + LIS20 (P < 0.01). UAE decreased significantly with LOS100 and to an even greater degree with LOS200 and LOS100 + LIS20 (P < 0.01 vs. baseline for both and P = 0.032, LOS100 + LIS20 vs. LOS200). The combination had a greater impact in patients with a high baseline proteinuria as suggested by a nonparallel leftward shift of the relationship between the changes in UAE induced by the combination and those induced by LOS200. The high dose of losartan was better tolerated than the combination. **CONCLUSION:** Increasing the dose of losartan from 100 mg once daily to 100 mg twice a day enables to obtain a greater decrease in BP and proteinuria and is better tolerated than combining the ARB with lisinopril, though the high dose appears to be slightly less effective than the combination in patients with a marked proteinuria.

Nakamura, T., N. Fujiwara, et al. (2010). "Effects of telmisartan and enalapril on renoprotection in patients with mild to moderate chronic kidney disease." European Journal of Clinical Investigation **40**(9): 790-796.

**BACKGROUND:** Blocking the renin-angiotensin system (RAS) with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors protects against renal injury in patients with chronic kidney disease (CKD). The aim of this study was to compare the chronic effects of telmisartan and enalapril on proteinuria, urinary liver-type fatty acid-binding protein (L-FABP) and endothelin (ET)-1 levels in patients with mild CKD. **MATERIALS AND METHODS:** Thirty CKD patients with mild to moderate renal insufficiency (20 men and 10 women; mean age, 37 years; estimated glomerular filtration rate (eGFR) > 60 mL min<sup>-1</sup>) and blood pressure > 130/85 mmHg) were included in the study. Patients were randomly assigned to receive telmisartan at 80 mg day<sup>-1</sup> (n = 15) or enalapril at 10 mg day<sup>-1</sup> (n = 15). We measured blood pressure, serum creatinine, eGFR, urinary protein, L-FABP and ET-1 before the start of treatment and 6 and 12 months after the start of treatment. **RESULTS:** The blood pressure reduction rate was similar between the two groups. Urinary protein, L-FABP and ET-1 levels were significantly reduced in both groups 6 and 12 months (P < 0.001) after treatment, but the reduction rates were more pronounced in patients receiving telmisartan than in those receiving enalapril (P < 0.001). Estimated glomerular filtration rate was increased similarly in both groups at 12 months. **CONCLUSIONS:** The study results suggest that telmisartan results in a greater reduction of urinary markers than does enalapril and that this effect occurs by a mechanism independent of blood pressure reduction. It would be needed to investigate whether the differences may be distinct or not the same when other dosages are used.

Nakamura, T., E. Sato, et al. (2012). "Addition of aliskiren to olmesartan ameliorates tubular injury in chronic kidney disease patients partly by reducing proteinuria." Journal of the Renin-Angiotensin-Aldosterone System **13**(1): 122-127.

**INTRODUCTION:** Tubular injury is more important than glomerulopathy for renal prognosis in chronic kidney disease (CKD) patients. Numerous studies have demonstrated the active participation of the renin-angiotensin system (RAS) in CKD. However, whether addition of aliskiren, a direct renin inhibitor, to olmesartan improves renal tubular injury in CKD patients is unknown. **METHODS:** This study compared the effects of aliskiren (300 mg daily), olmesartan (40 mg daily), and its combination therapy on urinary L-fatty acid binding protein (L-FABP), a marker of tubular injury in stage I or II CKD patients. It also examined which clinical variables were independently correlated with tubular damage. **RESULTS:** Olmesartan or aliskiren monotherapy for 6 months comparably decreased blood pressure (BP) and proteinuria. BP and proteinuria levels were reduced more by combination therapy than by either monotherapy. Olmesartan or aliskiren decreased urinary L-FABP level, and combination therapy produced more incremental reduction in L-FABP level relative to each monotherapy. Multiple stepwise regression analysis revealed that BMI, low-density lipoprotein (LDL)-cholesterol and proteinuria were independently related to urinary L-FABP level. **CONCLUSIONS:** The present study demonstrated that addition of aliskiren to olmesartan decreased urinary L-FABP level partly via reduction of proteinuria in stage I or II CKD patients.

Reyes-Marin FA, Calzada C, Ballesteros A, Amato D. Comparative study of enalapril vs. losartan on residual renal function preservation in automated peritoneal dialysis. A randomized controlled study. *Revista de Investigacion Clinica* 2012;64:315-21.

**BACKGROUND:** Residual renal function (RRF) is an important determinant of mortality and morbidity in patients receiving peritoneal dialysis (PD). Recent studies have shown a positive effect of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) on RRF in PD patients.

**OBJECTIVE:** To compare enalapril and losartan for RRF preservation in automated peritoneal dialysis (APD) patients.

**MATERIAL AND METHODS:** An open label randomized controlled trial (RCT) with a 12 month follow-up period was conducted to compare the effect of enalapril vs. losartan on RRF preservation in 60 APD patients. Measurements were done at the start of the study (baseline), 3, 6, 9, and 12 months. A historical control group (HCG) without treatment was included to assess the natural history of RRF loss.

**RESULTS:** RRF in the enalapril group dropped from 3.65 +/- 1.6 (baseline) to 2.36 +/- 0.38 mL/min/1.73 m<sup>2</sup> (12 months). In the losartan group RRF was reduced from 4.1 +/- 2.01 (baseline) to 2.54 +/- 0.47 mL/min/ 1.73 m<sup>2</sup> (12 months). There were not significant differences between the two groups regarding RRF at 12 months. In the HCG, RRF declined from 3.68 +/- 0.48 to 1.4 +/- 0.29 mL/min/ 1.73 m<sup>2</sup> (12 months). RRF in the HCG was significantly lower than RRF in the two treated groups at 12 months (P < 0.05).

**CONCLUSIONS:** There was not significant difference on RRF preservation between enalapril and losartan groups. Comparing these results to those of the HCG suggests that the treatment with any of the drugs is useful in preserving RRF.

Slagman, M. C. J., F. Waanders, et al. (2011). "Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial." *BMJ* **343**: d4366.

**OBJECTIVE:** To compare the effects on proteinuria and blood pressure of addition of dietary sodium restriction or angiotensin receptor blockade at maximum dose, or their combination, in patients with non-diabetic nephropathy receiving background treatment with angiotensin converting enzyme (ACE) inhibition at maximum dose. **DESIGN:** Multicentre crossover randomised controlled trial. **SETTING:** Outpatient clinics in the Netherlands.

**PARTICIPANTS:** 52 patients with non-diabetic nephropathy. **INTERVENTIONS:** All patients were treated during four 6 week periods, in random order, with angiotensin receptor blockade (valsartan 320 mg/day) or placebo, each combined with, consecutively, a low sodium diet (target 50 mmol Na<sup>(+)</sup>/day) and a regular sodium diet (target 200 mmol Na<sup>(+)</sup>/day), with a background of ACE inhibition (lisinopril 40 mg/day) during the entire study. The drug interventions were double blind; the dietary interventions were open label.

**MAIN OUTCOME MEASURES:** The primary outcome measure was proteinuria; the secondary outcome measure was blood pressure. **RESULTS:** Mean urinary sodium excretion, a measure of dietary sodium intake, was 106 (SE 5) mmol Na<sup>(+)</sup>/day during a low sodium diet and 184 (6) mmol Na<sup>(+)</sup>/day during a regular sodium diet (P<0.001). Geometric mean residual proteinuria was 1.68 (95% confidence interval 1.31 to 2.14) g/day during ACE inhibition plus a regular sodium diet. Addition of angiotensin receptor blockade to ACE inhibition reduced proteinuria to 1.44 (1.07 to 1.93) g/day (P=0.003), addition of a low sodium diet reduced it to 0.85 (0.66 to 1.10) g/day (P<0.001), and addition of angiotensin receptor blockade plus a low sodium diet reduced it to 0.67 (0.50 to 0.91) g/day (P<0.001). The reduction of proteinuria by the addition of a low sodium diet to ACE inhibition (51%, 95% confidence interval 43% to 58%) was significantly larger (P<0.001) than the reduction of proteinuria by the addition of angiotensin receptor blockade to ACE inhibition (21%, (8% to 32%) and was comparable (P=0.009, not significant after Bonferroni correction) to the reduction of proteinuria by the addition of both angiotensin receptor blockade and a low sodium diet to ACE inhibition (62%, 53% to 70%). Mean systolic blood pressure was 134 (3) mm Hg during ACE inhibition plus a regular sodium diet. Mean systolic blood pressure was not significantly altered by the addition of angiotensin receptor blockade (131 (3) mm Hg; P=0.12) but was reduced by the addition of a low sodium diet (123 (2) mm Hg; P<0.001) and angiotensin receptor blockade plus a low sodium diet (121 (3) mm Hg; P<0.001) to ACE inhibition. The reduction of systolic blood pressure by the addition of a low sodium diet (7% (SE 1%)) was significantly larger (P=0.003) than the reduction of systolic blood pressure by the addition of angiotensin receptor blockade (2% (1)) and was similar (P=0.14) to the reduction of systolic blood pressure by the addition of both angiotensin receptor blockade and low sodium diet (9% (1)), to ACE inhibition. **CONCLUSIONS:** Dietary sodium restriction to a level recommended in guidelines was more effective than dual blockade for reduction of proteinuria and blood pressure in non-diabetic nephropathy. The findings support the combined endeavours of patients and health professionals to reduce sodium intake. Trial registration Netherlands Trial Register NTR675.

Suzuki, H., K. Okada, et al. (2013). "Aliskiren reduces home blood pressure and albuminuria in patients with hypertensive nephrosclerosis." *Clinical & Experimental Nephrology* **17**(3): 386-395.

**BACKGROUND:** The aim of this study was to investigate the antialbuminuric and antihypertensive effects of aliskiren by monitoring home blood pressure (BP) in comparison with the effects of the angiotensin receptor blocker (ARB) valsartan in patients with hypertensive nephrosclerosis and albuminuria.

**METHODS:** We conducted an open-label, randomized trial to compare the effects of aliskiren with those of valsartan. Patients with BP <150/90 mmHg, an estimated glomerular filtration rate of 90-30 mL/min/1.73 m<sup>2</sup>, and albuminuria >30 mg/g, despite treatment with a 160 mg daily dose of valsartan, were randomly assigned to the following two groups: the aliskiren group, who switched from 160 mg/day valsartan to 150 mg/day aliskiren, which was later increased to 300 mg/day (n = 20); and the valsartan group, who continued with 160 mg/day valsartan (n = 20).

**RESULTS:** After 12 weeks of treatment, although there was no significant difference in clinic BP between groups, a significant reduction in morning and evening systolic BP was observed in the aliskiren group. The decrease in albuminuria in the aliskiren group was significantly better than that in the valsartan group, and a significant correlation was noted between the change in morning systolic BP and the change in albuminuria in the aliskiren group (r = 0.564, P = 0.0084).

**CONCLUSION:** We showed that aliskiren treatment leads to a greater reduction in albuminuria and home systolic BP values than valsartan in patients with nephrosclerosis. We propose that aliskiren therapy should be considered as a therapeutic modality to complement ARBs in hypertensive patients with nephrosclerosis.

Titan, S. M., R. Zatz, et al. (2011). "FGF-23 as a predictor of renal outcome in diabetic nephropathy." Clinical Journal of The American Society of Nephrology: CJASN 6(2): 241-247.

**BACKGROUND AND OBJECTIVES:** Fibroblast growth factor 23 (FGF-23) has emerged as a new factor in mineral metabolism in chronic kidney disease (CKD). An important regulator of phosphorus homeostasis, FGF-23 has been shown to independently predict CKD progression in nondiabetic renal disease. We analyzed the relation between FGF-23 and renal outcome in diabetic nephropathy (DN). **DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** DN patients participating in a clinical trial (enalapril+placebo versus enalapril+losartan) had baseline data collected and were followed until June 2009 or until the primary outcome was reached. Four patients were lost to follow-up. The composite primary outcome was defined as death, doubling of serum creatinine, and/or dialysis need.

**RESULTS:** At baseline, serum FGF-23 showed a significant association with serum creatinine, intact parathyroid hormone, proteinuria, urinary fractional excretion of phosphate, male sex, and race. Interestingly, FGF-23 was not related to calcium, phosphorus, 25OH-vitamin D, or 24-hour urinary phosphorus. Mean follow-up time was 30.7+/-10 months. Cox regression showed that FGF-23 was an independent predictor of the primary outcome, even after adjustment for creatinine clearance and intact parathyroid hormone (10 pg/ml FGF-23 increase = hazard ratio, 1.09; 95% CI, 1.01 to 1.16, P=0.02). Finally, Kaplan-Meier analysis showed a significantly higher risk of the primary outcome in patients with FGF-23 values of >70 pg/ml. **CONCLUSIONS:** FGF-23 is a significant independent predictor of renal outcome in patients with macroalbuminuric DN. Further studies should clarify whether this relation is causal and whether FGF-23 should be a new therapeutic target for CKD prevention.

Tylicki L, Lizakowski S, Rutkowski P, et al. The enhanced renin-angiotensin-aldosterone system pharmacological blockade--which is the best? *Kidney & Blood Pressure Research* 2012;36:335-43.

**BACKGROUND/AIMS:** Pharmacological inhibition of renin-angiotensin-aldosterone system (RAAS) may reduce proteinuria and the rate of chronic kidney disease progression. The aim was to compare the effects on albuminuria of the therapy with

either: (i) telmisartan 80 mg and aliskiren 300 mg, (ii) telmisartan 80 mg and eplerenone 50 mg, (iii) telmisartan 160 mg as monotherapy.

DESIGN AND PATIENTS: Randomized, double-center, double-blind, cross-over, three treatments-three periods of 8 weeks each study. 18 patients with non-diabetic proteinuric CKD stage 1-3 completed the protocol.

RESULTS: There was significant difference in albuminuria between studied therapies (ANOVA;  $p < 0.01$ ). The combination therapy with telmisartan plus aliskiren decreased albuminuria more effectively than the treatment with telmisartan plus eplerenone and monotherapy with telmisartan 160 mg OD [376 mg/g creatinine (286-686) vs. 707 (502-1204) vs. 525 (318-763); post-hoc  $p < 0.01$  and  $p < 0.05$ , respectively].

CONCLUSIONS: The study demonstrated that the combination therapy with angiotensin receptor blocker (ARB) and renin inhibitor was more effective in albuminuria lowering than the concomitant usage of ARB and mineralocorticoid receptor antagonist as well as than ARB in doses two-fold higher than usually used in treatment of hypertension in patients with non-diabetic CKD and that this higher antiproteinuric efficacy was independent on changes in blood pressure. Copyright 2012 S. Karger AG, Basel.

Woo, K. T., C. M. Chan, et al. (2009). "Beneficial effects of high-dose losartan in IgA nephritis." Clinical Nephrology **71**(6): 617-624.

AIM: Several short-term studies have reported the efficacy of high-dose ARB in reducing proteinuria in patients with diabetic nephropathy. The benefits of long-term high-dose ARB losartan in IgA nephritis have not been explored. METHOD: This was a 6-year randomized trial in 207 patients with IgA nephritis comparing high-dose ARB (losartan 200 mg/day) with normal dose ARB (losartan 100 mg/day), normal dose ACEI (20 mg/day) and low-dose ACEI (10 mg/day). Multivariate ANOVA was used to test the effect of drug treatment on both eGFR and total urinary protein (TUP). RESULTS: Comparing patients on high-dose ARB ( $n = 63$ ) with those on normal dose ARB ( $n = 43$ ), normal dose ACEI ( $n = 61$ ) and low-dose ACEI ( $n = 40$ ), patients on high Dose ARB had significantly higher eGFR ( $p < 0.0005$ ) and lower proteinuria ( $p < 0.005$ ) at the end of the study. The loss in eGFR was 0.7 ml/min/year for high-dose ARB compared to 3.2 - 3.5 ml/min/year for the other 3 groups ( $p = 0.0005$ ). There were more patients on high-dose ARB with improvement in eGFR compared to other 3 groups ( $p < 0.001$ ). CONCLUSION: Data from this study suggest that high-dose ARB therapy is more efficacious in reducing proteinuria and preserving renal function when compared with normal dose ARB and ACEI. In Year 5, patients on high-dose ARB had a gain in eGFR suggesting that there is possibility of recovery of renal function in these patients on long-term high-dose therapy.

Xie, D., F. F. Hou, et al. (2011). "High level of proteinuria during treatment with renin-angiotensin inhibitors is a strong predictor of renal outcome in nondiabetic kidney disease." Journal of Clinical Pharmacology **51**(7): 1025-1034.

This study investigated whether proteinuria not only could serve as a marker of renal outcome but also could monitor the renoprotection of renin-angiotensin system (RAS) inhibitor treatment in patients with nondiabetic chronic kidney disease (CKD). Data from the Renoprotection of Optimal Antiproteinuric Doses (ROAD) trial were used to examine the contribution of the antiproteinuric effect of benazepril and losartan on renal outcome (the primary composite end point of doubling of serum creatinine and end-stage renal disease or death) in 339 Chinese nondiabetic CKD patients with overt proteinuria and renal insufficiency. The degree of proteinuria at month 6 of treatment (residual proteinuria) and

during follow-up (time-average proteinuria) showed a close relationship with renal end points. Lowering of proteinuria reduced the risk of renal progression in patients with high, as well as low, proteinuria at baseline. After adjustment for baseline risk markers, therapy-induced change in these variables at month 6 and during follow-up--high residual proteinuria and time-average proteinuria ( $\geq 1.0$  g/d)--remained the independent predictors for renal end points. Therefore, minimization of proteinuria at least to less than 1.0 g/d should be a therapeutic goal in the management of nondiabetic patients with heavy proteinuria and renal insufficiency.

Yu, L.-T., J. Zhu, et al. (2011). "Telmisartan, ramipril, or both in high-risk Chinese patients: analysis of ONTARGET China data." *Chinese Medical Journal* **124**(12): 1763-1768.

**BACKGROUND:** The results from the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) indicated that the angiotensin-receptor blocker telmisartan was not inferior to the angiotensin-converting-enzyme inhibitor ramipril in reducing the composite endpoint of cardiovascular death, myocardial infarction, stroke or hospitalization for congestive heart failure in high-risk patients, and telmisartan was associated with slightly superior tolerability. The combination of the two drugs was associated with more adverse events without an increase in benefit. This study aimed to analyze the data from ONTARGET obtained from a subgroup of patients enrolled in China and to evaluate the demographic and baseline characteristics, the compliance, efficacy, and safety of the different treatment strategies in randomized patients in China. **METHODS:** A total of 1159 high-risk patients were randomized into three treatment groups: with 390 assigned to receive 80 mg of telmisartan, 385 assigned to receive 10 mg of ramipril and 384 assigned to receive both study medications. The median follow-up period was 4.3 years. **RESULTS:** The mean age of Chinese patients was 65.6 years, 73.6% of patients were male. The proportion of patients with stroke/transient ischemic attacks at baseline in China was two times more than the entire study population (47.7% vs. 20.9%). In Chinese patients the proportion of permanent discontinuation of study medication due to cough was 0.5% in the telmisartan group, which was much less than that in the combination or the ramipril group. There were no significant differences in the incidence of primary outcome among three treatment groups of Chinese patients. More strokes occurred in Chinese patients than in the entire study population (8.5% vs. 4.5%). Greater systolic blood pressure reduction (-9.8 mmHg), and more renal function failure were noted in the combination treatment group than in the ramipril or telmisartan group (2.6% vs. 1.6% and 1.0%). **CONCLUSIONS:** There was no evidence that the results of ONTARGET differed between Chinese patients and the entire study population with respect to the incidence of primary outcome, particularly safety. Compliance with study medications was good. The evidence from ONTARGET indicated that the treatment strategies in ONTARGET were applicable to patients in China.

## Placebo-controlled trials

Gheorghiade M, Bohm M, Greene SJ, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial.[Erratum appears in JAMA. 2013 Apr 10;309(14):1461]. *Jama* 2013;309:1125-35.

**IMPORTANCE:** Hospitalizations for heart failure (HHF) represent a major health burden, with high rates of early postdischarge rehospitalization and mortality.

**OBJECTIVE:** To investigate whether aliskiren, a direct renin inhibitor, when added to standard therapy, would reduce the rate of cardiovascular (CV) death or HF rehospitalization among HHF patients.

**DESIGN, SETTING, AND PARTICIPANTS:** International, double-blind, placebo-controlled study that randomized hemodynamically stable HHF patients a median 5 days after admission. Eligible patients were 18 years or older with left ventricular ejection fraction (LVEF) 40% or less, elevated natriuretic peptides (brain natriuretic peptide [BNP] > 400 pg/mL or N-terminal pro-BNP [NT-proBNP] > 1600 pg/mL), and signs and symptoms of fluid overload. Patients were recruited from 316 sites across North and South America, Europe, and Asia between May 2009 and December 2011. The follow-up period ended in July 2012.

**INTERVENTION:** All patients received 150 mg (increased to 300 mg as tolerated) of aliskiren or placebo daily, in addition to standard therapy. The study drug was continued after discharge for a median 11.3 months. **MAIN OUTCOME MEASURES** Cardiovascular death or HF rehospitalization at 6 months and 12 months.

**RESULTS:** In total, 1639 patients were randomized, with 1615 patients included in the final efficacy analysis cohort (808 aliskiren, 807 placebo). Mean age was 65 years; mean LVEF, 28%; 41% of patients had diabetes mellitus, mean estimated glomerular filtration rate, 67 mL/min/1.73 m<sup>2</sup>. At admission and randomization, median NT-proBNP levels were 4239 pg/mL and 2718 pg/mL, respectively. At randomization, patients were receiving diuretics (95.9%), beta-blockers (82.5%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (84.2%), and mineralocorticoid receptor antagonists (57.0%). In total, 24.9% of patients receiving aliskiren (77 CV deaths, 153 HF rehospitalizations) and 26.5% of patients receiving placebo (85 CV deaths, 166 HF rehospitalizations) experienced the primary end point at 6 months (hazard ratio [HR], 0.92; 95% CI, 0.76-1.12; P = .41). At 12 months, the event rates were 35.0% for the aliskiren group (126 CV deaths, 212 HF rehospitalizations) and 37.3% for the placebo group (137 CV deaths, 224 HF rehospitalizations; HR, 0.93; 95% CI, 0.79-1.09; P = .36). The rates of hyperkalemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with placebo.

**CONCLUSION AND RELEVANCE:** Among patients hospitalized for HF with reduced LVEF, initiation of aliskiren in addition to standard therapy did not reduce CV death or HF rehospitalization at 6 months or 12 months after discharge.

Maggioni, A. P., S. J. Greene, et al. (2013). "Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial." *European Heart Journal* **34**(40): 3117-3127.

**AIMS:** The objective of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) was to determine whether aliskiren, a direct renin inhibitor, would improve post-discharge outcomes in patients with hospitalization for heart failure (HHF) with reduced ejection fraction. Pre-specified subgroup analyses suggested potential heterogeneity in post-discharge outcomes with aliskiren in patients with and without baseline diabetes mellitus (DM).

**METHODS AND RESULTS:** ASTRONAUT included 953 patients without DM (aliskiren 489; placebo 464) and 662 patients with DM (aliskiren 319; placebo 343) (as reported by study investigators). Study endpoints included the first occurrence of

cardiovascular death or HHF within 6 and 12 months, all-cause death within 6 and 12 months, and change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 1, 6, and 12 months. Data regarding risk of hyperkalaemia, renal impairment, and hypotension, and changes in additional serum biomarkers were collected. The effect of aliskiren on cardiovascular death or HHF within 6 months (primary endpoint) did not significantly differ by baseline DM status ( $P = 0.08$  for interaction), but reached statistical significance at 12 months (non-DM: HR: 0.80, 95% CI: 0.64-0.99; DM: HR: 1.16, 95% CI: 0.91-1.47;  $P = 0.03$  for interaction). Risk of 12-month all-cause death with aliskiren significantly differed by the presence of baseline DM (non-DM: HR: 0.69, 95% CI: 0.50-0.94; DM: HR: 1.64, 95% CI: 1.15-2.33;  $P < 0.01$  for interaction). Among non-diabetics, aliskiren significantly reduced NT-proBNP through 6 months and plasma troponin I and aldosterone through 12 months, as compared to placebo. Among diabetic patients, aliskiren reduced plasma troponin I and aldosterone relative to placebo through 1 month only. There was a trend towards differing risk of post-baseline potassium  $>6$  mmol/L with aliskiren by underlying DM status (non-DM: HR: 1.17, 95% CI: 0.71-1.93; DM: HR: 2.39, 95% CI: 1.30-4.42;  $P = 0.07$  for interaction).

**CONCLUSION:** This pre-specified subgroup analysis from the ASTRONAUT trial generates the hypothesis that the addition of aliskiren to standard HHF therapy in non-diabetic patients is generally well-tolerated and improves post-discharge outcomes and biomarker profiles. In contrast, diabetic patients receiving aliskiren appear to have worse post-discharge outcomes. Future prospective investigations are needed to confirm potential benefits of renin inhibition in a large cohort of HHF patients without DM.

Nicholls SJ, Bakris GL, Kastelein JJP, et al. Effect of aliskiren on progression of coronary disease in patients with prehypertension: the AQUARIUS randomized clinical trial. *Jama* 2013;310:1135-44.

**IMPORTANCE:** Blood pressure reduction and renin-angiotensin-aldosterone system inhibition are targets for treatment of atherosclerosis. The effect of renin inhibition on coronary disease progression has not been investigated.

**OBJECTIVE:** To determine the effects of renin inhibition with aliskiren on progression of coronary atherosclerosis.

**DESIGN, SETTING, AND PARTICIPANTS:** A double-blind, randomized, multicenter trial (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study) comparing aliskiren with placebo in 613 participants with coronary artery disease, systolic blood pressure between 125 and 139 mm Hg (prehypertension range), and 2 additional cardiovascular risk factors conducted at 103 academic and community hospitals in Europe, Australia, and North and South America (enrollment from March 2009 to February 2011; end of follow-up: January 31, 2013).

**INTERVENTIONS:** Participants underwent coronary intravascular ultrasound (IVUS) imaging and were randomized to receive 300 mg of aliskiren ( $n=305$ ) or placebo ( $n=308$ ) taken orally daily for 104 weeks. Disease progression was measured by repeat IVUS examination after at least 72 weeks of treatment.

**MAIN OUTCOMES AND MEASURES:** The primary efficacy parameter was the change in percent atheroma volume (PAV) from baseline to study completion. Secondary efficacy parameters included the change in normalized total atheroma volume (TAV) and

the percentage of participants with atheroma regression. Safety and tolerability were also assessed.

**RESULTS:** Evaluable imaging data were available at baseline and follow-up for 458 participants (74.7%). The primary IVUS efficacy parameter, PAV, did not differ between participants treated with aliskiren (-0.33%; 95% CI, -0.68% to 0.02%) and placebo (0.11%; 95% CI, -0.24% to 0.45%) (between-group difference, -0.43% [95% CI, -0.92% to 0.05%];  $P=.08$ ). The secondary IVUS efficacy parameter, TAV, did not differ between participants treated with aliskiren (-4.1 mm<sup>3</sup>; 95% CI, -6.27 to -1.94 mm<sup>3</sup>) and placebo (-2.1 mm<sup>3</sup>; 95% CI, -4.21 to 0.07 mm<sup>3</sup>) (between-group difference, -2.04 mm<sup>3</sup> [95% CI, -5.03 to 0.95 mm<sup>3</sup>];  $P=.18$ ). There were no significant differences in the proportion of participants who demonstrated regression of PAV (56.9% vs 48.9%;  $P=.08$ ) and TAV (64.4% vs 57.5%;  $P=.13$ ) in the aliskiren and placebo groups, respectively.

**CONCLUSIONS AND RELEVANCE:** Among participants with prehypertension and coronary artery disease, the use of aliskiren compared with placebo did not result in improvement or slowing of progression of coronary atherosclerosis. These findings do not support the use of aliskiren for regression or prevention of progression of coronary atherosclerosis.

**TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00853827.

Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *New England Journal of Medicine* 2012;367:2204-13.

**BACKGROUND:** This study was undertaken to determine whether use of the direct renin inhibitor aliskiren would reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both.

**METHODS:** In a double-blind fashion, we randomly assigned 8561 patients to aliskiren (300 mg daily) or placebo as an adjunct to an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker. The primary end point was a composite of the time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum creatinine level.

**RESULTS:** The trial was stopped prematurely after the second interim efficacy analysis. After a median follow-up of 32.9 months, the primary end point had occurred in 783 patients (18.3%) assigned to aliskiren as compared with 732 (17.1%) assigned to placebo (hazard ratio, 1.08; 95% confidence interval [CI], 0.98 to 1.20;  $P=0.12$ ). Effects on secondary renal end points were similar. Systolic and diastolic blood pressures were lower with aliskiren (between-group differences, 1.3 and 0.6 mm Hg, respectively) and the mean reduction in the urinary albumin-to-creatinine ratio was greater (between-group difference, 14 percentage points; 95% CI, 11 to 17). The proportion of patients with hyperkalemia (serum potassium level, >6 mmol per liter) was significantly higher in the aliskiren group than in the placebo group (11.2% vs. 7.2%), as was the proportion with reported hypotension (12.1% vs. 8.3%) ( $P<0.001$  for both comparisons).

**CONCLUSIONS:** The addition of aliskiren to standard therapy with renin-angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. (Funded by Novartis; ALTITUDE ClinicalTrials.gov number, NCT00549757.).

Persson, F., J. B. Lewis, et al. (2010). "Impact of baseline renal function on the efficacy and safety of aliskiren added to losartan in patients with type 2 diabetes and nephropathy." *Diabetes Care* **33**(11): 2304-2309.

**OBJECTIVE:** Proteinuric diabetic patients with reduced glomerular filtration rate (GFR) are at high risk of renal and cardiovascular disease progression and treatment-related adverse events. This post hoc analysis assessed the efficacy and safety of aliskiren added to the maximal recommended dose of losartan according to baseline estimated GFR (eGFR) (stage 1-3 chronic kidney disease [CKD]). **RESEARCH DESIGN AND METHODS:** In the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study, 599 hypertensive patients with type 2 diabetes and nephropathy received 6 months of aliskiren (150 mg daily titrated to 300 mg daily after 3 months) or placebo added to 100 mg losartan and optimal antihypertensive therapy. Exclusion criteria included eGFR < 30 ml/min per 1.73 m<sup>2</sup> and serum potassium > 5.1 mmol/l. **RESULTS:** Baseline characteristics were similar between treatment groups in all CKD stages. The antiproteinuric effects of aliskiren were consistent across CKD stages (19, 22, and 18% reduction). In the stage 3 CKD group, baseline serum creatinine levels were equal, but renal dysfunction, prespecified as a postrandomization serum creatinine elevation > 176.8 μmol/l (2.0 mg/dl) occurred more frequently in the placebo group (29.2 vs. 13.6%, P=0.032). Serum potassium elevations > 5.5 mmol/l (based on a single measurement) were more frequent with aliskiren (22.5 vs. 13.6%) in stage 3 CKD. Adverse event rates were similar between treatments, irrespective of CKD stage. **CONCLUSIONS:** Aliskiren added to losartan reduced albuminuria and renal dysfunction and was well tolerated, except for hyperkalemia (stage 3), independent of baseline CKD stage in patients with type 2 diabetes, hypertension, and nephropathy.

Pitt, B., R. Latini, et al. (2011). "Neurohumoral effects of aliskiren in patients with symptomatic heart failure receiving a mineralocorticoid receptor antagonist: the Aliskiren Observation of Heart Failure Treatment study." *European Journal of Heart Failure* **13**(7): 755-764.

**AIMS:** We evaluated the influence of concomitant mineralocorticoid receptor antagonists (MRAs) on the safety and neurohumoral effects of a direct renin inhibitor in the ALiskiren Observation of Heart Failure Treatment (ALOFT) study. **METHODS AND RESULTS:** Patients with stable New York Heart Association class II-IV heart failure (HF), plasma B-type natriuretic peptide (BNP) concentration > 100 pg/mL, and treated with an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) and beta-blocker were randomized to once-daily, double-blind treatment with aliskiren 150 mg or placebo, added to optimal HF therapy, for 12 weeks. Safety, tolerability, and effects of aliskiren on neurohumoral biomarkers were assessed in patients who received (MRA+) and did not receive (MRA-) MRA treatment at baseline. Of the 302 randomized patients, 101 were receiving MRA treatment (aliskiren, n = 52; placebo, n = 49). Mineralocorticoid receptor antagonist status did not affect the ability of aliskiren 150 mg, added to standard HF therapy, to lower BNP, N-terminal proBNP, plasma renin activity, and urinary aldosterone. For example, the end-of-study to baseline ratio of geometric mean for BNP was: MRA+ group: aliskiren 0.68 [95% confidence interval (CI) 0.47, 0.98], placebo 0.85 (0.58, 1.24); MRA- group: aliskiren 0.62 (0.45, 0.84), placebo 0.85 (0.63, 1.15), interaction P= 0.720. The incidence of pre-specified adverse events (renal dysfunction, symptomatic hypotension, and hyperkalaemia) was low, and there were no significant differences between aliskiren and placebo in either MRA subgroup. **CONCLUSION:** Aliskiren 150 mg added to standard HF therapy was well tolerated over 12 weeks and provided beneficial changes in neurohumoral biomarkers regardless of concomitant MRA treatment.

Solomon, S. D., S. H. Shin, et al. (2011). "Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction." European Heart Journal **32**(10): 1227-1234.

**AIMS:** Direct renin inhibitors provide an alternative approach to inhibiting the renin-angiotensin-aldosterone system (RAAS) at the most proximal, specific, and rate-limiting step. We tested the hypothesis that direct renin inhibition would attenuate left ventricular remodelling in patients following acute myocardial infarction receiving stable, individually optimized therapy, including another inhibitor of the RAAS. **METHODS AND RESULTS:** We randomly assigned 820 patients between ~2 and 8 weeks following acute myocardial infarction, with the left ventricular ejection fraction (LVEF)  $\leq 45\%$ , and regional wall motion abnormalities ( $\geq 20\%$  akinetic area), to receive aliskiren (n = 423), titrated to 300 mg, or matched placebo (n = 397), added to the standard therapy. All patients were required to be on a stable dose of an ACE-inhibitor or ARB, and beta-blocker unless contraindicated or not tolerated. Echocardiograms were obtained at baseline, and following 26-36 weeks of treatment. The primary endpoint was change in left ventricular end-systolic volume from baseline to 36 weeks, and was evaluable in 329 patients in the placebo group and 343 patients in the aliskiren group. We observed no difference in the primary endpoint of end-systolic volume change between patients randomized to aliskiren (-4.4 +/- 16.8 mL) or placebo (-3.5 +/- 16.3 mL), or in secondary measures of end-diastolic volume, or LVEF. We also observed no differences in a composite endpoint of cardiovascular death, hospitalization for heart failure, or reduction in LVEF  $>6$  points. There were more investigator reported adverse events in the aliskiren group, including hypotension, increases in creatinine and hyperkalaemia. **CONCLUSION:** Adding the direct renin inhibitor aliskiren to the standard therapy, including an inhibitor of the RAAS, in high-risk post-MI patients did not result in further attenuation of left ventricular remodelling, and was associated with more adverse effects. These findings do not suggest that dual RAAS blockade with aliskiren would provide additional benefit in these high-risk post-MI patients.

Testani, J. M., S. E. Kimmel, et al. (2011). "Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction." Circulation: Heart Failure **4**(6): 685-691.

**BACKGROUND:** Worsening renal function (WRF) in the setting of heart failure has been associated with increased mortality. However, it is unclear if this decreased survival is a direct result of the reduction in glomerular filtration rate (GFR) or if the mechanism underlying the deterioration in GFR is driving prognosis. Given that WRF in the setting of angiotensin-converting enzyme inhibitor (ACE-I) initiation is likely mechanistically distinct from spontaneously occurring WRF, we investigated the relative early WRF-associated mortality rates in subjects randomized to ACE-I or placebo. **METHODS AND RESULTS:** Subjects in the Studies Of Left Ventricular Dysfunction (SOLVD) limited data set (n=6337) were studied. The interaction between early WRF (decrease in estimated GFR  $\geq 20\%$  at 14 days), randomization to enalapril, and mortality was the primary end point. In the overall population, early WRF was associated with increased mortality (adjusted hazard ratio [HR], 1.2; 95% CI, 1.0-1.4; P=0.037). When analysis was restricted to the placebo group, this association strengthened (adjusted HR, 1.4; 95% CI, 1.1-1.8; P=0.004). However, in the enalapril group, early WRF had no adverse prognostic significance (adjusted HR, 1.0; 95% CI, 0.8-1.3; P=1.0; P=0.09 for the interaction). In patients who continued to receive study drug despite early WRF, a survival advantage remained with enalapril therapy (adjusted HR, 0.66; 95% CI, 0.5-0.9; P=0.018). **CONCLUSIONS:** These data support the notion that the mechanism underlying WRF is important in determining its prognostic significance.

Specifically, early WRF in the setting of ACE-I initiation appears to represent a benign event that is not associated with a loss of benefit from continued ACE-I therapy.

Villa G, Le Breton S, Ibram G, Keefe DL. Efficacy, safety, and tolerability of aliskiren monotherapy administered with a light meal in elderly hypertensive patients: a randomized, double-blind, placebo-controlled, dose-response evaluation study. *Journal of clinical pharmacology* 2012;52:1901-11.

This randomized, double-blind, placebo-controlled study assessed the efficacy, safety, and tolerability of aliskiren 75, 150, and 300 mg to clarify the dose-response relationship and characterize the optimum aliskiren dose when given with a light meal to elderly hypertensive patients. After washout, 754 patients aged >65 years with hypertension (mean sitting systolic blood pressure [msSBP] >150 and <180 mm Hg; mean sitting diastolic blood pressure [msDBP] <110 mm Hg) were randomized to aliskiren 75, 150, or 300 mg or placebo for 8 weeks; medication was taken each morning with a light meal. The primary efficacy variable was change in msSBP from baseline to week 8 end point. Change from baseline in msDBP and dose-response curves for aliskiren 75, 150, and 300 mg were also assessed. At week 8 end point, all 3 aliskiren doses provided significantly greater least squares mean reductions in msSBP/msDBP (75 mg, 13/5 mm Hg; 150 mg, 15/6 mm Hg; 300 mg, 14/7 mm Hg) compared with placebo (8/4 mm Hg;  $P < .05$ ).

Aliskiren was generally well tolerated at all doses. There was a significant dose-response relationship for aliskiren, with an estimated minimum effective dose of 81.9 mg. In conclusion, aliskiren 150 and 300 mg provided effective blood pressure control in elderly patients. Webb NJA, Shahinfar S, Wells TG, et al. Losartan and enalapril are comparable in reducing proteinuria in children. *Kidney International* 2012;82:819-26.

Angiotensin-converting enzyme inhibitors and angiotensin II type I receptor blockers delay progression of chronic kidney disease and have antiproteinuric effects beyond their effects on blood pressure. They are routinely used in adults; however, their efficacy and safety in children, in whom the causes of chronic kidney disease are significantly different relative to adults, is uncertain. Here we assessed an open-label extension of a previous 3-month blinded trial, in which the efficacy and tolerability of losartan was compared to placebo or amlodipine in 306 normotensive and hypertensive children with proteinuria. In this study, 268 children were re-randomized to losartan or enalapril and followed until 100 patients completed 3 years of follow-up for proteinuria and renal function. The least squares percent mean reduction from baseline in the urinary protein/creatinine ratio was 30.01% for losartan and 40.45% for enalapril. The least squares mean change from baseline in eGFR was 3.3ml/min per 1.73m<sup>2</sup> for losartan and 7.0ml/min per 1.73m<sup>2</sup> for enalapril. The incidence of specific adverse events such as hyperkalemia and renal dysfunction was low and similar in both groups. Both were generally well tolerated and, overall, fewer drug-related adverse events occurred with losartan than with enalapril. Thus, in children with proteinuria, losartan and enalapril significantly reduced proteinuria without any appreciable changes in eGFR, effects that were maintained throughout the study. Both losartan and enalapril were generally well tolerated in patients when given with a light meal.

## Appendix C. Safety Warnings

### Warning about Fetal Toxicity

#### *Safety Labeling Changes Approved By US Food and Drug Administration Center for Drug Evaluation and Research – January 2012*

- Accupril (quinapril hydrochloride) 5 mg, 10 mg 20 mg, 40 mg Tablets
- Accuretic (quinapril HCl/ hydrochlorothiazide) 10/12.5 mg, 20/12.5 mg, 20/25 mg Tablets
- Altace (ramipril) 1.25, 2.5, 5, and 10 mg Tablets
- Avalide (irbesartan/hydrochlorothiazide) Tablets, 150/12.5 mg and 300/12.5 mg
- Avapro (irbesartan) 75 mg, 150 mg, and 300 mg Tablets
- Azor (amlodipine/olmesartan) 5/20 mg, 10/20 mg, 5/40 mg, and 10/40 mg Tablets
- Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) 20/12.5 mg, 40/12.5 mg, and 40/25 mg Tablets
- Diovan (valsartan) 40 mg, 80 mg, 160 mg, and 320 mg Tablets
- Diovan HCT (valsartan/hydrochlorothiazide) 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, and 320/25 mg Tablets
- Exforge (amlodipine/valsartan) 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg Tablets
- Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg Tablets
- Lotensin (benazepril) 5 mg, 10 mg, 20 mg, and 40 mg Tablets
- Lotensin HCT (benazepril/hydrochlorothiazide) 5/6.25 mg, 10/12.5 mg, 20/12.5 mg, and 25/25/mg Tablets
- Lotrel (amlodipine besylate and benazepril hydrochloride) 2.5/10 mg, 5/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, and 10/40 mg Tablets
- Mavik (trandolapril) 1 mg, 2 mg and 4 mg Tablets
- Micardis (telmisartan) 20 mg, 40 mg, and 80 mg Tablets
- Micardis HCT (telmisartan/hydrochlorothiazide) 40/12.5 mg, 80/12.5 mg, and 80/25 mg Tablets
- Tarka (trandolapril/verapamil hydrochloride) 2/180 mg, 1/240 mg 2/240 mg and 4/240 mg Tablets
- Teveten (eprosartan mesylate) 400 mg and 600 mg Tablets
- Teveten HCT (eprosartan mesylate/hydrochlorothiazide) 600/12.5 mg and 600/25 mg Tablets
- Tribenzor (olmesartan medoxomil/amlodipine/hydrochlorothiazide) 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 and 40/10/25 mg Tablets
- Univasc (moexipril hydrochloride) 7.5 mg and 15 mg Tablets
- Uniretic (moexipril hydrochloride/hydrochlorothiazide) 7.5/12.5 mg, 15/12.5 mg and 15/25 mg Tablets

Added to the above list, before or after January 2012, are individual safety labeling changes below (Note that the exact wording of the precaution may be slightly different than what is provided below from the January 2012 safety labeling change)

- Aceon (perindopril erbumine) tablets (Apr 2012)
- Atacand (candesartan cilexetil) Tablets (Apr 2012)
- Atacand HCT (candesartan cilexetil/hydrochlorothiazide) Tablets (Mar 2012)
- Capoten (captopril) Tablets (Dec 2011)
- Cozaar (losartan potassium) Tablets (Jan 2014)
- Edarbi (azilsartan medoxomil) Tablets (Dec 2011)
- Prinivil (lisinopril) and Prinzide (lisinopril/hydrochlorothiazide) Tablets (Jun 2012)
- Tekturna (aliskiren) and Tekturna HCCT (aliskiren/hydrochlorothiazide) Tablets (Feb 2012)
- Valtorna (aliskiren/valsartan) Tablets (Feb 2012)
- Vasotec (enalapril maleate) and Vaseretic (enalapril maleate/hydrochlorothiazide) Tablets (Feb 2012)

## BOXED WARNING

### WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning

- When pregnancy is detected, discontinue [xxx] as soon as possible
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

## WARNINGS AND PRECAUTIONS

### *Fetal Toxicity*

Pregnancy Category D

- Use of drugs that act on the renin-angiotensin system during the second and trimesters of pregnancy reduces.....

## USE IN SPECIAL POPULATIONS

### *Pregnancy*

Pregnancy Category D

- Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.....

### *Pediatric Use [new section]*

Neonates with a history of in utero exposure to [xxx]:

- If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

### **Warning against Dual Blockade of the Renin-Angiotensin System**

#### ***Safety Labeling Changes Approved By US Food and Drug Administration Center for Drug Evaluation and Research – September 2012***

All drugs in this report now carry a warning about dual blockade of the renin-angiotensin system by combining a DRI with an ACE-I or and ARB, such as the following:

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on xxxx and other agents that affect the RAS. Do not co-administer aliskiren with xxxx in patients with diabetes. Avoid use of aliskiren with xxxx in patients with renal impairment (GFR <60ml/min).

- Accupril (quinapril hydrochloride) 5 mg, 10 mg, 20 mg and 40 mg Tablets
- Accuretic (quinapril HCL/hydrochlorothiazide) 10/12.5 mg, 20/12.5 mg and 20/25 mg Tablets
- Avapro (irbesartan) 75 mg, 150 mg, and 300 mg tablets
- Azor (amlodipine/olmesartan medoxomil) 5/20 mg, 5/40 mg, 10/20 mg and 10/40 mg Tablets
- Benicar (olmesartan medoxomil) 5 mg 20 mg and 40 mg Tablets
- Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) 20/12.5 mg, 40/12.5 mg and 40/25 mg Tablets
- Cozaar (losartan potassium) 25 mg, 50 mg and 100 mg Tablets
- Hyzaar (losartan potassium/HCTZ) 50/12.5 mg, 100/25 mg, and 100/12.5 mg Tablets
- Lotensin (benazepril HCl) 5 mg, 10 mg 20 mg and 40 mg Tablets
- Lotensin HCT (benazepril HCl and hydrochlorothiazide) 5/6.25 mg, 10/12.5 mg 20/12.5 mg and 20/25 mg Tablets
- Mavik (trandolapril) 1 mg, 2 mg and 4 mg Tablets
- Tarka (trandolapril/verapamil hydrochloride) 2/180 mg, 1/240 mg, and 4/240 mg Tablets
- Teveten (eprosartan mesylate) 400 mg and 600 mg Tablets
- Teveten HCT (eprosartan mesylate hydrochlorothiazide) 600/12.5 mg and 600/25 mg Tablets
- Tribenzor (olmesartan medoxomil amlodipine/hydrochlorothiazide) 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg 40/10/12.5 and 40/10/25 mg Tablets
- Uniretic (moexipril hydrochloride/hydrochlorothiazide) 7.5/12.5 mg, 15/12.5 mg and 15/25 mg Tablets
- Vaseretic (enalapril maleate/hydrochlorothiazide) 10/25 mg Tablets
- Vasotec (enalapril maleate) 2.5 mg, 5 mg, 10 mg, and 20 mg Tablets
- Univasc (moexipril hydrochloride) 7.5 mg and 15 mg Tablets

Added to the above list, before or after September 2012, are individual safety labeling changes below (Note that the exact wording of the precaution may be slightly different than what is provided below from the September 2012 safety labeling change)

- Diovan (valsartan) Tablets and Diovan HCT (valsartan/hydrochlorothiazide) (Oct 2012)
- Capoten (captopril) Tablets (Aug 2012)
- Edarbi (azilsartan medoxomil) and Dearbyclor (azilsartan medoxomil/chlorthalidone) Tablets (Oct 2012)
- Avalide (irbesartan/hydrochlorothiazide) tablets (Oct 2012)
- Prinivil (lisinopril) and Prinizide (lisinopril/hydrochlorothiazide) Tablets (Nov 2011)

## CONTRAINDICATIONS

- Do not co-administer aliskiren with xxxx in patients with diabetes (see PRECAUTIONS, Drug Interactions).

## PRECAUTIONS

### *Drug Interactions*

#### **Dual Blockade of the Renin-Angiotensin System (RAS)**

- Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on xxxx and other agents that affect the RAS. Do not co-administer aliskiren with xxxx in patients with diabetes. Avoid use of aliskiren with xxxx in patients with renal impairment (GFR <60ml/min).

#### ***Dual Blockade of the Renin-Angiotensin-Aldosterone System***

- Telmisartan: The ONTARGET trial enrolled 25,620 patients >55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any benefit in the composite endpoint of cardiovascular death, MI, stroke and heart failure hospitalization compared to monotherapy, but experienced an increased incidence of clinically important renal dysfunction (death, doubling of serum creatinine, or dialysis) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended. (Nov 2009)
- Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg qd and ramipril 10 mg qd to healthy subjects increases steady-state C<sub>max</sub> and AUC of ramipril 2.3 and 2.1 fold, respectively, and C<sub>max</sub> and AUC of ramiprilat 2.4 and 1.5 fold, respectively. In contrast, C<sub>max</sub> and AUC of telmisartan decrease by 31% and 16%, respectively. When coadministering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of

the increased exposure to ramipril and ramiprilat in the presence of telmisartan. (Aug 2009)

### **Warning against Coadministration of NSAIDs**

#### ***Safety Labeling Changes Approved By US Food and Drug Administration Center for Drug Evaluation and Research – August 2011***

ACE-Is and ARBs now have a warning or precaution statement about con-administration of NSAIDs.

- Altace (ramipril) Tablets
- Avapro (irbesartan) Tablets
- Zestoretic (lisinopril and hydrochlorothiazide) Tablets
- Zestril (lisinopril) Tablets

Added to the above list, before or after August 2011, are individual safety labeling changes below (Note that the exact wording of the precaution may be slightly different than what is provided below from the August 2011 safety labeling change)

- Mavik (trandolapril) Tablets (Sep 2011)
- Diovan HCT (valsartan/hydrochlorothiazide) Tablets (Feb 2012)
- Aceon (perindopril erbumine) Tablets (Aug 2011)
- Valturna (aliskiren/valsartan) Tablets (May 2011)
- Tekturna (aliskiren) and Tekturna HCT (aliskiren/hydrochlorothiazide) Tablets (Feb 2012)
- Teveten (eprosartan mesylate) Tablets (May 2011)
- Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) Tablets (May 2011)
- Micardis HCT (telmisartan/hydrochlorothiazide) Tablets (May 2011)
- Benicar (olmesartan medoxomil) Tablets (Jun 2011)
- Capoten (captopril) Tablets (May 2011)
- Diovan (valsartan) Tablets (Jun 2011)
- Atacand (candesartan cilexetil) and Atacand HCT (candesartan cilexetil/hydrochlorothiazide) Tablets (Jun 2011)
- Avalide (irbesartan/hydrochlorothiazide) Tablets (Jun 2011)
- Lotensin HCT (benazepril HCl and hydrochlorothiazide) Tablets (Jun 2011)
- Uniretic (moexipril hydrochloride/hydrochlorothiazide) Tablets (Aug 2011)
- Vasotec (enalapril maleate) and Vaseretic (enalapril maleate/hydrochlorothiazide) Tablets (Feb 2012)

### **PRECAUTIONS**

#### ***Drug Interactions***

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase – 2 Inhibitors (COX-2 Inhibitors)

- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including irbesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving irbesartan and NSAID therapy.