RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

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

A. Citiation: 1: Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ,Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators. Bedtimehypertension treatment improves cardiovascular risk reduction: the HygiaChronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. doi:10.1093/eurheartj/ehz754. [Epub ahead of print] PubMed PMID: 31641769.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/31641769
C. First date published study available to readers: 10/22/2019
D. PubMed ID: 31641769
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: MO – University of Missouri-Columbia
G. Date Nominated: 10/22/2019
H. Identified Through: European Heart Journal
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 10/23/2019
K. Potential PURL Review Form (PPRF) Type: RCT
L. Assigned Potential PURL Reviewer: Bob Marshall
M. Reviewer Affiliation: WA - Madigan
A. Abstract: The Hygia Chronotherapy Trial, conducted within the clinical primary care setting, was designed to test whether bedtime in comparison to usual upon awakening hypertension therapy exerts better cardiovascular disease (CVD) risk reduction.

METHODS AND RESULTS:
In this multicentre, controlled, prospective endpoint trial, 19 084 hypertensive patients (10 614 men/8470 women, 60.5 ± 13.7 years of age) were assigned (1:1) to ingest the entire daily dose of ≥1 hypertension medications at bedtime (n = 9552) or all of them upon awakening (n = 9532). At inclusion and at every scheduled clinic visit (at least annually) throughout follow-up, ambulatory blood pressure (ABP) monitoring was performed for 48 h. During the 6.3-year median patient follow-up, 1752 participants experienced the primary CVD outcome (CVD death, myocardial infarction, coronary revascularization, heart failure, or stroke). Patients of the bedtime, compared with the upon-waking, treatment-time regimen showed significantly lower hazard ratio-adjusted for significant influential characteristics of age, sex, type 2 diabetes, chronic kidney disease, smoking, HDL cholesterol, asleep systolic blood pressure (BP) mean, sleep-time relative systolic BP decline, and previous CVD event-of the primary CVD outcome [0.55 (95% CI 0.50-0.61),

P < 0.001] and each of its single components (P < 0.001 in all cases), i.e. CVD death [0.44 (0.34-0.56)], myocardial infarction [0.66 (0.52-0.84)], coronary revascularization [0.60 (0.47-0.75)], heart failure [0.58 (0.49-0.70)], and stroke [0.51 (0.41-0.63)].

CONCLUSION:
Routine ingestion by hypertensive patients of ≥1 prescribed BP-lowering medications at bedtime, as opposed to upon waking, results in improved ABP control (significantly enhanced decrease in asleep BP and increased sleep-time relative BP decline, i.e. BP dipping) and, most importantly, markedly diminished occurrence of major CVD events.

TRIAL REGISTRATION:
ClinicalTrials.gov, number NCT00741585.

B. Pending PURL Review Date**:** 12/1/2019

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

A. Number of patients starting each arm of the study?
9532 in the treatment upon awakening arm and 9552 in the treatment at bedtime arm (please note apparent error in publication with inaccurate depiction of bedtime vs awakening arm in figure 1 which is opposite from all other figures in the paper)

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Adult hypertensive patients on diurnal schedules who take blood pressure medication with once daily dosing. Excluded patients include pregnancy, history of alcoholism or narcotic addition, acquired immunodeficiency syndrome, night or rotating shift-work employment, secondary hypertension, cardiovascular disease and certain associated medical conditions (unstable angina pectoris, heart failure, life-threatening arrhythmia, atrial fibrillation, kidney failure, and grade III-IV retinopathy), intolerance to ambulatory blood pressure monitoring, and inability to communicate and comply with all study requirements.

C. Intervention(s) being investigated?
Administration of blood pressure medication at bedtime

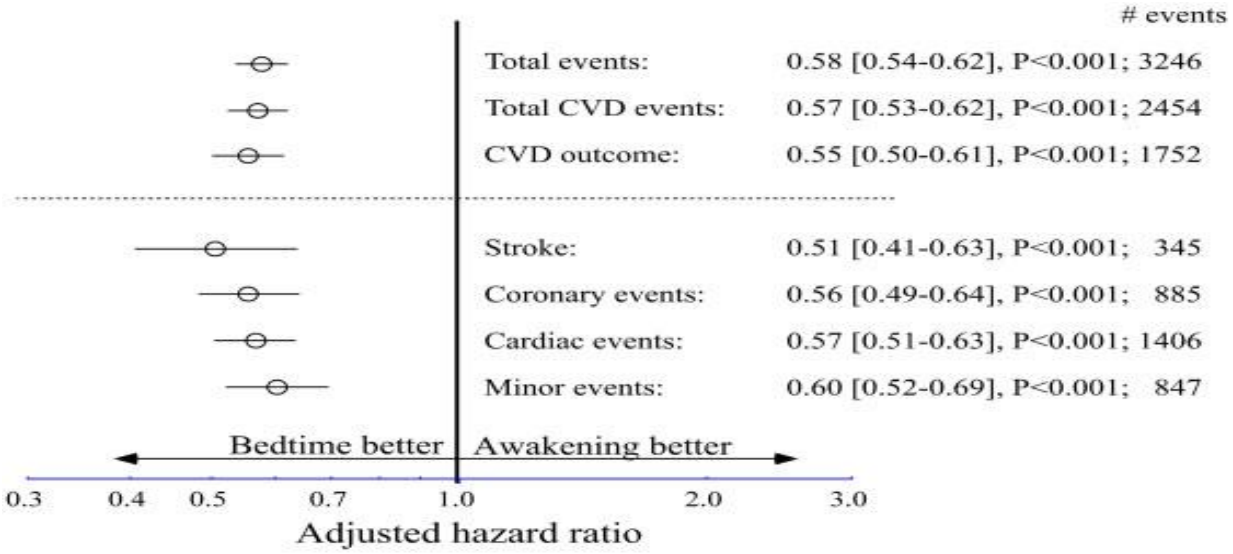
D. Comparison treatment(s), placebo, or nothing?
Administration of blood pressure medication in morning

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
Follow up was minimum greater/equal to 1 year with

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

Primary outcome measures are myocardial infarction, coronary revascularization, heart failure, ischemic stroke, hemorrhagic stroke, and cardiovascular disease death. Secondary outcome measures were the grouping of stroke, coronary events, and cardiac events.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
The effect of the intervention is all primary outcomes improved with p-values less than 0.001 as calculated by the hazard ratio. The hazard ratios for each primary outcome demonstrated statistically significant improvement in the bedtime treatment arm. Total CVD death Hazard Ratio is 0.44 with a CI of 0.34-0.56 p<0.001.



H. What are the adverse effects of intervention compared with no intervention?
None

I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments:

J. Random allocation to comparison groups:
(select one) Well covered

Comments:

K. Concealed allocation to comparison groups:
(select one) Well covered

Comments:

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Well covered

Comments: Single blinded

M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments:

N. 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 sources of bias. (select one) Well covered
Comments: There are no differences between the groups/arms in this study.

O. Were all relevant outcomes measured in a standardized, valid, and reliable way? (select one) Well covered
Comments:

P. Are patient oriented outcomes included? If yes, what are they?
myocardial infarction, coronary revascularization, heart failure, ischemic stroke, hemorrhagic stroke, and cardiovascular disease death

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
0.3-0.5% drop out rate. This rate is too small to bias the results.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes

S. If a multi-site study, are results comparable for all sites?
All numbers are reported together. There was no differentiation between sites.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
There is little potential bias as the funding comes from a Spanish government funding agency which is unrestricted.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
The findings of this study might apply to all patients taking once daily dosing medication to treat primary hypertension. This could potentially apply to all adult patients who meet the exclusion criteria in the study.

V. In what care settings might the finding apply, or not apply?
These findings apply in both the inpatient and outpatient settings.

W. To which clinicians or policy makers might the finding be relevant?
This applies to those who are entrusted with the treatment of adult patients with hypertension.

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 up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on 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 date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

- DynaMed excerpts

  - **taking ≥ 1 antihypertensive medication at bedtime associated with greater blood pressure control and decreased risk of cardiovascular events compared to taking medication in morning in patients with CKD (level 2 [mid-level] evidence)**
  - based on randomized trial without blinding
  - 661 patients (mean age 59 years) with CKD were randomized to ≥ 1 antihypertensive medication at bedtime vs. all medication in the morning and followed for mean 5.4 years
  - patients had mean 2.3 medications
  - 38.9% had any event, including death, cardiovascular event (myocardial infarction, angina pectoris, coronary revascularization), cerebrovascular event (stroke, transient ischemic attack), heart failure, acute arterial occlusion of lower extremities, or thrombotic occlusion of retinal artery
  - comparing ≥ 1 bedtime medication vs. morning medication regimen
    - blood pressure control
      - controlled ambulatory BP in 56.5% vs. 45.2% (p = 0.003, NNT 9)
      - sleep-time relative systolic BP decline < 10% (nondipper) in 41% vs. 71.1% (p < 0.001, NNT 4)
      - controlled asleep BP (< 120 mmHg/70 mmHg) in 67.2% vs. 54.8% (p < 0.001, NNT 13)
      - controlled awake BP in 64.1% vs. 67.2% (not significant)
    - cardiovascular events
      - total events in 19.8% vs. 57.9% (p < 0.001, NNT 3)
      - major events (cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke) in 5.1% vs. 14.5% (p < 0.001, NNT 11)
      - cardiovascular events in 6.2% vs. 26.1% (p < 0.001, NNT 5)
      - all-cause mortality among 4% vs. 7.8% (p = 0.056)
  - Reference - J Am Soc Nephrol 2011 Dec;22(12):2313full-text, commentary can be found in Ann Intern Med 2012 Jun 19;156(12):JC6EBSCOhost Full Text, J Am Soc Nephrol 2011 Dec;22(12):2152, Nat Rev Nephrol 2011 Nov 22;8(1):4
  -
- **bedtime antihypertensive dosing may not improve nocturnal blood pressure control in African American patients with CKD (level 2 [mid-level] evidence)**

- based on randomized crossover trial with inadequate statistical power
- 151 patients (mean age 65 years) with hypertensive CKD from African American Study of Kidney (AASK) Disease cohort were randomized to 1 of 3 initial antihypertensive drug regimens for 6 weeks each
  - AM dosing (all antihypertensives in the morning)
  - PM dosing (all antihypertensives at bedtime)
  - add-on dosing (antihypertensives in the morning and 1 additional antihypertensive at bedtime)
- 24-hour ambulatory blood pressure monitoring performed between each 6-week regimen
- study underpowered to detect differences in primary outcome of systolic nocturnal blood pressure (power calculation estimated 180 patients required for 80% power to detect difference of ≥ 4.3 mm Hg for nocturnal systolic BP)
- comparing AM dosing vs. PM dosing
  - mean difference between daytime and nocturnal systolic BP 4.6 mm Hg vs. 7.8 mm Hg ($p < 0.001$)
  - mean night/day systolic BP ratio 0.97 vs. 0.94 ($p < 0.001$)
- no significant differences among regimens in nocturnal BP, daytime BP, and 24-hour BP
- Reference - Hypertension 2013 Jan;61(1):82full-text

- authors of review note possibly meaningful differences to explain disparate results in 2 studies above (J Am Soc Nephrol 2011 Dec;22(12):2313and Hypertension 2013 Jan;61(1):82), where AASK patients[5]
  - were older (age 65 years vs. 59 years)
  - had shorter duration of hypertension (7 years vs. 30 years)
  - had higher estimated glomerular filtration rate (GFR) (66 mL/minute/1.73 m^2 vs. 45 mL/minute/1.73 m^2)
  - had higher mean nocturnal systolic blood pressure (129 mm Hg vs. 124 mm Hg)

A. DynaMed citation/ access date

Hypertension Treatment in Patients With Chronic Kidney Disease. In: DynaMed [database online]. Available at http://www.DynamicMedical.com <http://www.DynamicMedical.com> . Last updated November 30, 2018. Accessed December 4, 2019.

B. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
DynaMed references two studies showing contradicting results regarding blood pressure management and cardiovascular events in patients with chronic kidney disease.

C. UpToDate excerpts
https://www.uptodate.com/contents/ambulatory-and-home-blood-pressure-monitoring-and-white-coat-hypertension-in-adults?sectionName=Nocturnal%20blood%20pressure%20and%20nondippers&search=timing%20of%20blood%20pressure%20medication&topicRef=3869&anchor=H10&source=see_link#H10

Nocturnal blood pressure and non-dippers — Considerable data suggest that measurement of nighttime blood pressure yields additional prognostic data in terms of all-cause mortality and cardiovascular events [17,25,26,44,45]:

●A cohort study of 7458 patients in six countries from Europe, Asia, and South America found that both daytime and nighttime blood pressure predicted all cardiovascular events [44]. Nighttime blood pressure, adjusted for daytime blood pressure, predicted total, cardiovascular, and non-cardiovascular mortality. By contrast, daytime blood pressure, adjusted for blood pressure measured during sleep, only predicted non-cardiovascular mortality.

●In a second cohort of 63,910 patients who underwent ambulatory monitoring, both nighttime and daytime blood pressure predicted all-cause and cardiovascular mortality, but nighttime was not more predictive than daytime blood pressure [26].

Independent of the degree of hypertension, non-dipping is a risk factor for the development of LVH, heart failure, and other cardiovascular complications [3,46-49]. However, "extreme dipping" (eg, >20 percent nocturnal decline in blood pressure) and a large morning increase in blood pressure are also potentially deleterious [48,50]. (See 'Dipping' above.)

Non-dipping has also been associated with moderately increased albuminuria (formerly called "microalbuminuria") and more rapid progression of nephropathy in patients with diabetes mellitus [51,52]. More importantly, non-dipping may be a risk factor for decline in glomerular filtration rate, as well as for ESRD and death among patients with chronic kidney disease [30,53]. The presence of sleep apnea should also be evaluated in non-dippers. (See "Obstructive sleep apnea and cardiovascular disease in adults", section on 'Hypertension'.)

Whether reversal of non-dipping is possible or beneficial is uncertain. There are conflicting data about whether or not nocturnal dosing of antihypertensive medications can restore a dipping pattern. This issue is discussed in detail elsewhere. (See "Choice of drug therapy in primary (essential) hypertension", section on 'Bedtime versus morning dosing'.)

UpToDate citation

Townsend,R.R., Ambulatory and home blood pressure monitoring and white coat hypertension in adults. In: Basow DS, ed. UpToDate [database online]. Waltham, MA: UpToDate; 2019. Available at http://www.uptodate.com. Last updated: August 15, 2019. Accessed December 4, 2019.

D. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
Nocturnal hypertension or non-dippers (failure of BP to fall at least 10% during sleep) is a stronger predictor of adverse CV outcomes than daytime blood pressure. Consider nocturnal dosing of antihypertensives in patients that are non-dippers.

E. Other excerpts (USPSTF; other guidelines; etc.) None

F. Citations for other excerpts None

G. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences) N/A

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

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", 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?
N/A

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes, the RCT was performed in a primary care clinical setting c/w that found in typical primary care settings in the U.S.

D. If **C** was coded "Other, explain or No", please provide an explanation.
N/A

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

Specifically, adult patient with primary hypertension who meet inclusion/exclusion criteria taking once daily medication for hypertension should be instructed to take their antihypertensive medication at bedtime rather than daytime dosing.

G. **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 ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**. This can be done by any primary care provider treating hypertensive patients with one or more medications.

I. **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? No; the only potential barrier is patient preference for taking diuretics in the AM vice at bedtime (i.e., patient adherence to a bedtime-only regimen if diuretics are included).

J. If **I** was coded "Other, explain or No", please explain why.
There are no barriers to implementation and no change in the cost of treatment.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

L. If **K** was coded "Other, explain or No", please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. 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.

4. Performed in and applicable to any primary care setting.

5. Immediacy of implementation – can be implemented at any time.

N. Comments on your response for question M. The recommendation to change the timing of antihypertensive medication administration to bedtime dosing should be the standard based on the findings of this study. It is feasible, cost effective, highly applicable, and can be implemented immediately, resulting in significant benefit to patients. Because the RCT was performed in a primary care clinical setting similar to standard family medicine practice settings, the results should be reproducible in any practice. As noted, there may be some patient adherence issues with bedtime dosing of diuretics, which are first-line HTN agents.