

Title: ACE inhibitors and ARBs: □ One or the other—not both—□ for high-risk patients. *J Fam Pract.* 2009;58:24-26, 28.

Potential PURL Review Form: Randomized controlled trials

SECTION 1: IDENTIFYING INFORMATION FOR NOMINATED POTENTIAL PURL

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|--|---|
| 1. Citation | Mann JF, Schmieder RE, McQueen M, et al, for the ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. <i>Lancet.</i> 2008;372:547-553. |
| 2. Hypertext link to PDF of full article | http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?PrId=3048&itool=AbstractPlus-def&uid=18707986&db=pubmed&url=http://linkinghub.elsevier.com/retrieve/pii/S0140-6736(08)61236-2 |
| 3. First date published study available to readers | August 16, 2008 |
| 4. PubMed ID | 18707986 |
| 5. Nominated By | Sarah-Anne Schumann |
| 6. Institutional Affiliation of Nominator | University of Chicago |
| 7. Date Nominated | August 15, 2008 |
| 8. Identified Through | <i>Lancet</i> |
| 9. PURLS Editor Reviewing Nominated Potential PURL | Bernard Ewigman |
| 10. Nomination Decision Date | August 15, 2008 |
| 11. Potential PURL Review Form (PPRF) Type | RCT |
| 12. Other comments, materials or discussion | |
| 13. Assigned Potential PURL Reviewer | Gail Patrick |
| 14. Reviewer Affiliation | University of Chicago |
| 15. Date Review Due | September 10, 2008 |
| 16. Abstract | BACKGROUND: Angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors are known to reduce proteinuria. Their combination might be more effective than either treatment alone, but long-term |

data for comparative changes in renal function are not available. We investigated the renal effects of ramipril (an ACE inhibitor), telmisartan (an ARB), and their combination in patients aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. METHODS: The trial ran from 2001 to 2007. After a 3-week run-in period, 25,620 participants were randomly assigned to ramipril 10 mg a day (n=8576), telmisartan 80 mg a day (n=8542), or to a combination of both drugs (n=8502; median follow-up was 56 months), and renal function and proteinuria were measured. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00153101. FINDINGS: 784 patients permanently discontinued randomised therapy during the trial because of hypotensive symptoms (406 on combination therapy, 149 on ramipril, and 229 on telmisartan). The number of events for the composite primary outcome was similar for telmisartan (n=1147 [13.4%]) and ramipril (1150 [13.5%]; hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.92-1.09), but was increased with combination therapy (1233 [14.5%]; HR 1.09, 1.01-1.18, $P=.037$). The secondary renal outcome, dialysis or doubling of serum creatinine, was similar with telmisartan (189 [2.21%]) and ramipril (174 [2.03%]; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212 [2.49%]; HR 1.24, 1.01-1.51, $P=.038$). Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (-2.82 [SD 17.2] mL/min/1.73 m² vs -4.12 [17.4], $P<.0001$) or combination therapy (-6.11 [17.9], $P<.0001$). The increase in urinary albumin excretion was less with telmisartan ($P=.004$) or with combination therapy ($P=.001$) than with ramipril. INTERPRETATION: In people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

- | | |
|---|--|
| 1. Number of patients starting each arm of the study? | 8542 to telmisartan; 8576 to ramipril; 8502 to both. |
| 2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)? | Inclusion: age 55 or older, established atherosclerotic vascular disease or diabetes mellitus (DM) with end-organ damage; Exclusions: major renal arterial stenosis, uncorrected volume or sodium depletion, Cr >256 micromoles, uncontrolled hypertension (HTN; >160/100 mm Hg); baseline characteristics |

published previously.

3. Intervention(s) being investigated?

Telmisartan 80 mg PO daily; ramipril 10 mg PO daily; or both.

4. Comparison treatment(s), placebo, or nothing?

See above.

5. Length of follow up? Note specified end points, eg, death, cure, etc.

Single-blind 3- to 4-week run-in period of increasing doses of ramipril with telmisartan 40 mg then randomization, then follow-up at 6 weeks, then every 6 months (median 56 months).

6. What outcome measures are used? List all that assess effectiveness.

Primary outcomes: first occurrence of any dialysis (acute = <2 months or chronic = >2 months), renal transplantation (no actual cases during study), doubling of serum creatinine, or death.
Secondary outcomes: composite of dialysis plus doubling creatinine, components of composite outcomes, progression of proteinuria, change in eGFR (by modification of diet in renal disease formula).

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, *P*-values, etc.

Outcomes all similar for ACE or ARB alone, except higher risk of dialysis for ARB alone over ACE alone but not statistically significant (HR=1.55, 0.77-3.11, *P*=.221); telmisartan and combo showed a worsening eGFR over the study period compared to ACE alone; occurrence of primary/secondary outcomes higher in combo therapy; "combination therapy had no clear benefit in the highest renal risk group (overt DM nephropathy), in participants with HTN and DM, or in participants with eGFR <60, tended to be harmful in individuals with low renal risk (no DM or HTN).

8. Study addresses an appropriate and clearly focused question - **select one**

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

9. Random allocation to comparison groups

Well covered

Comments: Blocks and stratified by center with automated telephone service

10. Concealed allocation to comparison groups

Well covered

11. Subjects and investigators kept “blind” to comparison group allocation	Comments: Need to look at prior publication
12. Comparison groups are similar at the start of the trial	Comments: Need to look at prior publication
13. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Comments: Need to look at prior publication
14. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered
15. Are patient-oriented outcomes included? If yes, what are they?	Yes and no - need for dialysis and death are patient-oriented outcomes, but creatinine, eGFR, and proteinuria are not.
16. What percent dropped out, and were lost to follow up? Could this bias the results? How?	784 discontinued due to hypotension (406 on combo, 149 on ACE, and 229 on ARB); renal abnormalities reported as a reason for stopping meds in 60 (0.7%) ACE, 68 (0.8%) ARB, and 94 (1.1%) of combination.
17. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Does not say specifically.
18. If a multisite study, are results comparable for all sites?	
19. Is the funding for the trial a potential source of bias? If yes, what measures were taken to	No. Although funding was "sponsored," the trial was coordinated and analyzed independently by the McMaster University Population Health Research Institute; data were later transferred to the sponsor at the end of the study.

insure scientific integrity?

20. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized. Patients with risk for chronic kidney disease (CKD).

21. In what care settings might the findings apply, or not apply? Primary care office, nephrology clinic.

22. To which clinicians or policy makers might the findings be relevant? Not sure.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts Bottom line: DynaMed references a different arm of this same trial.

2. DynaMed citation/access date
Angiotensin II receptor blockers (ARBs)
Updated 2008 Apr 11, 04:24 PM: combination ramipril plus telmisartan does not reduce mortality or cardiovascular morbidity compared to ramipril alone and may worsen renal impairment (N Engl J Med 2008 Mar 31)
Lancet 2007 Dec 1 commentary (Individual drugs)
Insufficient evidence comparing ACE inhibitors vs. ARBs for clinical outcomes (AHRQ Comparative Effectiveness Review 2007 Nov 1) in DynaMed, accessed on September 8, 2008.

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

4. UpToDate excerpts Bottom line: UpToDate does not include this new reference. This would represent a practice change, as UpToDate recommends combination therapy to

achieve reduction in proteinuria as a means to slow progression of CKD.

5. UpToDate citation/access date

Antihypertensive therapy and progression of nondiabetic chronic kidney disease

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Last literature review version 16.2: May 2008.

This topic last updated: June 11, 2008 in UpToDateonline.com. Accessed September 8, 2008.

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

7. PEPID PCP excerpts

Is combining ACE inhibitors and ARBs helpful or harmful?

Evidence-Based Answer (Published February 2004)

- Several trials have investigated the effect of combination therapy on diabetic and nondiabetic proteinuria.
- Conclusions from these trials are limited by their small sample size and by measurement of intermediate outcomes without mortality data.
- The largest trial, COOPERATE, was conducted in Japan and included 336 patients with nondiabetic renal disease.
- The investigators found that significantly fewer patients receiving combination therapy reached the combined primary endpoint of time to doubling of serum creatinine or end-stage renal disease compared with patients receiving monotherapy.
- The CALM study included 199 patients with hypertension, microalbuminuria, and type 2 diabetes mellitus, and demonstrated significantly greater attenuation of urinary albumin-to-creatinine ratio and significantly improved blood pressure control with combination therapy

- compared with either therapy alone.
- Another trial, ONTARGET, is currently being conducted to assess the impact of ACEI or ARB monotherapy and combination therapy on reducing cardiovascular risk and includes a combined primary endpoint of morbidity and mortality.
 - The study involves 23,400 high-risk patients and will have a follow-up period of 5.5 years.
 - This trial enrolls patients who have coronary disease, cerebrovascular disease, peripheral vascular disease, or diabetes with end-organ damage (inclusion and exclusion criteria are based on those used in the HOPE study).

Adding ARBs to ACE inhibitors: Good in theory, but clinical evidence is still weak

There is good evidence of the benefits of angiotensin inhibition in multiple diseases, so it is logical to ask if adding receptor blockers adds further benefit. For now, it appears that the addition of an ARB to an ACE inhibitor is an idea that sounds good in theory, but needs more data to prove its clinical benefit and safety.

The clinical evidence for the combo in heart failure and hypertension is weak, since mortality data are lacking and there is the troubling association with increased mortality in the presence of beta-blockers. Using the combination is not currently recommended by the major national guidelines for those areas (eg, American Heart Association, Joint National Committee VII). Although the benefit for patients with proteinuria appears promising, we still await evidence for decreasing mortality. Given cost and the combination's uncertain benefit, it would be prudent to wait until the completion of studies currently in progress before we embrace combination therapy.

Are ARBs or ACE inhibitors preferred for nephropathy in diabetes?

Evidence-Based Answer (Published March 2004)

- Brett H. Foreman, MD, Moses Cone Health System, Greensboro, NC
- Lee Chambliss, MD, MPH, Moses Cone Health System, Greensboro, NC

Recommendations from Others

The American Diabetes Association recommends both ACEIs and ARBs for the treatment of early nephropathy in hypertension to delay the progression of microalbuminuria to macroalbuminuria and overt nephropathy.

Clinical Commentary

ARBs not yet shown to be as good as ACE inhibitors at reducing mortality
The evidence is good that ARBs delay the progression of type 2 diabetic nephropathy. Although more studies have looked at ARBs than ACE inhibitors in nephropathy from type 2 diabetes, ARBs have not been shown to be as good as ACE inhibitors at reducing all-cause mortality, the most important patient-oriented outcome.

Bottom line: PEPID does not have a separate topic on proteinuria. Under ACE inhibitors, there are two nice EBM summaries - one of which references the potential outcomes of this ONTARGET trial - which has now been published.

8. PEPID citation/access data

Is combining ACE inhibitors and ARBs helpful or harmful?

Evidence-Based Answer (Published February 2004)

1. Clinical Inquiry Author:
 - o William E. Chavey, MD, MS
Department of Family Medicine
University of Michigan
Ypsilanti, MI
 - o Joan Nashelsky, MLS
Family Practice Inquiries Network
Iowa City, IA
2. Clinical Commentator:
 - o David Kilgore, M.D.
Tacoma Family Medicine
Tacoma, WA

In PepidOnline.com. Accessed on September 8, 2008.

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?

Yes, there is important evidence or recommendations that are missing

If yes, which PEPID Topic, Title(s):

Improvement in proteinuria does not equal improved renal outcomes.

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (E) that should be updated on the basis of the review?

Yes, there is important evidence or recommendations that are missing

If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry),

Title(s):

Is combining ACE inhibitors and ARBs helpful or harmful?

Evidence-Based Answer (Published February 2004)

SECTION 4: CONCLUSIONS

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? 1

Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. Relevance: Are the results of this study generalizable and relevant to the health care needs of patients cared for by “full-scope” family physicians? 3
Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

5. Practice-changing potential: 3

If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population, and the expected benefit.

Many specialists do this and recommend it. Fewer primary care physicians appear to do so, but some do and many see patients started by other physicians on this combination. UpToDate recommends combination therapy.

7. Applicability to a Family Medical Care Setting: 1

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure;

advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

8. If you coded 4.7 as a 4, 5, 6 or 7 please explain.

9. Immediacy of Implementation: 1

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinically meaningful outcomes or patient-oriented 3-4

outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

13. In your opinion, is this a Pending PURL? 1

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine.
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting.
- Immediacy of implementation.

Give one number on a scale of

1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

SECTION 5: EDITORIAL DECISIONS

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|---|--|
| 1. FPIN PURLs editorial decision | Pending PURL |
| 2. Follow-up issues for Pending PURL Reviewer | N/A |
| 3. FPIN PURLS Editor making decision | Bernard Ewigman |
| 4. Date of decision | September 11, 2008 |
| 5. Brief summary of decision | Although combining ACE inhibitors and ARBs reduces proteinuria, it appears that patient oriented-outcomes are adversely affected. UpToDate recommends this combination, so even if family physicians and other primary care clinicians are not following this recommendation, it seems to me to be an important "change in practice recommendation." |