RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015 Sep 18. pii: S0140-6736(15)00257-3.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/26414968
3. First date published study available to readers	09/18/2015
4. PubMed ID	26414968
5. Nominated By	Other Other: Niladri Das
6. Institutional Affiliation of Nominator	Other Other:
7. Date Nominated	10/06/2015
8. Identified Through	Other Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland Other:
10. Nomination Decision Date	11/02/2015
11. Potential PURL Review Form (PPRF) Type	RCT
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Anne Mounsey
14. Reviewer Affiliation	Other Other: UNC
15. Date Review Due	11/18/2015
16. Abstract	BACKGROUND: Optimal drug treatment for patients with resistant hypertension is undefined. We aimed to test the hypotheses that resistant hypertension is most often caused by excessive sodium retention, and that spironolactone would therefore be superior to non-diuretic add-on drugs at lowering blood pressure. METHODS:

In this double-blind, placebo-controlled, crossover trial, we enrolled patients aged 18-79 years with seated clinic systolic blood pressure 140 mm Hg or greater (or ≥135 mm Hg for patients with diabetes) and home systolic blood pressure (18 readings over 4 days) 130 mm Hg or greater, despite treatment for at least 3 months with maximally tolerated doses of three drugs, from 12 secondary and two primary care sites in the UK. Patients rotated, in a preassigned, randomised order, through 12 weeks of once daily treatment with each of spironolactone (25-50 mg), bisoprolol (5-10 mg), doxazosin modified release (4-8 mg), and placebo, in addition to their baseline blood pressure drugs. Random assignment was done via a central computer system. Investigators and patients were masked to the identity of drugs, and to their sequence allocation. The dose was doubled after 6 weeks of each cycle. The hierarchical primary endpoints were the difference in averaged home systolic blood pressure between spironolactone and placebo, followed (if significant) by the difference in home systolic blood pressure between spironolactone and the average of the other two active drugs, followed by the difference in home systolic blood pressure between spironolactone and each of the other two drugs. Analysis was by intention to treat. The trial is registered with EudraCT number 2008-007149-30, and ClinicalTrials.gov number, NCT02369081.

FINDINGS:

Between May 15, 2009, and July 8, 2014, we screened 436 patients, of whom 335 were randomly assigned. After 21 were excluded, 285 patients received spironolactone, 282 doxazosin, 285 bisoprolol, and 274 placebo; 230 patients completed all treatment cycles. The average reduction in home systolic blood pressure by spironolactone was superior to placebo (-8·70 mm Hg [95% CI -9·72 to -7·69]; p<0·0001), superior to the mean of the other two active treatments (doxazosin and bisoprolol; -4·26 [-5·13 to -3·38]; p<0·0001), and superior when compared with the individual treatments; versus doxazosin (-4·03 [-5·04 to -3·02]; p<0·0001) and versus bisoprolol (-4·48 [-5·50 to -3·46]; p<0·0001). Spironolactone was the most effective blood pressure-lowering treatment, throughout the distribution of baseline plasma renin; but its margin of superiority and likelihood of being the best drug for the individual patient were many-fold greater in the lower than higher ends of the distribution. All treatments were well tolerated. In six of the 285 patients who received spironolactone, serum potassium exceeded 6·0 mmol/L on one occasion.

INTERPRETATION:

Spironolactone was the most effective add-on drug for the treatment of resistant hypertension. The superiority of spironolactone supports a primary role of sodium retention in this condition.

17. Pending PURL Review Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?	285 patients received spironolactone, 282 doxazosin, 285 bisoprolol, and 274 placebo;
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	• On ACE/ARB, CCB and diuretic checked for adherence. BPs in clinic > 140 and home > 130 • Exclusion criteria • Abnormal potassium • GFR<45 • <70% compliance during 4 week run in period.
3. Intervention(s) being investigated?	Spironolactone
4. Comparison treatment(s), placebo, or nothing?	versus placebo, bisoprolol, and doxazosin •Spironolactone 25-50mg •Doxazosin 4-8mg •Bisoprolol 5-10mg
5. Length of follow up? Note specified end points e.g. death, cure,	4 cycles of 12 weeks

etc.

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

•Primary end points:

•Average home SBP of 3 taken in pm and 3 in am on 4 consecutive days prior to study visit
•Difference in SBPs between spironolactone and other drugs

•Secondary end points:

•Mean of 2 clinic SBPs
•SBP < 135 at home
•Renin levels
•Adverse events.
•Relationship between plasma renin and BP response

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

The average reduction in home systolic blood pressure was superior with spironolactone compared to placebo (–8.70 mm Hg, 95% CI -9.72 to -7.69; p<0・0001), doxazosin (-4.03 mmHg, 95% CI–5.04 to -3.02; p<0・0001) and bisoprolol (-4.48 mm Hg 95% CI, -5.50 to –3.46;p<0・0001).

8. What are the adverse effects of intervention compared with no intervention?

Spironolactone compared to bisoprolol and doxazosin was not associated with increased adverse effects.
No increase in discontinuation due to hyperkalemia and renal failure with spironolactone.

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

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable

Comments:

10. Random allocation to comparison groups

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

11. Concealed allocation to comparison groups

☐ Well covered
☒ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Subjects and investigators kept “blind” to comparison group allocation

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

12. Comparison groups are similar at the start of the trial

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

14. Were there any differences between the groups/arms of the study other than the intervention under

☒ Well covered
☐ Adequately addressed
☐ Poorly addressed
☐ Not applicable
Comments:

investigation? If yes, please indicate whether the differences are a potential source of bias.	
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed ☐ Not applicable Comments:
16. Are patient oriented outcomes included? If yes, what are they?	BP is not a true patient orientated outcome
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	314 in ITT analysis with 274 to 285 completing each treatment cycle
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	yes
19. If a multi-site study, are results comparable for all sites?	not given
20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	no
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Mainly Caucasian. Pts with GFR<45 excluded.
22. In what care settings might the findings apply, or not apply?	primary and secondary
23. To which clinicians or policy makers might the findings be relevant?	PC physicians and cardiologists

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:

1. DynaMed excerpts	Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}
2. DynaMed citation/access date	Title. Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: . Accessed
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	
4. UpToDate excerpts	The pharmacologic treatment of resistant hypertension involves combinations of three or more drugs. Some patients have a specific indication for a class of drugs (eg, beta blocker or nondihydropyridine calcium channel blocker for rate control in atrial fibrillation). If there is no such indication, the preferred three-drug regimen consists of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a long-acting calcium channel blocker such as amlodipine, and a long-acting thiazide diuretic, preferably chlorthalidone. Among patients with an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m2, a loop diuretic, such as furosemide or torsemide, is usually necessary for effective volume control. (See 'Pharmacologic therapy' above.) ●In patients with persistent uncontrolled hypertension despite the above three-drug regimen in optimal dose, we suggest adding spironolactone (Grade 2B). We typically begin at 12.5 mg/day and titrate up to, but not above, 50 mg/day in the absence of proven primary aldosteronism. Monitoring of serum potassium levels for both hypokalemia and hyperkalemia are necessary if chlorthalidone and spironolactone are used. For patients who cannot tolerate spironolactone, eplerenone and amiloride are alternatives
5. UpToDate citation/access date	Always use Basow DS as editor & current year as publication year. Title. resistant HTNAuthor. calhoun/townsend In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: feb 2016. Accessed3/16
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	Use spironolactone as your 4th agent
7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp	no rx recs. (following publication of this study)
8. PEPID citation/access data	Author. Title. resistant HTN In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: 2013. Accessed3/16
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 ☐ No, this topic is current, accurate and up to date. If yes, which PEPID Topic, Title(s): 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review? ☒ Yes, there is important evidence or recommendations that are missing ☐ No, this topic is current, accurate and up to date. If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
10. Other excerpts (USPSTF; other guidelines; etc.)	JNC 8 recs for resistant HTN Reinforce medication and lifestyle adherence. Add additional medication class (eg, β-blocker, aldosterone antagonist, or others)

and/or refer to physician with expertise in hypertension management.

11. Citations for other excerpts

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

UTD has been updated to recommend spironolactone

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

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

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

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 to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

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

5. Practice changing potential: 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)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

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.

7. Applicability to a Family Medical Care Setting: 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

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)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: 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?
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

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)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?
12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

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)
☐1 ☒2 ☒3 ☐4 ☐5 ☐6 ☐7

13. In your opinion, is this a Pending PURL?
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)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

14. Comments on your response in 4.13