

AHRQ Systematic Review Surveillance Program

CER #34: Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update

Original Release Date: June 2011

Surveillance Report Date: March 2016

Summary of Key Findings from Surveillance Report:

- 1) Key Question 1: Conclusions on the effectiveness of the ACEIs and ARBs included in the original systematic review are likely current. However, one new RCT found that the ARB azilsartan – approved after the original systematic review was published, may be more effective than ramipril (ACEI) at improving systolic BP. In addition, one new RCT found that aliskiren (DRI) and irbesartan (ARB) had similar effects on glucose and lipid profiles. No evidence had previously been identified. Finally, while the original review found no evidence comparing ACEIs or ARBs on progression to type II diabetes, we identified one retrospective cohort study which found a lower risk of type II diabetes onset associated with candesartan (ARB) as compared to enalapril (ACEI). All other conclusions are likely current.
- 2) Key Question 2: Conclusions on withdrawal rates due to adverse events associated with the ACEIs and ARBs included in the original systematic review are likely current. However, we identified an RCT examining the new ARB azilsartan, which found lower withdrawal rates associated with azilsartan as compared to ramipril (ACEI). All other conclusions are likely current. Of note, the 2012 VA NEPHRON-D trial, recommended by an expert reviewer, highlights safety concerns such as increased rates of

serious adverse events, hyperkalemia, and acute kidney injury for Chronic Kidney Disease (CKD) patients undergoing combination therapy with ACEIs plus ARBs. Combination therapies were outside of the scope of the original review.

3) Key Question 3: Conclusions are likely current.

Signal Assessment: The signals examined in this surveillance assessment suggest that the original systematic review may no longer be current.

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the Evidence-based Practice Center (EPC) Program is to decide if the findings of a systematic review are current. Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #34, titled *Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update*,¹ was originally released in June 2011.

The key questions for the original systematic review are as follows:

Key Question 1. For adult patients with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor antagonists), and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?

Key Question 3. Are there subgroups of patients—based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications)—for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Our surveillance assessment began in July 2015. We conducted an electronic search for literature published since the end date of the original systematic review. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

Methods

Literature Searches

We conducted a literature search of PubMed covering January 2010 to July 2015, using the identical search strategy used for the original report¹ and searching for studies published since the end date of the original systematic review.

The search was conducted to assess the currency of conclusions. This process included selecting journals from among the top 10 journals from relevant specialty subject areas (Appendix A) and among those most highly represented among the references for the original report (Appendix B). The included journals were six high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Cochrane Database of Systematic Reviews, Journal of the American Medical Association, Lancet, and New England Journal of

Medicine), and five specialty journals (American Journal of Hypertension, Clinical Therapeutics, Hypertension, Journal of Hypertension, and Journal of Human Hypertension). The search strategy is reported in Appendix C.

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix D), one investigator reviewed the titles and abstracts of the 11 high-impact journal search results (Appendix E).

Expert Opinion

We shared the conclusions of the original report and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with eight experts in the field (original peer reviewers and technical expert panel [TEP] members) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix F shows the form experts were asked to complete.

Horizon Scanning

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for the Agency for Healthcare Research and Quality's (AHRQ) 14 priority conditions.² We reviewed the Cardiovascular Disease section to identify new potentially high-impact interventions related to the key questions in this systematic review. Potentially high-impact interventions were considered in the final assessment of the need to update.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this systematic review.

Check for Qualitative Signals

The authors of the original systematic review conducted qualitative synthesis of data on the effectiveness and harms of ACEIs, ARBs, and DRIs for treating essential hypertension. We compared the conclusions of the included abstracts to the conclusions of the original systematic review and assessed expert opinions to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix G) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this systematic review, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current;
- Original conclusion is possibly out of date and this portion of the systematic review may not be current; and
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely not out of date.
- If we found new evidence that might change the systematic review's conclusion, and/or a minority of responding experts assessed the systematic review's conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as possibly out of date.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce *prima facie* evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may no longer be current, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal if little or no new evidence is identified that would change the conclusions from the original systematic review. This may occur when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

Results

Literature Search

The literature search identified 40 unique titles from the 11 selected high profile general medical and specialty journals (Appendix E). Upon abstract review, 27 studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix D). Three

additional studies were excluded³⁻⁵, as two were included in the original systematic review,^{4,5} and one was excluded from the original systematic review.³ Two^{6,7} additional meta-analyses and one additional systematic review⁸ were excluded because all included studies were either included in the original systematic review, included in the current surveillance report, or did not meet inclusion criteria (e.g., treatment duration, time to follow-up). The remaining seven studies⁹⁻¹⁵ were examined for potential to change the conclusions of the original systematic review.

Of these seven studies, one was a pooled analysis¹⁴ of two studies. One of the studies⁴ was included in the original systematic review. The other study,¹⁶ and not the pooled analysis, was examined for potential to change the conclusions of the original review.

Horizon Scanning

None of the interventions in the horizon scanning report for Priority Area 03: Cardiovascular Disease overlapped with the key questions in the original systematic review.¹ Thus, we did not identify new interventions with high-impact potential for this topic.

FDA Black Box Warnings

We did not find any FDA black box warnings relevant to the key questions in this systematic review.

Expert Opinion

We shared the conclusions of the original report with eight experts in the field (original peer reviewers and TEP members) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

For Key Question 1, one expert noted that the original review did not discuss the ARB azilsartan because it became available in 2011 after the original literature search was completed. This expert also suggested that we consider the differences within drug classes (i.e. certain ARBs have been shown to be more effective than others) in addition to differences between drug classes, as well as discuss the nuances of studies to explain the impact of potential confounders.

For Key Question 2, one expert suggested reviewing the VA NEPHRON-D trial.¹⁷ Although this trial did not meet our inclusion criteria (it was conducted among chronic kidney disease [CKD] patients rather than hypertensive patients), it highlights safety concerns associated with combining ACEI and ARB treatments for patients with impaired kidney function. In October 2012, trial researchers discovered that CKD patients undergoing combination therapy had increased rates of serious adverse events, hyperkalemia, and acute kidney injury compared to monotherapy groups, and the trial was stopped.

Both experts agreed conclusions related to Key Question 3 were current.

Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original report, the results of the literature search, the experts' assessments, and the conclusions regarding the currency of the original systematic review.

For Key Question 1, conclusions on the effectiveness of ACEIs and ARBs included in the original review are likely current. However, a new ARB, azilsartan was approved in 2011. We identified one RCT⁹ comparing azilsartan to ramipril (ACEI), favoring azilsartan for the improvement of systolic BP.

In addition, conclusions related to specific outcomes-including lipid and glucose levels and progression to type II diabetes - may no longer be current. While the original systematic review did not identify any studies comparing DRIs to ACEIs or ARBs on lipid levels and glucose control, we identified one new RCT¹² that found that aliskiren (DRI) and irbesartan (ARB) have similar effects on glucose and lipid profiles. In addition, while the original systematic review found no evidence comparing ACEIs and ARBs on progression to type II diabetes, we identified one retrospective cohort study¹¹ which found a lower risk of type II diabetes onset among patients taking candesartan (ARB) compared to patients taking enalapril (ACEI). All other conclusions related to Key Question 1 are likely current.

For Key Question 2, conclusions on withdrawal rates due to adverse events associated with the ACEIs and ARBs included in the original systematic review are likely current. However, we identified an RCT comparing azilsartan (ARB) - approved after the original systematic review was published- to ramipril (ACEI), which found lower withdrawal rates associated with azilsartan. All other conclusions are likely current. In addition, one expert suggested reviewing the VA NEPHRON-D trial.¹⁷ Although this trial did not meet our inclusion criteria (it was conducted among chronic kidney disease [CKD] patients rather than hypertensive patients), it highlights safety concerns such as increased rates of serious adverse events, hyperkalemia, and acute kidney injury for CKD patients undergoing combination therapy with ACEIs and ARBs. While this study does not affect the currency of report conclusions, the safety warnings highlighted are worth mention.

Conclusions related to Key Question 3 are likely current.

Signal Assessment

The SRC conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA boxed warnings, horizon scanning, and expert assessment is that:

- 1) Key Question 1: Conclusions on the effectiveness of the ACEIs and ARBs included in the original systematic review are likely current. However, one new RCT found that the ARB azilsartan – approved after the original systematic review was published, may be more effective than ramipril (ACEI) at improving systolic BP. In addition, one new RCT found that aliskiren (DRI) and irbesartan (ARB) had similar effects on glucose and lipid profiles. No evidence had previously been identified. Finally, while the original review found no evidence comparing ACEIs or ARBs on progression to type II diabetes, we identified one retrospective cohort study which found a lower risk of type II diabetes onset associated with candesartan (ARB) as compared to enalapril (ACEI). All other conclusions are likely current.
- 2) Key Question 2: Conclusions on withdrawal rates due to adverse events associated with the ACEIs and ARBs included in the original systematic review are likely current.

However, we identified an RCT examining the new ARB azilsartan, which found lower withdrawal rates associated with azilsartan as compared to ramipril (ACEI). All other conclusions are likely current. Of note, the 2012 VA NEPHRON-D trial, recommended by an expert reviewer, highlights safety concerns such as increased rates of serious adverse events, hyperkalemia, and acute kidney injury for Chronic Kidney Disease (CKD) patients undergoing combination therapy with ACEIs plus ARBs. Combination therapies were outside of the scope of the original review.

3) Key Question 3: Conclusions are likely current.

The signal for this report is medium suggesting that the conclusions in the original systematic review may not be current.

References

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Appendices

Appendix A: Top 10 Journals

Appendix B: Most Cited Journals from Original Systematic Review

Appendix C: Search Strategy

Appendix D: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix E: Literature Search Results

Appendix F: Questionnaire Sent to Expert Reviewers

Appendix G: Summary Table

Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area. For each subject area discipline, the list was constructed by selecting the top 10 journals from the 5 year citation impact factor average list. Selected citations were downloaded in .csv format.

Cardiovascular:	Top 10 General Medical:
1. Circulation	1. Annals of Internal Medicine
2. Journal of the American College of Cardiology (JACC)	2. Archives of Internal Medicine
3. European Heart Journal	3. BMC Medicine
4. Circulation Research	4. The BMJ
5. Nature Reviews Cardiology	5. Journal of Cachexia, Sarcopenia and Muscle
6. JACC- Cardiovascular Interventions	6. JAMA Internal Medicine
7. JACC- Cardiovascular Imaging	7. JAMA
8. Circulation- Cardiovascular Interventions	8. The Lancet
9. Circulation- Heart Failure	9. New England Journal of Medicine
10. Circulation- Cardiovascular Imaging	10. PLOS Medicine

Appendix B. Most Cited Journals from Original Systematic Review

Rank	Journal	# of Citations
1	Journal of Human Hypertension	18
2	Journal of Hypertension	12
3	Clinical Therapeutics	10
4	American Journal of Hypertension	7
5	Hypertension	4
6	Current Medical Research and Opinion	3
6	The Journal of Clinical Hypertension	3
8	Advances in Therapy	2
8	American Journal of Cardiology	2
8	Annals of Allergy, Asthma, & Immunology	2
8	Blood Pressure Monitoring	2
8	BMJ	2
8	Canadian Journal of Cardiology	2
8	Diabetes Research and Clinical Practice	2
8	International Heart Journal	2
8	JAMA	2
8	Kidney & Blood Pressure Research	2
8	New England Journal of Medicine	2
8	Nephrology Dialysis Transplantation	2

Appendix C. Search Strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 4 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 06, 2015> Search Strategy:	
1 (losartan or valsartan or telmisartan or eprosartan or candesartan or irbesartan or olmesartan).mp. (16411) 2 losartan/ (5910) 3 exp angiotensin II type 1 receptor blockers/ or exp Receptors, Angiotensin/ai (13281) 4 (cozaar or micardis or atacand or tevetan or avapro or benicar or diovan).mp. (149) 5 or/1-4 (20440) 6 (quinapril or perindopril or ramipril or captopril or enalapril or benazepril ortrandolapril or fosinopril or moexipril or enalaprilat or cilazapril or saralasin or teprotide).mp. (27504) 7 angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or saralasin/ or teprotide/ (40442) 8 6 or 7 (44909) 9 5 and 8 (7048) 10 limit 9 to yr="2006 - current" (2979) 11 limit 10 to english language (2633) 12 exp hypertension/dt (58289) 13 11 and 12 (750) 14 randomized controlled trial.pt. (398697) 15 controlled clinical trial.pt. (89792) 16 Randomized Controlled Trials/ (98553) 17 Random Allocation/ (83948) 18 Double-Blind Method/ (131101) 19 Single-Blind Method/ (20681) 20 or/14-19 (655733) 21 Animal/ not Human/ (3969936) 22 20 not 21 (604443) 23 clinical trial.pt. (495972) 24 exp Clinical Trial/ (819647) 25 (clinic\$ adj25 trial\$).tw. (296731) 26 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw. (137170) 27 Placebos/ (33055) 28 placebo\$.tw. (169422) 29 random\$.tw. (779124) 30 Research Design/ (81640) 31 (latin adj square).tw. (3732) 32 or/23-31 (1542539) 33 32 not 21 (1428320) 34 Comparative Study/ (1714432) 35 exp Evaluation Studies/ (205921) 36 Follow-Up Studies/ (521880) 37 Prospective Studies/ (393517) 38 (control\$ or prospectiv\$ or volunteer\$).tw. (3286504) 39 Cross-Over Studies/ (36320) 40 or/34-39 (5132055) 41 40 not 21 (4091128) 42 22 or 33 or 41 (4751302) 43 13 and 42 (494)	Original Search Strategy

44	limit 43 to abstracts (468)	
45	(aliskiren or tekturna).mp. (986)	
46	(renin inhibitor or renin inhibitors).mp. (1420)	
47	renin/ai (1777)	
48	or/45-47 (2530)	
49	5 and 48 (439)	
50	49 and 42 and 12 (110)	
51	8 and 48 (699)	
52	51 and 42 and 12 (120)	
53	50 or 52 (175)	
54	limit 53 to english language (161)	
55	43 or 54 (611)	
56	"annals of internal medicine".jn. (30458)	Journal limits general medical interest
57	bmj.jn. (62902)	
58	"cochrane database of systematic reviews".jn. (11505)	
59	jama.jn. (66896)	
60	lancet.jn. (130265)	
61	"new england journal of medicine".jn. (72471)	Journal limits specialty journals
62	"american journal of hypertension".jn. (6544)	
63	clinical therapeutics.jn. (5227)	
64	hypertension.jn. (13129)	
65	"journal of hypertension".jn. (8834)	
66	"journal of human hypertension".jn. (4040)	
67	56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 (412271)	
68	55 and 67 (113)	
69	limit 68 to yr="2010 -Current" (43)	Date Limits

Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Abstract Screening Criteria

An abstract will be included if all of the following criteria apply:

- The study is a direct comparison (any study design) of an angiotensin-converting enzyme inhibitor (ACEI) versus an angiotensin II receptor antagonist (ARB), or an ACEI versus a renin inhibitor, or an ARB versus a renin inhibitor (see lists at end of this document for included drugs; additional antihypertensive therapy OK if the same in both groups);
- Original data.

An abstract will be excluded if any of the following criteria apply:

- No patients have hypertension OR some patients have hypertension, but results not reported separately for this subgroup;
- All subjects aged < 18 years OR some subjects aged < 18 years, but results not broken down by age;
- Only comparison is an ACEI + an ARB versus placebo.

An abstract will be identified as a review if it is a relevant review article, meta-analysis, methods article, or cost-effectiveness analysis.

Full-Text Screening Criteria

Note: Screeners were instructed to work from top to bottom of the following list, choosing the first (if any) exclusion reason that applied.

1. Condition of interest = essential hypertension
 - a. Exclude if no patients have essential hypertension or if results not reported separately for subgroup with essential hypertension
2. Population of interest = adults (≥ 18 years)
 - a. Exclude if all subjects < 18 or if results not reported separately for ≥ 18 subgroup
3. Interventions & comparators of interest:
ACEIs, ARBs, and direct renin inhibitors listed at end of this document
 - Include “grouped” comparisons, e.g., specific ARB vs. “ACE inhibitors” or unspecified “ARBs” vs. unspecified “ACEIs”
 - Include ACEI + drug X vs. ARB + drug X (e.g., losartan + HCTZ vs. enalapril + HCTZ)
 - Exclude ACEI + drug X vs. ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ)
 - Exclude if ACEI, ARB, or direct renin inhibitor not on lists at end of this document
4. Study designs:
 - a. Include all clinical study designs (RCTs, non-RCTs, cohorts, etc.); cross-sectional studies OK if time on treatment reported and ≥ 12 weeks
 - b. Exclude if not clinical study (review, etc. – please specify)
5. Outcomes of interest:
For Key Question 1 and 3:
 - Intermediate outcomes:
 - Blood pressure control
 - Rate of use of a single antihypertensive agent for blood pressure control
 - Lipid levels
 - Progression to type 2 diabetes

- Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, aggregated measures of serial glucose measurements)
- LV mass/function
- Creatinine/GFR
- Proteinuria
- Health outcomes:
 - Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific)
 - Morbidity (cardiac events (myocardial infarction, heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end-stage renal disease, PVD [as clinically manifest, not markers of], quality of life)

For Key Question 2 and 3:

- Safety (overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, switch rates)
 - Specific adverse events (including, but not limited to: weight gain, impaired renal function, angioedema, cough, hyperkalemia)
 - Tolerability
 - Persistence
 - Adherence
6. Sample size:
- a. We will not exclude articles based on sample size during the full text screening but may re-visit this decision when performing the full-text abstraction and synthesis.
7. Treatment duration/length of follow-up:
- a. Exclude if treatment duration or longest follow-up < 12 weeks

Included ACEIs

Benazepril (Lotensin)
 Captopril (Capoten)
 Enalapril/Enalaprilat (Vasotec; Enalaprilat IV)
 Fosinopril (Monopril)
 Lisinopril (Prinivil, Zestril)
 Moexipril (Univasc)
 Perindopril (Aceon)
 Quinapril (Accupril)
 Ramipril (Altace)
 Trandolapril (Mavik)

Included ARBs

Candesartan cilexetil (Atacand)
 Eprosartan (Teveten)
 Irbesartan (Avapro)
 Losartan (Cozaar)
 Olmesartan medoxomil (Benicar)
 Telmisartan (Micardis)
 Valsartan (Diovan)

Included direct renin inhibitor

Aliskiren (Tekturna)

Appendix E. Literature Search Results

1. Appel LJ, Wright JT, Jr., Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med*. 2010;363(10):918-929.
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Appendix F. Questionnaire Sent to Expert Reviewers

AHRQ Comparative Effectiveness Review Surveillance Program

Reviewer Form

Title of Original Review: Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report

[Link to Report](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies and ensure the accuracy of our synthesis of the recently published literature.

Key Question 1:

For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes?

Blood Pressure Control**SRC Literature Analysis:**

- **ACEIs vs. ARBs**

We identified three RCTs comparing ACEIs (ramipril, lisinopril, amlodipine/benazepril) to ARBs (telmisartan, valsartan/hydrochlorothiazide), with one also comparing the combination of ramipril + telmisartan that found no significant differences in systolic or diastolic blood pressure control.

Four studies (one RCT, one pooled analysis of 10 studies, a pooled analysis of two RCTs, and one systematic review) compared ramipril to ARBs (azilsartan medoxomil, telmisartan/amlodipine, olmesartan medoxomil) and found larger BP reductions, reductions in systolic morning rise, and higher smoothness indices in ARBs.

- **DRI vs. ACEIs or ARBs**

We identified two RCTs comparing DRI aliskiren to an ACEI (ramipril) or an ARB (irbesartan) that found better decreases in sitting systolic and diastolic blood pressure and better blood pressure control with aliskiren. Two RCTs examined the mean increase in systolic and diastolic blood pressure after missed dose (24 hours)/treatment withdrawal (7-days) and found aliskiren superior to telmisartan (7-day) and irbesartan and ramipril (24-hours). One RCT and a meta-analysis of ten studies found no difference between aliskiren and ACEI ramipril or ARBs telmisartan, losartan, valsartan, and irbesartan in BP reduction, with one study finding similar reductions with aliskiren and irbesartan, with both significantly greater than ramipril.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Mortality and Major Cardiovascular Events**SRC Literature Analysis:**

- No studies were identified

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Quality of Life**SRC Literature Analysis:**

- An RCT of ACEI lisinopril compared with ARB telmisartan of patients with ADPKD found no difference in quality of life

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Rate of Use of a Single Antihypertensive Medication

SRC Literature Analysis:

• **DRI vs. ACEIs or ARBs**

- One non-inferiority RCT of DRI aliskiren compared with ACEI ramipril found that at week 36, fewer patients receiving aliskiren-based therapy required add-on treatment with hydrochlorothiazide or amlodipine (P=0.01 and 0.048, respectively).
- A meta-analysis of eight RCTs examined incidence of paradoxical blood pressure increases above predefined thresholds, after > or =4 weeks of treatment with DRI aliskiren, ARBs irbesartan, losartan, or valsartan, and ACEI ramipril. Findings indicate no significant differences.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Risk Factor Reduction and Other Intermediate Outcomes

SRC Literature Analysis:

• **ACEIs vs. ARBs**

- One retrospective cohort study compared ACEI enalapril to ARB candesartan and found no difference between the groups in CVD risk (HR 0.99, 95% CI 0.87-1.13, P=0.86).
- One non-inferiority RCT of ACEI amlodipine/benazepril compared with valsartan/hydrochlorothiazide suggest that patients in the amlodipine/benazepril group may have better metabolic outcomes than those in the valsartan/hydrochlorothiazide group; specifically, a preservation of the estimated glomerular filtration rate (5.7 mL/min/1.73 m²) [95% CI, 1.9 to 9.6]; P = 0.004) and improvements in glycosylated hemoglobin (-0.5% [95% CI, -0.7 to -0.2]; P < 0.001), fasting triglycerides (-0.4 mmol/L [95% CI, -0.7 to -0.2]; P = 0.002), HDL-C (0.07 mmol/L [95% CI, 0.01 to 0.12]; P = 0.022), and uric acid (-57.5 μmol/L [95% CI, -74.8 to -40.3]; P < 0.001).
- An RCT of ACEI lisinopril compared with ARB telmisartan of patients with ADPKD found no difference in urinary aldosterone excretion, rates of decline in the estimated glomerular filtration rate, urinary albumin excretion, rates of hospitalization, and incidence of pain.

- **DRI vs. ACEIs or ARBs**

- An RCT of DRI aliskiren vs. ARB irbesartan and found aliskiren treatment led to a 60% decrease in PRA from baseline, whereas irbesartan increased PRA by 99% (both $P < 0.001$). Aliskiren and irbesartan had similar effects on glucose and lipid profiles and on a panel of biomarkers of inflammation and cardiovascular risk.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Progression to Type-2 Diabetes and LV Mass/Function

SRC Literature Analysis:

- **ACEIs vs. ARBs**

- One retrospective cohort study compared ACEI enalapril to ARB candesartan and found that the risk of new diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69-0.96, $P = 0.01$) compared with the enalapril group.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 2:

For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?

Cough

SRC Literature Analysis:

- **DRI vs. ACEIs or ARBs**

- One non-inferiority RCT of DRI aliskiren compared with ACEI ramipril found that more patients receiving ramipril reported cough ($P < 0.001$).
- A meta-analysis of 10 trials of DRI aliskiren compared to ARBs (losartan, valsartan, and irbesartan) found that aliskiren and ARB treatment led to a similar number of adverse events and serious adverse events.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Withdrawals due to adverse events

SRC Literature Analysis:

- **ACEIs vs. ARBs**
 - An RCT of ACEI ramipril vs. ARB azilsartan medoxomil in patients with systolic BP of 150-180mm found that adverse events leading to discontinuation were less frequent with both 40 mg (2.4%) and 80 mg of azilsartan medoxomil (3.1%) than with ramipril (4.8%).
- **DRI vs. ACEIs or ARBs**
 - A meta-analysis of 10 trials of DRI aliskiren compared to ARBs (losartan, valsartan, and irbesartan) found that aliskiren and ARB treatment led to a similar number of withdrawals due to adverse events.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Angioedema**SRC Literature Analysis:**

- No studies were identified

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Persistence with drug therapy/treatment adherence**SRC Literature Analysis:**

- **ACEIs vs. ARBs**
 - One retrospective cohort study compared ACEI enalapril to ARB candesartan and found that more patients discontinued treatment in the enalapril group (38.1%) vs the candesartan group (27.2%).

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 3:

Are there subgroups of patients – based on demographics and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

SRC Literature Analysis:

- No studies were identified

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Title of Original Review: Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report

[Link to Report](#)

The conclusions from the original report and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review, SOE = Strength of Evidence	SRC Literature Analysis
Key Question 1: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes?	
<p>Blood Pressure Control SOE: High (ACEI vs. ARB)</p> <p>ACEIs vs. ARBs:</p> <ul style="list-style-type: none"> 77 studies (70 RCTs, 5 non-randomized controlled trials, 1 retrospective cohort study, and 1 case-control study) found both to have similar long-term effects on blood pressure among individuals with hypertension. Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols. <p>SOE: Low (DRI vs. ACEI ARB)</p> <p>Direct Renin Inhibitors (DRI):</p> <ul style="list-style-type: none"> vs. ACEI Ramipril (2 studies) found DRI to have greater reduction in blood pressure vs. ARB Losartan (1 study) found DRI to have greater reduction in blood pressure 	<p>ACEIs vs. ARBs</p> <p>One non-inferiority RCT of ACEI amlodipine/benazepril compared with valsartan/hydrochlorothiazide found no significant differences in mean change in diastolic or systolic blood pressure.</p> <p>One RCT of ACEI ramipril (R) vs. ARB telmisartan (T) vs. ramipril + telmisartan (R+T) no difference between R and T in 24-hour systolic BP reductions, with reductions for the R+T group twice as large. Similar results were found for diastolic BP.</p> <p>An RCT of ACEI lisinopril compared with ARB telmisartan of patients with ADPKD found no difference in blood pressure control.</p> <p>An RCT of ACEI ramipril vs. ARB azilsartan medoxomil in patents with systolic BP of 150-180mm found that both 40 mg and 80 mg of azilsartan medoxomil resulted in greater reductions in seated clinic systolic blood pressure than 10 mg daily of ramipril (P < 0.001).</p> <p>A pooled analysis of two RCTs comparing ACEI ramipril to ARB olmesartan medoxomil</p>

	<p>found greater 24-hour systolic and diastolic BP with olmesartan medoxomil ($P=0.009$), as well as larger BP reductions in the last 6 hours from dosing and higher smoothness indices. Olmesartan medoxomil reduced systolic BP morning rise, and ramipril did not ($P = 0.004$). 582 patients with sustained hypertension (office and 24-h ambulatory hypertension) showed the largest antihypertensive effect, with between-treatment differences still in favor of olmesartan medoxomil (SBP $P = 0.019$; DBP $P = 0.032$).</p> <p>A pooled analysis of 10 studies examining ARB telmisartan/amlodipine combination with various monotherapies and found that the systolic and diastolic smoothness index and treatment on variability (TOV) values were significantly higher than ACEI ramipril ($P < 0.0001$), indicating a smoother 24 hour BP reduction profile and significantly lower and smoother BP levels over 24 hours.</p> <p>A systematic review examining ARB azilsartan medoxomil found that that both 40 mg and 80 mg resulted in greater reductions in systolic blood pressure than 10 mg daily of ACEI ramipril ($P < 0.001$).</p> <p>DRI vs. ACEIs or ARBs One non-inferiority RCT of DRI aliskiren compared with ACEI ramipril found decreases from baseline mean sitting systolic and diastolic BP with aliskiren monotherapy (-14.0 and -5.1 mm Hg, respectively) were non-inferior ($P<0.001$ for both values) and superior to ramipril monotherapy (-11.6, -3.6 mm Hg; $P=0.02$, $P<0.01$, respectively). More patients achieved BP control with aliskiren (42%) than ramipril (33%; $P<0.01$).</p>
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	<p>An RCT of DRI aliskiren compared with ARB telmisartan for sustained BP lowering effect after a 7-day treatment withdrawal found similar decreases in mean ambulatory BP at the end of active treatment. were observed with aliskiren and telmisartan. From the end of treatment to the end of withdrawal, (EoW), the mean increase in 24-h mean ambulatory SBP and DBP were smaller for aliskiren vs. telmisartan ($P < 0.0001$). Mean sitting SBP and DBP were also significantly lower with aliskiren than telmisartan after EoW.</p> <p>An RCT of DRI aliskiren vs. ARB irbesartan and found greater reductions in mean sitting BP with aliskiren ($P = 0.019$).</p> <p>An RCT of DRI aliskiren vs. ACEI ramipril vs. ARB irbesartan found that the 24-hour mean ambulatory systolic or diastolic BP reductions from baseline after a missed dose were similar in aliskiren and irbesartan, with both significantly larger than ramipril ($P < \text{or} = 0.008$). Loss of BP-lowering effect with aliskiren in the 24 h after a missed dose was significantly lower than with irbesartan ($P < 0.01$) or ramipril ($P < 0.0001$). This equates to maintenance of 91/91% of the systolic or diastolic BP-lowering effect with aliskiren, greater than irbesartan (73/77%) or ramipril (64/65%).</p> <p>A meta-analysis of 10 trials of DRI aliskiren compared to ARBs (losartan, valsartan, and irbesartan) found that 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,</p>
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	respectively). Aliskiren and ARB treatment did not differ in rates of BP control or therapeutic response.
<p>Mortality and Major Cardiovascular Events SOE: Low (ACEI vs. ARB)</p> <p>Due to low numbers of deaths or major cardiovascular events reported, it was difficult to discern any differential effect of ACEIs vs. ARBs vs. DRIs with any certainty for these critical outcomes.</p> <ul style="list-style-type: none"> • 21 studies reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects. From these, 38 deaths and 13 strokes were reported. • May reflect low event rates among otherwise healthy patients and relatively few studies with extended follow-up <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>DRI vs. ACEI or ARB (3 studies, including 1 death) is insufficient to discern any differential effects between these drug classes on mortality and major cardiovascular events.</p>	No studies were identified
<p>Quality of Life SOE: Low (ACEI vs. ARB)</p> <p>ACEIs vs. ARB (4 studies) found no difference in measures of general QoL. 2 studies lacked quantitative data.</p> <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No study evaluated the comparative effectiveness of DRIs for QoL outcomes.</p>	<p>ACEIs vs. ARBs</p> <p>An RCT of ACEI lisinopril compared with ARB telmisartan of patients with ADPKD found no difference in quality of life</p>
<p>Rate of use of a single antihypertensive medication SOE: High (ACEI vs. ARB)</p> <p>ARBs vs. ACEIs:</p> <ul style="list-style-type: none"> • No statistically evident difference in the rate of treatment success. • Trend toward less frequent addition of second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients and by RCTs with very loosely defined protocols for medication titration and switching. 	<p>DRI vs. ACEIs or ARBs</p> <p>One non-inferiority RCT of DRI aliskiren compared with ACEI ramipril found that at week 36, fewer patients receiving aliskiren-based therapy required add-on treatment with hydrochlorothiazide or amlodipine (P=0.01 and 0.048, respectively).</p> <p>A meta-analysis of eight RCTs examined incidence of paradoxical blood pressure</p>

<p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No relevant studies.</p>	<p>increases above predefined thresholds, after > or =4 weeks of treatment with DRI aliskiren, ARBs irbesartan, losartan, or valsartan, and ACEI ramipril. Findings indicate no significant differences.</p>
<p>Risk factor reduction and other intermediate outcomes SOE: Moderate (ACEI vs. ARB)</p> <p>ACEI vs. ARB:</p> <ul style="list-style-type: none"> • No consistent differential effects on several potentially important clinical outcomes: lipid levels and markers of carbohydrate metabolism/diabetes control. • Small difference in change in renal function, favoring ACEIs. Likely not clinically significant. • Relatively few studies assessed outcomes over long-term. <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No relevant studies.</p>	<p>ACEIs vs. ARBs</p> <p>One retrospective cohort study compared ACEI enalapril to ARB candesartan and found no difference between the groups in CVD risk (HR 0.99, 95% CI 0.87-1.13, P=0.86).</p> <p>One non-inferiority RCT of ACEI amlodipine/benazepril compared with valsartan/hydrochlorothiazide suggest that patients in the amlodipine/benazepril group may have better metabolic outcomes than those in the valsartan/hydrochlorothiazide group; specifically, a preservation of the estimated glomerular filtration rate (5.7 mL/min/1.73 m²) [95% CI, 1.9 to 9.6]; P = 0.004) and improvements in glycosylated hemoglobin (-0.5% [95% CI, -0.7 to -0.2]; P < 0.001), fasting triglycerides (-0.4 mmol/L [95% CI, -0.7 to -0.2]; P = 0.002), HDL-C (0.07 mmol/L [95% CI, 0.01 to 0.12]; P = 0.022), and uric acid (-57.5 μmol/L [95% CI, -74.8 to -40.3]; P < 0.001).</p> <p>An RCT of ACEI lisinopril compared with ARB telmisartan of patients with ADPKD found no difference in urinary aldosterone excretion, rates of decline in the estimated glomerular filtration rate, urinary albumin excretion, rates of hospitalization, and incidence of pain.</p> <p>DRIs vs. ACEIs or ARBs</p> <p>An RCT of DRI aliskiren vs. ARB irbesartan and found aliskiren treatment led to a 60% decrease in PRA from baseline, whereas</p>

	irbesartan increased PRA by 99% (both $P<0.001$). Aliskiren and irbesartan had similar effects on glucose and lipid profiles and on a panel of biomarkers of inflammation and cardiovascular risk.
<p>Progression to Type 2 Diabetes and LV mass/function SOE: Low (ACEI vs. ARB)</p> <ul style="list-style-type: none"> Impact on ACEIs, ARBs, or DRIs on glucose or A1c: No evidence Progression to Type-2 diabetes mellitus: No included studies LV mass/function: (13 studies), most of which were poor quality with small sample sizes <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> 1 study 	<p>ACEIs vs. ARBs</p> <p>One retrospective cohort study compared ACEI enalapril to ARB candesartan and found that the risk of new diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69-0.96, $P=0.01$) compared with the enalapril group.</p>
<p>Key Question 2: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?</p>	
<p>Cough SOE: High (ACEI vs. ARB)</p> <p>ACEIs vs. ARB:</p> <ul style="list-style-type: none"> ACEIs have been consistently shown to be associated with greater risk (odds ratio 0.211; 95% CI: 0.159 to 0.281) For RCTs, this shows a rate difference of 7.8% For cohort studies with lower rates of cough, this translates to 1.2% <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>DRIs vs. ACEIs (2 studies) that gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933).</p>	<p>DRI vs. ACEIs or ARBs</p> <p>One non-inferiority RCT of DRI aliskiren compared with ACEI ramipril found that more patients receiving ramipril reported cough ($P<0.001$)</p> <p>A meta-analysis of 10 trials of DRI aliskiren compared to ARBs (losartan, valsartan, and irbesartan) found that aliskiren and ARB treatment led to a similar number of adverse events and serious adverse events.</p>
<p>Withdrawals due to adverse events SOE: High (ACEI vs. ARB)</p> <p>ARBs vs. ACEIs:</p> <ul style="list-style-type: none"> Withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI: 0.453 to 0.704) compared with ACEIs. 	<p>ACEIs vs. ARBs</p> <p>An RCT of ACEI ramipril vs. ARB azilsartan medoxomil in patients with systolic BP of 150-180mm found that adverse events leading to discontinuation were less frequent with both 40 mg (2.4%) and 80 mg of azilsartan medoxomil</p>

<ul style="list-style-type: none"> For RCTs, this translated to an absolute difference of 2.3% (5.4% vs. 3.1%) <p>SOE: Low (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> vs. ACEI: No statistically significant difference (odds ratio 0.886; 95% CI: 0.458 to 1.714). <p>No evidence of difference across treatments in rate of other commonly reported specific adverse events.</p>	<p>(3.1%) than with ramipril (4.8%).</p> <p>DRI vs. ACEIs or ARBs A meta-analysis of 10 trials of DRI aliskiren compared to ARBs (losartan, valsartan, and irbesartan) found that aliskiren and ARB treatment led to a similar number of withdrawals due to adverse events.</p>
<p>Angioedema SOE: Low (ACEI vs. ARB) SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited the ability to accurately characterize the frequency of angioedema.</p> <ul style="list-style-type: none"> 4 studies reported episodes of angioedema; observed only in patients treated with an ACEI (5 patients from 3 studies) or a DRI (1 study) 	<p>No studies were identified</p>
<p>Persistence with drug therapy/treatment adherence SOE: Low (ACEI vs. ARB)</p> <p>ACEIs vs. ARBs:</p> <ul style="list-style-type: none"> Treatment adherence: Similar rates based on pill counts; may not be applicable outside the clinical setting. Rates of continuation with therapy: Somewhat better with ARBs. Due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> Treatment adherence (3 studies) did not find evidence of differences compared with ACEIs or ARBs <p>Persistence: Not evaluated by any of the studies</p>	<p>ACEIs vs. ARBs One retrospective cohort study compared ACEI enalapril to ARB candesartan and found that more patients discontinued treatment in the enalapril group (38.1%) vs the candesartan group (27.2%).</p>
<p>Key Question 3: Are there subgroups of patients – based on demographics and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?</p>	

<p>SOE: Insufficient (ACEI vs. ARB; DRI vs. ACEI or ARB)</p> <p>Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.</p> <p>○</p>	No studies were identified
<p>Hoarseness</p> <p>SOE: Low</p> <ul style="list-style-type: none"> • PPIs vs. placebo (1 meta-analysis of 4 studies) showed no significant difference in total resolution of cough (odds ratio 0.46; 95% CI: 0.19 to 1.15) • PPIs vs. placebo (1 meta-analysis of 4 RCTs) found a borderline significant improvement in the mean cough scores at the end of the trial with PPIs compared with placebo (0.38 SMDU; 95% CI: 0.77 to 0.11, P=0.05) • PPIs vs. placebo (1 meta-analysis) showed a significant improvement in cough scores from baseline favoring PPIs compared with placebo (0.39 SMDU; 95% CI: 0.71 to -0.08) 	No studies were identified

Abbreviations: ACEI= Angiotensin-Converting-Enzyme Inhibitor; ADKPD= Autosomal Dominant Polycystic Kidney Disease; ARB = Angiotensin Receptor Blockers; BP= Blood Pressure; CI= Confidence Interval; CKD= Chronic Kidney Disease; DRI = Direct Renin Inhibitors; EOW= End of Withdrawal; LV = Left Ventricular; MI = Myocardial Infarction; QoL = Quality of Life; PRA= Plasma Renin Activity; RCT = Randomized Controlled Trial; SOE= Strength of Evidence; VA= Veteran's Affairs; WMD= Weighted Mean Difference.

Abstracts from Relevant Literature

Bonner, G., Bakris, G. L., Sica, D., Weber, M. A., White, W. B., Perez, A., Cao, C., Handley, A. and Kupfer, S. 2013.

Antihypertensive efficacy of the angiotensin receptor blocker azilsartan medoxomil compared with the angiotensin-converting enzyme inhibitor Ramipril. Journal of Human Hypertension.

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 vs12.2+/-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.

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*Duprez, D. A., Munger, M. A., Botha, J., Keefe, D. L. and Charney, A. N. 2010.

Aliskiren for geriatric lowering of systolic hypertension: a randomized controlled trial. Journal of Human Hypertension.

Efficacy and safety of the direct renin inhibitor aliskiren was compared with ramipril for treatment of essential systolic hypertension in elderly patients. A 36-week, randomized, double-blind, parallel-group, active-controlled, optional-titration study was performed in 901 patients (aliskiren, n=457; ramipril, n=444) > or =65 years of age with systolic blood pressure (SBP) > or =140 mm Hg. Aliskiren 150-300 mg per day or ramipril 5-10 mg per day for was administered for 12 weeks with optional add-on therapy of hydrochlorothiazide (12.5-25 mg per day) at week 12 and amlodipine (5-10 mg per day) at week 22. The primary end point was non-inferiority of aliskiren vs ramipril monotherapy for change from baseline in mean sitting SBP (msSBP) at week 12. Decreases from baseline msSBP and mean sitting diastolic BP with aliskiren monotherapy (-14.0 and -5.1 mm Hg, respectively) were non-inferior ($P < 0.001$ for both values) and superior to ramipril monotherapy (-11.6, -3.6 mm Hg; $P = 0.02$, $P < 0.01$, respectively). More patients achieved BP control with aliskiren (42%) than ramipril (33%; $P < 0.01$). At week 36, fewer patients receiving aliskiren-based therapy required add-on treatment with hydrochlorothiazide or amlodipine ($P = 0.01$ and 0.048 , respectively). Tolerability was similar, but more patients receiving ramipril reported cough ($P < 0.001$). In elderly patients with systolic hypertension, aliskiren proved to be more effective and better overall anti-hypertensive therapy compared to ramipril.

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Dusing, R., Brunel, P., Baek, I. and Baschiera, F. 2012.

Sustained decrease in blood pressure following missed doses of aliskiren or telmisartan: the ASSERTIVE double-blind, randomized study. Journal of Hypertension.

OBJECTIVES: The AliSkiren Study of profound antihypERTensive efficacy in hyperTensIVE patients (ASSERTIVE) study was designed to assess the sustained blood pressure (BP)-lowering effect of aliskiren vs. telmisartan after a 7-day treatment withdrawal in patients with hypertension. METHODS: Patients were randomized to once-daily aliskiren 150 mg (N = 414) or telmisartan 40 mg (N = 408). After 2 weeks, all patients were uptitrated to double the initial dose for 10 weeks; subsequently, all patients were treated with placebo to simulate a 7-day treatment withdrawal. RESULTS: At the end of active treatment (EoA), similar decreases in mean ambulatory BP were observed with aliskiren and telmisartan. From EoA to day 7 of treatment withdrawal (end of withdrawal, EoW), the least squares mean increase in 24-h mean ambulatory SBP was smaller for aliskiren (2.7 mmHg) vs. telmisartan (6.5 mmHg). Between-treatment difference was significant in favour of aliskiren (-3.8 mmHg; $P < 0.0001$). Similar effects were observed for the increase in 24-h mean ambulatory DBP after EoW (-2.1 mmHg; $P < 0.0001$). Mean sitting SBP and DBP were also significantly lower with aliskiren than telmisartan after EoW with SBP (2.0 mmHg) and DBP (1.1 mmHg) differences in favour of aliskiren, already evident on day 2 after a single 'missed dose'. CONCLUSION: Aliskiren showed a greater and more sustained BP-lowering effect than telmisartan during a 7-day treatment withdrawal. Aliskiren may provide sustained BP lowering during 1 day or more missed dose.

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*Gao, D., Ning, N., Niu, X., Wei, J., Sun, P. and Hao, G. 2011.

Aliskiren vs. angiotensin receptor blockers in hypertension: meta-analysis of randomized controlled trials. American Journal of Hypertension.

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.

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 Hasvold, L. P., Bodegard, J., Thuresson, M., Stalhammar, J., Hammar, N., Sundstrom, J., Russell, D. and Kjeldsen, S. E. 2014.
Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15,990 patients. Journal of Human Hypertension.

Differences in clinical effectiveness between angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in the primary treatment of hypertension are unknown. The aim of this retrospective cohort study was to assess the prevention of type 2 diabetes and cardiovascular disease (CVD) in patients treated with ARBs or ACEis. Patients initiated on enalapril or candesartan treatment in 71 Swedish primary care centers between 1999 and 2007 were included. Medical records data were extracted and linked with nationwide hospital discharge and cause of death registers. The 11,725 patients initiated on enalapril and 4265 on candesartan had similar baseline characteristics. During a mean follow-up of 1.84 years, 36,482 patient-years, the risk of new diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69-0.96, P=0.01) compared with the enalapril group. No difference between the groups was observed in CVD risk (HR 0.99, 95% CI 0.87-1.13, P=0.86). More patients discontinued treatment in the enalapril group (38.1%) vs the candesartan group (27.2%). In a clinical setting, patients initiated on candesartan treatment had a lower risk of new-onset type 2 diabetes and lower rates of drug discontinuation compared with patients initiated on enalapril. No differences in CVD risk were observed.

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 Krone, W., Hanefeld, M., Meyer, H. F., Jung, T., Bartlett, M., Yeh, C. M., Rajman, I., Prescott, M. F. and Dole, W. P. 2011.
Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome. Journal of Human Hypertension.

Metabolic syndrome, a cluster of risk factors that increase the risk of cardiovascular morbidity and mortality, is common in patients with hypertension. Chronic renin-angiotensin-aldosterone system (RAAS) activation, shown by elevated plasma renin activity (PRA), is implicated in many of the features of metabolic syndrome. The direct renin inhibitor aliskiren may be of benefit in this patient group as aliskiren targets the RAAS at the rate-limiting step. In this double-blind study, 141 patients with hypertension (mean baseline BP 155/93mmHg) and metabolic syndrome (modified National Cholesterol Education Program ATP III criteria) were randomized to aliskiren 300mg or irbesartan 300mg once daily. Patients treated with aliskiren 300mg had their mean sitting blood pressure (BP) lowered by 13.8/7.1mmHg after 12 weeks, significantly greater (P<0.001) than the 5.8/2.8mmHg reduction observed in patients treated with irbesartan 300mg. A significantly greater proportion of patients treated with aliskiren achieved BP control to <135/85mmHg (29.2 vs 16.7% with irbesartan; P=0.019). Aliskiren treatment led to a 60% decrease in PRA from baseline, whereas irbesartan increased PRA by 99% (both P<0.001). Aliskiren and irbesartan had similar effects on glucose and lipid profiles and on a panel of biomarkers of inflammation and cardiovascular risk. Both aliskiren and irbesartan were well tolerated. Collectively, these

results suggest that aliskiren 300mg may offer treatment benefits compared with irbesartan 300mg for BP reduction in patients with hypertension and metabolic syndrome.

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**Lee, I. T., Hung, Y. J., Chen, J. F., Wang, C. Y., Lee, W. J. and Sheu, W. H. 2012.*

Comparison of the efficacy and safety profiles of two fixed-dose combinations of antihypertensive agents, amlodipine/benazepril versus valsartan/hydrochlorothiazide, in patients with type 2 diabetes mellitus and hypertension: a 16-week, multicenter, randomized, double-blind, noninferiority study. Clinical Therapeutics.

BACKGROUND: Hypertension is a prevalent condition that is closely associated with chronic complications in patients with diabetes. Fixed-dose combination therapy is currently recommended for the treatment of hypertension due to the advantage of reducing the pill burden. However, the effects of combination therapy may be diverse because of the different components. OBJECTIVES: We examined blood pressure reduction and metabolic alterations after amlodipine/benazepril and valsartan/hydrochlorothiazide treatment in patients with type 2 diabetes mellitus and hypertension and microalbuminuria. METHODS: This randomized, double-blind, parallel comparison, noninferiority clinical trial included patients with type 2 diabetes mellitus and hypertension and microalbuminuria detected within the past year. After a 2-week, placebo run-in period, patients were assigned to treatment with amlodipine/benazepril or valsartan/hydrochlorothiazide for 16 weeks. The primary end point was mean change in diastolic blood pressure. The prespecified boundary for noninferiority was 3.5 mm Hg of the mean change in diastolic blood pressure between treatments (amlodipine/benazepril minus valsartan/hydrochlorothiazide). If the upper limit of the 95% CI fell within 3.5 mm Hg, amlodipine/benazepril would be considered noninferior to valsartan/hydrochlorothiazide. RESULTS: Of the 226 patients assessed for eligibility, 169 satisfied the inclusion/exclusion criteria and were assigned to a treatment group; 83 patients (54.2% male, mean age of 60.5 [10.0] years) in the amlodipine/benazepril group and 84 patients (64.3% male, mean age of 59.0 [10.6] years) in the valsartan/hydrochlorothiazide group received at least 1 dose of study medication and were included in the intention-to-treat population. In the per-protocol population, amlodipine/benazepril (n = 74) was noninferior to valsartan/hydrochlorothiazide (n = 78) with regard to the mean change in diastolic blood pressure (difference, -0.9 mm Hg; 95% CI, -3.5 to 1.6). The mean change in systolic blood pressure was not significantly different (2.4 mm Hg; 95% CI, -1.2 to 6.0) between study groups (P = 0.195) in the per-protocol population. However, data from the intention-to-treat population suggest that patients in the amlodipine/benazepril group may have better metabolic outcomes than those in the valsartan/hydrochlorothiazide group; specifically, a preservation of the estimated glomerular filtration rate (5.7 mL/min/1.73 m²) [95% CI, 1.9 to 9.6]; P = 0.004) and improvements in glycosylated hemoglobin (-0.5% [95% CI, -0.7 to -0.2]; P < 0.001), fasting triglycerides (-0.4 mmol/L [95% CI, -0.7 to -0.2]; P = 0.002), HDL-C (0.07 mmol/L [95% CI, 0.01 to 0.12]; P = 0.022), and uric acid (-57.5 μmol/L [95% CI, -74.8 to -40.3]; P < 0.001). There were no significant differences in adverse effects between groups, with the exception of more respiratory disorders in the amlodipine/benazepril group than in the valsartan/hydrochlorothiazide group (17 vs 5; P = 0.006). CONCLUSIONS: The study results suggest that amlodipine/benazepril is noninferior to valsartan/hydrochlorothiazide with regard to blood pressure reduction and that this combination exerts beneficial effects on renal function, glucose control, HDL-C, and triglyceride levels compared with valsartan/hydrochlorothiazide. However, respiratory adverse events (particularly coughing) were more frequently reported in the amlodipine/benazepril group. ClinicalTrials.gov identifier: NCT01375322. Copyright © 2012 Elsevier HS Journals, Inc. All rights reserved.

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Mancia, G., Parati, G., Bilo, G., Gao, P., Fagard, R., Redon, J., Czuriga, I., Polak, M., Ribeiro, J. M., Sanchez, R., Trimarco, B., Verdecchia, P., Van Mieghem, W., Teo, K., Sleight, P. and Yusuf, S. 2012.

Ambulatory blood pressure values in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). Hypertension.

In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, telmisartan (T; 80 mg daily) and ramipril (R; 10 mg daily) caused similar clinic blood pressure (BP) reductions, with a similar incidence of cardiovascular and renal events. The R+T combination lowered clinic BP somewhat more with no further cardiovascular or renal protection. The aim of this substudy was to see whether these clinic BP changes reflected the changes of 24-hour BP, a BP with a better prognostic value. In 422 patients in whom 24-hour BP monitoring was performed either before or after 6 to 24 months of treatment, demographic and clinical characteristics were similar in the 3 treated groups. Twenty-four-hour systolic BP was similarly reduced by R (-2.0 mm Hg) and T (-2.1 mm Hg), whereas the reduction was more than twice as large in the T+R group (-5.3 mm Hg), which showed a lower on-treatment 24-hour BP also in additional patients (n=408) in whom ambulatory BP was performed only on-treatment. Twenty-four-hour systolic BP was = 14 mm Hg lower than clinic systolic BP at baseline, whereas during treatment the 2 values became progressively closer as clinic systolic BP was more tightly controlled and superimposable when clinic systolic BP was <120 mm Hg. Similar results were obtained for diastolic BP. These findings provide evidence on the relationship of clinic and ambulatory BP target drug treatment. They also show that in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, failure of the R+T combination to enhance cardiovascular and renal protection was not because of inability to more effectively control daily life BP.

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Omboni, S., Malacco, E., Mallion, J. M., Volpe, M., Zanchetti, A. and Study, G. 2012.

Twenty-four hour and early morning blood pressure control of olmesartan vs. ramipril in elderly hypertensive patients: pooled individual data analysis of two randomized, double-blind, parallel-group studies. Journal of Hypertension.

OBJECTIVE: To assess the antihypertensive efficacy of olmesartan medoxomil and ramipril on 24-h ambulatory blood pressure (ABP) in elderly hypertensive patients by pooled data analysis of two studies with identical designs (one Italian, one European).;METHODS: After a 2-week placebo wash-out 1453 elderly hypertensive patients (65-89 years; sitting office DBP 90-109 mmHg and/or sitting office SBP 140-179 mmHg) were randomized to a 12-week double-blind treatment with olmesartan medoxomil 10 mg or ramipril 2.5 mg once-daily, up-titrated (20 and 40 mg olmesartan medoxomil; 5 and 10 mg ramipril) after 2 and 6 weeks in patients without normalized office BP. 24-h ABP was recorded at randomization and after 12 weeks. RESULTS: In 715 patients with valid baseline and end-of-treatment recordings baseline-adjusted 24-h SBP and DBP reductions were greater with olmesartan medoxomil (n = 356) than with ramipril (n = 359) [between-treatment differences and 95% confidence interval (CI), SBP: 2.2 (3.8, 0.6), P = 0.006; DBP: 1.3 (2.2, 0.3), P = 0.009]. Olmesartan medoxomil showed larger BP reductions in the last 6 h from the dosing interval and higher smoothness indices than ramipril. Olmesartan medoxomil reduced the SBP morning rise [-2.8 (-4.9, -0.8) mmHg], whereas ramipril did not [+1.5 (-0.6, +3.6) mmHg; P = 0.004 between-treatments]. Five hundred and eighty-two patients with sustained hypertension (office and 24-h ambulatory hypertension) showed the largest antihypertensive effect, with between-treatment differences still in favor of olmesartan medoxomil [SBP: 2.1 (3.9, 0.4), P = 0.019; DBP: 1.2 (2.3, 0.1), P = 0.032].;CONCLUSIONS: Olmesartan medoxomil provides a more effective and sustained 24-h BP control than ramipril in elderly hypertensive patients, particularly in the hours farthest from last intake.

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**Palatini, P., Jung, W., Shlyakhto, E., Botha, J., Bush, C. and Keefe, D. L. 2010.*

Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study. Journal of Human Hypertension.

Most patients inadvertently miss an occasional dose of antihypertensive therapy, and hence drugs that provide sustained blood-pressure (BP) reduction beyond the 24-h dosing interval are desirable. The primary objective of this study was to compare the 24-h mean ambulatory BP reductions from baseline after a simulated missed dose of the direct renin inhibitor aliskiren, irbesartan or ramipril. In this double-blind study, 654 hypertensive patients (24-h mean ambulatory diastolic BP (MADBP) ≥ 85 mm Hg) were randomized 1:1:1 to once-daily aliskiren 150 mg, irbesartan 150 mg or ramipril 5 mg. Doses were doubled after 2 weeks. At day 42, patients were again randomized equally within each group to receive 1 day of placebo ('missed dose') on either day 42 or day 49. Patients with a successful 24-h ambulatory BP measurement at baseline and on day 42/49 were included in the analyses. The 24-h mean ambulatory systolic BP (MASBP)/MADBP reductions from baseline after a missed dose of aliskiren 300 mg (9.3/7.0 mm Hg) were similar to irbesartan 300 mg (9.5/7.3 mm Hg) and significantly larger than ramipril 10 mg (7.1/5.0 mm Hg, $P \leq 0.008$). Loss of BP-lowering effect with aliskiren in the 24 h after a missed dose (1.0/0.7 mm Hg for 24-48-h vs 0-24-h MASBP/MADBP) was significantly lower than with irbesartan (3.6/2.2 mm Hg, $P < 0.01$) or ramipril (4.0/2.6, $P < 0.0001$). This equates to maintenance of 91/91% of the MASBP/MADBP-lowering effect with aliskiren, greater than irbesartan (73/77%) or ramipril (64/65%). The incidence of adverse events was similar across treatments (32.9-36.0%), although ramipril treatment was associated with an increased incidence of cough (ramipril, 6.1%; aliskiren, 0.5%; irbesartan, 1.8%). Aliskiren 300 mg provided a sustained BP-lowering effect beyond the 24-h dosing interval, with a significantly smaller loss of BP-lowering effect in the 24-48 h period after dose than irbesartan 300 mg or ramipril 10 mg.

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**Parati, G., Dolan, E., Ley, L. and Schumacher, H. 2014.*

Impact of antihypertensive combination and monotherapies on blood pressure variability: assessment by old and new indices. Data from a large ambulatory blood pressure monitoring database. Journal of Hypertension.

OBJECTIVES: High 24-h ambulatory blood pressure (ABP) variability is associated with poor cardiovascular outcomes. We analysed a large ABP monitoring database containing data from hypertensive patients treated with telmisartan/amlodipine combination or various monotherapies with the aim of quantifying the 24-h distribution of blood pressure (BP) reduction by treatment through the smoothness index and of developing and testing a new treatment-on-variability index (TOVI) to quantify the effects of treatment on both mean BP and BP variability. METHODS: ABP data were pooled from 10 studies (N = 4294) with a median follow-up of 60 days. Smoothness index was calculated by dividing the mean of treatment-induced hourly BP reductions by its SD. TOVI was calculated as the ratio of the mean of hourly BP reductions to weighted 24-h BP SD (weighted mean of daytime and night-time SDs) under treatment. RESULTS: The SBP/DBP smoothness index and TOVI values of telmisartan/amlodipine combination were significantly ($P < 0.0001$) higher (smoothness index: 1.81/1.51; TOVI: 2.71/2.13) compared with telmisartan 80 mg (smoothness index: 1.12/0.90; TOVI: 1.55/1.23), amlodipine 10 mg (smoothness index: 1.33/1.09; TOVI: 2.09/1.58), valsartan 160 mg (smoothness index: 1.01/0.81; TOVI: 1.35/1.07), ramipril 10 mg (smoothness index: 0.83/0.63; TOVI: 1.11/0.87) and placebo (smoothness index: 0.23/0.18; TOVI: 0.34/0.30), indicating a smoother 24-h BP reduction profile (higher smoothness index) as well as the achievement of significantly lower and smoother BP levels over 24 h (higher TOVI) with the combination. CONCLUSION: As compared with various monotherapies, the telmisartan/amlodipine combination was associated with a smoother BP reduction over 24 h and with a more favourable balance between mean 24-h BP reduction and the degree of BP variability on treatment, reflecting both its effectiveness in lowering BP levels and its longer duration of action. The agreement between smoothness index and TOVI demonstrates that they are similarly effective in the differentiation of antihypertensive treatments, although providing conceptually different information, the clinical relevance of which needs to be tested by ad-hoc outcome studies.

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**Stanton, A. V., Gradman, A. H., Schmieder, R. E., Nussberger, J., Sarangapani, R. and Prescott, M. F. 2010.*

Aliskiren monotherapy does not cause paradoxical blood pressure rises: meta-analysis of data from 8 clinical trials. Hypertension.

Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and diuretics all cause reactive rises in plasma renin concentration, but particularly high levels have been reported with aliskiren. This prompted speculation that blockade of plasma renin activity with aliskiren could be overwhelmed, leading to paradoxical increases in blood pressure. This meta-analysis of data from 4877 patients from 8 randomized, double-blind, placebo- and/or active-controlled trials examined this hypothesis. The analysis focused on the incidence of paradoxical blood pressure increases above predefined thresholds, after ≥ 4 weeks of treatment with 300 mg of aliskiren, angiotensin receptor blockers (300 mg of irbesartan, 100 mg of losartan, or 320 mg of valsartan), 10 mg of ramipril, 25 mg of hydrochlorothiazide, or placebo. There were no significant differences in the frequency of increases in systolic (>10 mm Hg; $P=0.30$) or diastolic (>5 mm Hg; $P=0.65$) pressure among those treated with aliskiren (3.9% and 3.1%, respectively), angiotensin receptor blockers (4.0% and 3.7%), ramipril (5.7% and 2.6%), or hydrochlorothiazide (4.4% and 2.7%). Increases in blood pressure were considerably more frequent in the placebo group (12.6% and 11.4%; $P<0.001$). None of the 536 patients with plasma renin activity data who received 300 mg of aliskiren exhibited an increase in systolic pressure >10 mm Hg that was associated with an increase in plasma renin activity >0.1 ng/mL per hour. In conclusion, the incidence of blood pressure increases with aliskiren was similar to that during treatment with other antihypertensive drugs. Blood pressure rises on aliskiren treatment were not associated with increases in plasma renin activity. This meta-analysis found no evidence that aliskiren uniquely causes paradoxical rises in blood pressure.

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Torres, V. E., Abebe, K. Z., Chapman, A. B., Schrier, R. W., Braun, W. E., Steinman, T. I., Winklhofer, F. T., Brosnahan, G., Czarnecki, P. G., Hogan, M. C., Miskulin, D. C., Rahbari-Oskoui, F. F., Grantham, J. J., Harris, P. C., Flessner, M. F., Moore, C. G., Perrone, R. D. and Investigators, H.-P. T. 2014.
Angiotensin blockade in late autosomal dominant polycystic kidney disease. New England Journal of Medicine.

BACKGROUND: Hypertension develops early in patients with autosomal dominant polycystic kidney disease (ADPKD) and is associated with disease progression. The renin-angiotensin-aldosterone system (RAAS) is implicated in the pathogenesis of hypertension in patients with ADPKD. Dual blockade of the RAAS may circumvent compensatory mechanisms that limit the efficacy of monotherapy with an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II-receptor blocker (ARB).;METHODS: In this double-blind, placebo-controlled trial, we randomly assigned 486 patients, 18 to 64 years of age, with ADPKD (estimated glomerular filtration rate [GFR], 25 to 60 ml per minute per 1.73 m² of body-surface area) to receive an ACE inhibitor (lisinopril) and placebo or lisinopril and an ARB (telmisartan), with the doses adjusted to achieve a blood pressure of 110/70 to 130/80 mm Hg. The composite primary outcome was the time to death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR. Secondary outcomes included the rates of change in urinary aldosterone and albumin excretion, frequency of hospitalizations for any cause and for cardiovascular causes, incidence of pain, frequency of ADPKD-related symptoms, quality of life, and adverse study-medication effects. Patients were followed for 5 to 8 years. RESULTS: There was no significant difference between the study groups in the incidence of the composite primary outcome (hazard ratio with lisinopril-telmisartan, 1.08; 95% confidence interval, 0.82 to 1.42). The two treatments controlled blood pressure and lowered urinary aldosterone excretion similarly. The rates of decline in the estimated GFR, urinary albumin excretion, and other secondary outcomes and adverse events, including hyperkalemia and acute kidney injury, were also similar in the two groups. CONCLUSIONS: Monotherapy with an ACE inhibitor was associated with blood-pressure control in most patients with ADPKD and stage 3 chronic kidney disease. The addition of an ARB did not alter the decline in the estimated GFR. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; HALT-PKD [Study B] ClinicalTrials.gov number, NCT01885559.).

*Zaiken, K. and Cheng, J. W. 2011.

Azilsartan medoxomil: a new Angiotensin receptor blocker. Clinical Therapeutics.

BACKGROUND: Azilsartan medoxomil is an angiotensin receptor blocker, approved on February 25, 2011 by the US Food and Drug Administration (FDA) for hypertension management. OBJECTIVE: The purpose of this study was to review the pharmacology, pharmacokinetics, efficacy, safety profile, and role of azilsartan for hypertension management. METHODS: Peer-reviewed clinical trials, review articles, and relevant treatment guidelines were identified from MEDLINE and Current Contents (both 1966 to August 31, 2011) using the search terms azilsartan, TAK-491, TAK-536, pharmacology, pharmacokinetics, pharmacodynamics, pharmacoeconomics, and cost-effectiveness. The FDA Web site and manufacturer prescribing information were also reviewed to identify other relevant information. RESULTS: Compared with olmesartan 40 mg daily, azilsartan 80 mg reduced mean systolic blood pressure (SBP) by an additional 2.1 mm Hg ($P = 0.038$), whereas azilsartan 40 mg was noninferior to olmesartan 40 mg. Azilsartan 40 mg or 80 mg added to chlorthalidone 25 mg daily significantly reduced SBP to a greater extent than did chlorthalidone alone ($P < 0.05$), but there was no difference between azilsartan 40 mg and 80 mg (40 mg: -31.72 mm Hg; 80 mg: -31.3 mm Hg [$P > 0.05$]). When coadministered with amlodipine 5 mg daily, both azilsartan 40 mg and 80 mg + amlodipine decreased SBP significantly more than amlodipine alone (amlodipine: -13.6 mm Hg; with azilsartan 40 mg: -24.79 mm Hg; with azilsartan 80 mg: -24.51 mm Hg [$P < 0.05$]). Compared with ramipril 10 mg daily, both azilsartan 40 mg and 80 mg resulted in significantly ($P < 0.001$) greater reductions in mean SBP (-20.63 and -21.24 mm Hg, respectively; ramipril: -12.22 mm Hg). The most common adverse events reported were dizziness (4%), dyslipidemia (3.3%), and diarrhea (2%).;CONCLUSIONS: At the recommended dose of 80 mg once daily, azilsartan is reported to be an efficacious BP-lowering agent. With once-daily dosing and a favorable side-effect profile, azilsartan is an attractive option for the treatment of hypertension. There is a lack of data supporting the use of azilsartan for improvement in cardiovascular outcomes; therefore, azilsartan is not approved for indications other than the treatment of hypertension. Copyright © 2011 Elsevier HS Journals, Inc. All rights reserved.

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*These articles were removed from the summary of new evidence after sending to expert reviewers. Upon further review, these articles did not meet inclusion criteria (e.g., treatment duration, time to follow-up, study design, already included in original systematic review, etc.)

Appendix G. Summary Table*

Conclusions From Original Systematic Review Executive Summary	SRC Literature Search (July 2015)	Expert Opinion	Conclusion from SRC
Key Question 1: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes?			
<p>Blood Pressure Control SOE: High (ACEI vs. ARB)</p> <p>77 studies (70 RCTs, 5 non-randomized controlled trials, 1 retrospective cohort study, and 1 case-control study) found ACEIs and ARBs to have similar long-term effects on blood pressure among individuals with hypertension. Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.</p> <p>SOE: Low (DRI vs. ACEI ARB)</p> <p>Direct Renin Inhibitors (DRI):</p> <ul style="list-style-type: none"> vs. ACEI Ramipril (2 studies) found DRI to have greater reduction in blood pressure vs. ARB Losartan (1 study) found DRI to have equal reduction in blood pressure 	<p>ACEIs vs. ARBs</p> <p>One RCT¹ of 422 patients assessed treatment with ACEI ramipril (R) vs. ARB telmisartan (T) vs. ramipril + telmisartan (R+T). This study found no difference between R and T in 24-hour systolic and diastolic BP reductions, but two-fold reductions for the R+T group.</p> <p>A RCT² of 486 patients with autosomal dominant polycystic kidney disease (ADPKD) and hypertension assessed ACEI lisinopril compared with ARB telmisartan and found no difference in blood pressure control.</p> <p>A RCT³ of ACEI ramipril vs. ARB azilsartan medoxomil in 884 patients with systolic BP of 150-180mm found that both 40 mg and 80 mg of azilsartan medoxomil resulted in greater reductions in seated clinic systolic blood pressure than 10 mg daily of ramipril (P < 0.001).</p> <p>One review conducted a pooled analysis⁴ of two RCTs⁵⁻⁶ comparing ACEI ramipril to ARB olmesartan medoxomil in elderly</p>	<p>One expert felt the original review's conclusions were current while another felt conclusions may no longer be current. The second expert noted that because the ARB azilsartan was not available in the U.S. until 2011, it was not included in the original conclusions. Furthermore, this expert noted that it is problematic to look at ARBs as a single class because there is evidence that losartan and valsartan are less effective than other ARBs such as candesartan, irbesartan, olmesartan, and telmisartan.</p>	<p>ACEIs vs. ARBs</p> <p>Conclusions on the comparative effectiveness of ACEIs and ARBs included in the original systematic review are likely current. However, one new RCT³ reported that azilsartan, an ARB that was introduced after the original systematic review was published, was more effective than ACEI ramipril at lowering clinic systolic BP.</p> <p>DRI vs. ACEIs or ARBs</p> <p>Conclusions are likely current.</p>

	<p>patients. One RCT⁵ was included in the original systematic review, and the other⁶ was not as it was published after the original search was completed. The new RCT⁶ found greater reductions in 24-hour systolic and diastolic BP with olmesartan medoxomil.</p> <p>DRI vs. ACEIs or ARBs A RCT⁷ of 822 patients assessed treatment with DRI aliskiren compared with ARB telmisartan for sustained BP lowering effect after a 7-day treatment withdrawal. Results indicated similar decreases in mean ambulatory BP at the end of active treatment with both aliskiren and telmisartan. From the end of treatment to the end of withdrawal, (EoW), the mean increase in 24-h mean ambulatory SBP and DBP were smaller for aliskiren vs. telmisartan ($P < 0.0001$). Mean sitting SBP and DBP were also significantly lower with aliskiren than telmisartan after EoW.</p> <p>A RCT⁸ 141 patients tested DRI aliskiren vs. ARB irbesartan and found greater reductions in mean sitting BP with aliskiren ($P = 0.019$).</p>		
<p>Mortality and Major Cardiovascular Events SOE: Low (ACEI vs. ARB)</p> <p>Due to low numbers of deaths or major</p>	No studies were identified	Both experts agreed the conclusions were up to date.	Conclusions are likely current.

<p>cardiovascular events reported, it was difficult to discern any differential effect of ACEIs vs. ARBs vs. DRIs with any certainty for these critical outcomes.</p> <ul style="list-style-type: none"> 21 studies reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects. From these, 38 deaths and 13 strokes were reported. May reflect low event rates among otherwise healthy patients and relatively few studies with extended follow-up <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>DRI vs. ACEI or ARB (3 studies, including 1 death) is insufficient to discern any differential effects between these drug classes on mortality and major cardiovascular events.</p>			
<p>Quality of Life SOE: Low (ACEI vs. ARB)</p> <p>ACEIs vs. ARB (4 studies) found no difference in measures of general QoL. 2 studies lacked quantitative data.</p> <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No study evaluated the comparative effectiveness of DRIs for QoL outcomes.</p>	<p>ACEIs vs. ARBs A RCT² 486 patients with autosomal dominant polycystic kidney disease (ADPKD) and hypertension assessed ACEI lisinopril compared with ARB telmisartan and found no difference in measures of quality of life.</p>	<p>One expert felt the conclusions were up to date, and the other felt that the new RCT may enhance the strength of the original conclusion due to the RCT's inclusion of quantitative data on quality of life.</p>	<p>Conclusions are likely current.</p>
<p>Rate of use of a single antihypertensive medication</p>	<p>No new studies were identified.</p>	<p>One expert felt the conclusions were up to date, and the other</p>	<p>Conclusions are likely current.</p>

<p>SOE: High (ACEI vs. ARB)</p> <p>ARBs vs. ACEIs:</p> <ul style="list-style-type: none"> No statistically evident difference in the rate of treatment success. Trend toward less frequent addition of second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients and by RCTs with very loosely defined protocols for medication titration and switching. <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No relevant studies.</p>		<p>felt that new data on DRI aliskiren may enhance the strength of this conclusion as little evidence was previously available on DRIs vs ACEIs.</p>	
<p>Lipid levels, markers of carbohydrate metabolism/diabetes control, & progression of renal disease</p> <p>SOE: Moderate (ACEI vs. ARB)</p> <p>ACEI vs. ARB:</p> <ul style="list-style-type: none"> No consistent differential effects on several potentially important clinical outcomes: lipid levels and markers of carbohydrate metabolism/diabetes control. Small difference in change in renal function, favoring ACEIs. Likely not clinically significant. Relatively few studies assessed outcomes over long- 	<p>ACEIs vs. ARBs</p> <p>A RCT² of 486 patients with autosomal dominant polycystic kidney disease (ADPKD) and hypertension assessed ACEI lisinopril compared with ARB telmisartan and found no difference in urinary aldosterone excretion, rates of decline in the estimated glomerular filtration rate, urinary albumin excretion, rates of hospitalization, and incidence of pain.</p> <p>DRIs vs. ACEIs or ARBs</p> <p>A RCT⁸ of 141 patients tested DRI aliskiren vs. ARB irbesartan and found aliskiren treatment led to a</p>	<p>Both experts felt that the conclusions were up to date. However, one expert noted that nuances of studies should be better explained, such as identifying the risk of potential confounding when an add-on drug is added to ACEI, ARB, or DRI treatment.</p>	<p>ACEIs vs. ARBs</p> <p>Conclusions on ACEIs vs. ARBs are likely current.</p> <p>DRIs vs. ACEIs or ARBs</p> <p>Conclusions may no longer be current. While the original review did not identify any studies related to this comparison, we identified one RCT⁸ that found that DRI aliskiren and ARB irbesartan had similar effects on glucose and lipid profiles.</p>

<p>term.</p> <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>No relevant studies.</p>	<p>60% decrease in PRA from baseline, whereas irbesartan increased PRA by 99% (both $P < 0.001$). Aliskiren and irbesartan had similar effects on glucose and lipid profiles and on a panel of biomarkers of inflammation and cardiovascular risk.</p>		
<p>Progression to Type 2 Diabetes and LV mass/function</p> <p>SOE: Low (ACEI vs. ARB)</p> <ul style="list-style-type: none"> Impact on ACEIs, ARBs, or DRIs on glucose or A1c: No evidence Progression to Type-2 diabetes mellitus: No included studies LV mass/function: (13 studies), most of which were poor quality with small sample sizes <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> 1 study 	<p>ACEIs vs. ARBs</p> <p>One retrospective cohort study⁹ of 15,900 patients compared ACEI enalapril to ARB candesartan and found that the risk of new type II diabetes onset was lower in the candesartan group (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69-0.96, $P = 0.01$) compared with the enalapril group.</p>	<p>Both experts felt the conclusions are up to date.</p>	<p>ACEIs vs. ARBs</p> <p>Conclusions may no longer be current. The original review did not identify any studies on the effect of ACEIs or ARBs on progression to type II diabetes. We identified one retrospective cohort study⁹ that found the risk of type II diabetes onset was lower among patients taking candesartan compared to those taking enalapril.</p>
<p>Key Question 2: For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?</p>			
<p>Cough</p> <p>SOE: High (ACEI vs. ARB)</p> <p>ACEIs vs. ARB:</p> <ul style="list-style-type: none"> ACEIs have been consistently shown to be associated with greater risk (odds ratio 0.211; 95% CI: 0.159 to 0.281) For RCTs, this shows a rate difference of 7.8% For cohort studies with lower rates of cough, this translates 	<p>DRI vs. ACEIs or ARBs</p> <p>No new studies were identified.</p>	<p>Both experts felt the conclusions are up to date.</p>	<p>DRI vs. ACEIs or ARBs</p> <p>Conclusions are likely current.</p>

<p>to 1.2%</p> <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>DRIs vs. ACEIs (2 studies) that gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933).</p>			
<p>Withdrawals due to adverse events SOE: High (ACEI vs. ARB)</p> <p>ARBs vs. ACEIs:</p> <ul style="list-style-type: none"> Withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI: 0.453 to 0.704) compared with ACEIs. For RCTs, this translated to an absolute difference of 2.3% (5.4% vs. 3.1%) <p>SOE: Low (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> vs. ACEI: No statistically significant difference (odds ratio 0.886; 95% CI: 0.458 to 1.714). <p>No evidence of difference across treatments in rate of other commonly reported specific adverse events.</p>	<p>ACEIs vs. ARBs A RCT³ of 884 patients compared ACEI ramipril vs. ARB azilsartan medoxomil in patents with systolic BP of 150-180mm found that adverse events leading to discontinuation were less frequent with both 40 mg (2.4%) and 80 mg of azilsartan medoxomil (3.1%) than with ramipril (4.8%).</p> <p>DRI vs. ACEIs or ARBs No new studies were identified.</p>	<p>Both experts felt the conclusions are up to date. One expert noted that new evidence on the ARB azilsartan enhances the strength of the original ACEI vs. ARB conclusion.</p> <p>The other expert suggested the VA NEPHRON-D trial¹⁰ as potentially relevant to this key question. Although this trial did not meet our inclusion criteria (it was conducted among chronic kidney disease [CKD] patients rather than hypertensive patients), it highlights the safety concerns associated with combining ACEI and ARB treatments for patients with impaired kidney function. In October 2012, trial researchers discovered that combination therapy patients had increased rates of serious adverse events, hyperkalemia, and acute kidney injury compared to monotherapy groups, and the trial was stopped.</p>	<p>ACEIs vs. ARBs Conclusions on withdrawal rates associated with the ACEIs and ARBs included in the original systematic review are likely current. One new RCT³ reported that azilsartan, an ARB that was introduced after the original systematic review was published, had a lower withdrawal rate than ACEI ramipril.</p> <p>DRI vs. ACEIs or ARBs Conclusions are likely current.</p>

<p>Angioedema SOE: Low (ACEI vs. ARB) SOE: Insufficient (DRI vs. ACEI or ARB)</p> <p>Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited the ability to accurately characterize the frequency of angioedema.</p> <ul style="list-style-type: none"> 4 studies reported episodes of angioedema; observed only in patients treated with an ACEI (5 patients from 3 studies) or a DRI (1 study) 	<p>No studies were identified</p>	<p>Both experts felt the conclusions are up to date.</p>	<p>Conclusions are likely current.</p>
<p>Persistence with drug therapy/treatment adherence SOE: Low (ACEI vs. ARB)</p> <p>ACEIs vs. ARBs:</p> <ul style="list-style-type: none"> Treatment adherence: Similar rates based on pill counts; may not be applicable outside the clinical setting. Rates of continuation with therapy: Somewhat better with ARBs. Due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. <p>SOE: Insufficient (DRI vs. ACEI or ARB)</p> <ul style="list-style-type: none"> Treatment adherence (3 studies) did not find evidence 	<p>ACEIs vs. ARBs One retrospective cohort study⁹ of 15,900 patients compared ACEI enalapril to ARB candesartan and found that more patients discontinued treatment in the enalapril group (38.1%) vs the candesartan group (27.2%).</p>	<p>Both experts felt the conclusions are up to date.</p>	<p>Conclusions are likely current.</p>

of differences compared with ACEIs or ARBs			
Persistence: Not evaluated by any of the studies			
Key Question 3: Are there subgroups of patients – based on demographics and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?			
SOE: Insufficient (ACEI vs. ARB; DRI vs. ACEI or ARB) Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.	No studies were identified.	Both experts felt the conclusions are up to date.	Conclusions are likely current.

Abbreviations: ACEI= Angiotensin-Converting-Enzyme Inhibitor; ADKPD= Autosomal Dominant Polycystic Kidney Disease; ARB = Angiotensin Receptor Blockers; BP= Blood Pressure; CI= Confidence Interval; CKD= Chronic Kidney Disease; DRI = Direct Renin Inhibitors; EOW= End of Withdrawal; LV = Left Ventricular; MI = Myocardial Infarction; QoL = Quality of Life; PRA= Plasma Renin Activity; RCT = Randomized Controlled Trial; SOE= Strength of Evidence; VA= Veteran's Affairs; WMD= Weighted Mean Difference. * No relevant FDA warnings or Horizon Scanning interventions were identified.

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