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: Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-1461. doi:10.1056/NEJMoa2107038
B. Link to PubMed Abstract: https://pubmed.ncbi.nlm.nih.gov/34449189/
C. First date published study available to readers: 8/27/2021
D. PubMed ID: 34449189
E. Nominated By: Jim Stevermer
F. Institutional Affiliation of Nominator: MO – U of Missouri-Columbia
G. Date Nominated: 10/18/2021
H. Identified Through: N Engl J Med
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 11/9/2021
K. Potential PURL Review Form (PPRF) Type: RCT
L. Abstract: Background: Sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

Methods: In this double-blind trial, we randomly assigned 5988 patients with class II-IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

Results: Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

Conclusions: Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

M. Pending PURL Review Date**:** 2/1/2022

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

A. Number of patients starting each arm of the study?
2997 in emagliflozin and 2991 in placebo.

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
The characteristics of the patients at baseline were similar in the two treatment groups (Table 1 and Table S2). Nearly half the patients had diabetes and half had an eGFR of less than 60 ml per minute per 1.73 m2. Two thirds of the patients had a left ventricular ejection fraction of 50% or more; the median left ventricular ejection fraction was 54%.

C. Intervention(s) being investigated?
Empagliflozin 10 mg daily

D. Comparison treatment(s), placebo, or nothing?
Placebo.

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
26.2 months.

F. What outcome measures are used? List all that assess effectiveness.
Primary outcome was a composite of CV death or hospitalization for HF. Secondary outcomes were all hospitalizations for HF, rate of eGFR decline.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). NNT of 31

H. What are the adverse effects of intervention compared with no intervention?
Uncomplicated genital and urinary infections were more common in treatment group.

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

Comments:

J. Random allocation to comparison groups:
(select one) Adequately addressed

Comments:

K. Concealed allocation to comparison groups:
(select one) Adequately addressed

Comments:

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

Comments:

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:

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?
Yes, hospitalization.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
19% vs 18% in each group dropped out.

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?
yes

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
Yes. BI collected the data. Stored the data.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
Patients with HFpEF.

V. In what care settings might the finding apply, or not apply?
FM, cardiology, inpatient and outpatient.

W. To which clinicians or policy makers might the finding be relevant?
FM, cardiology, inpatient and outpatient.

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 the AMA style. For example: Norton JM, Bavendam TG, Elwood W, et al. Research needs to understand self-management of lower urinary tract symptoms: summary of NIDDK workshop. *J Urol*. 2018;199(6):1408-1410. doi:10.1016/j.juro.2017.11.079

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: https://www.uptodate.com/login. {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 https://www.dynamed.com/. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

Sodium–glucose Cotransporter 2 (SGLT2) Inhibitors

- **Drug/Device Alert**Updated 2 Mar 2022

  empagliflozin (Jardiance) receives expanded FDA approval for reduction of cardiovascular death and hospitalization for heart failure in adults with heart failure

  - efficacy based on
    - EMPEROR-Preserved trial for patients with heart failure with preserved ejection fraction
    - EMPEROR-Reduced trial for patients with heart failure with reduced ejection fraction
  - dosing and administration
    - before starting empagliflozin
      - assess volume status and correct volume depletion
      - assess renal function in older patients, those with impaired renal function, and/or in those taking loop diuretics
    - dosing: 10 mg orally once daily in the morning with or without food; dose may be increased to 25 mg once daily for additional glycemic control in patients with concomitant diabetes
    - insufficient data to provide dosing recommendations for patients with heart failure and estimated GFR < 20 mL/minute/1.73 m^2
  - contraindicated in patients on dialysis
  - not recommended for use during second and third trimesters of pregnancy based on adverse renal effects in nonclinical studies
  - adverse effects in patients with heart failure generally similar to adverse effects in patients with diabetes; most common adverse effects (incidence of ≥ 5%) in patients with diabetes include urinary tract infections and female genital mycotic infections
  - References - FDA Press Release 2022 Feb 24, FDA Label 2022 Feb
- STUDY SUMMARY
  addition of empagliflozin to usual therapy decreases hospitalization for heart failure in adults with mostly NYHA class II heart failure and preserved ejection fraction with and without diabetes
  DynaMed Level1

RANDOMIZED TRIAL: N Engl J Med 2021 Aug 27 early online

Details

- based on randomized trial
- 5,988 adults (mean age 71 years, 55% men, 75% White, 14% Asian) with NYHA functional class II-IV heart failure and left ventricular ejection fraction > 40% receiving usual therapy were randomized to empagliflozin 10 mg orally once daily vs. placebo and followed for median 26.2 months
  - 81% had NYHA class II and 18% had NYHA class III heart failure, and 49% had diabetes mellitus
  - 50% had estimated GFR < 60 mL/minute/1.73 m^2
- all patients had NT-proBNP > 300 pg/mL or atrial fibrillation at baseline plus NT-proBNP > 900 pg/mL
- 97% completed follow-up, 100% included in analysis
- comparing empagliflozin vs. placebo
  - cardiovascular death or hospitalization for heart failure per 100 person-years 6.9 vs. 8.7 (hazard ratio 0.79, 95% CI 0.69-0.9)
    - cardiovascular death 3.4 vs. 3.8 (not significant)
    - hospitalization for heart failure 4.3 vs. 6 (hazard ratio 0.73, 95% CI 0.61-0.88)
  - mean slope decrease in estimated GFR per year 1.25 mL/minute/1.73 m^2 vs. 2.62 mL/minute/1.73 m^2 ($p < 0.001$)
  - all-cause death per 100 person-years 6.6 vs. 6.7 (not significant)
  - serious adverse event in 47.9% vs. 51.6% (no p value reported)
  - discontinuation due to adverse event in 19.1% vs. 18.4% (no p value reported)
  - hypotension in 10.4% vs. 8.6% (no p value reported)
  - urinary tract infection in 9.9% vs. 8.1% (no p value reported)
  - genital infection in 2.2% vs. 0.7% (no p value reported)
- no significant differences in health status assessed by Kansas City Cardiomyopathy Questionnaire and in onset of new diabetes in patients with prediabetes
- consistent results for composite of cardiovascular death or hospitalization for heart failure in subgroup analyses of patients with and without diabetes
- Reference - EMPEROR-Preserved trial (N Engl J Med 2021 Aug 27 early online), editorial can be found in N Engl J Med 2021 Aug 27 early online

B. DynaMed citation

Heart Failure with Presereved Ejection Fraction. Andrikopoulou E. In: DynaMed [database online]. www.dynamed.com. Last updated: 3/2/2022. Accessed: 03/21/2022

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

May be added to HFpEF patients for hospitalization reduction due to HF.

D. UpToDate excerpts

Our suggestion for SGLT2 inhibitors and MRAs as first-line therapies for patients with HFpEF is based upon clinical trials demonstrating that these agents reduce the risk of hospitalization in this population. As examples:

●SGLT2 inhibitors – In trials that included patients with HFpEF, SGLT2 inhibitors reduced the risk of HF hospitalization and improved quality of life but did not clearly reduce the risk of mortality. The benefit of SGLT2 inhibitors must be weighed against the risk of recurrent urinary tract infections and genital infections.

•In a trial (EMPEROR-preserved) of patients with an LVEF >40 percent, NYHA class II to IV HF symptoms, and an elevated NT-proBNP level, patients randomly assigned to treatment with empagliflozin had a lower risk of HF hospitalization (9 versus 12 percent in the placebo group; hazard ratio [HR] 0.71, 95% CI 0.6-0.83) [15]. The risk of cardiovascular death was similar between the empagliflozin and placebo groups (7 versus 8 percent; HR 0.91, 95% CI 0.76-1.09). Treatment with empagliflozin was associated with a higher rate of urinary tract infections (10 versus 8 percent with placebo treatment; odds ratio [OR] 1.24, 95% CI 1.04-1.49) and genital infections (2.2 versus 0.7 percent; OR 3.1, 95% CI 1.9-5.01).

In a prespecified subgroup analysis, empagliflozin had a similar effect in patients who were or were not treated with an MRA at baseline.

A limitation of the trial was the large number of patients with an LVEF less than 50 percent (33 percent of the sample), who by definition do not have HFpEF.

•In the SOLOIST-HF trial, recently hospitalized patients with type 2 diabetes and either HFpEF (20 percent of patients) or HFrEF were randomly assigned to treatment with sotagliflozin (a combined SGLT2/SGLT1 inhibitor) or placebo [16]. At a median follow-up of 7.7 months, the primary endpoint of cardiovascular death, hospitalization, or urgent visit for HF was lower in the sotagliflozin group (51 versus 76 events per 100 patient-years; HR 0.67, 95% CI 0.52-0.85). The effect was driven entirely by a reduction in hospitalization and urgent visits for HF (40 versus 64 events per 100 patient-years; HR 0.64, 95% CI 0.49-0.83). The two groups had a similar risk of urinary tract infection (4.8 versus 5.1 percent in the placebo group).

In a preplanned subgroup analysis of patients with HFpEF (ie, LVEF ≥50 percent), sotagliflozin therapy reduced the risk of the primary outcome (31 versus 64 events per 100 patient-years; HR 0.48, 95% CI 0.27-0.86).

•In a separate trial (PRESERVED-HF), patients with an LVEF ≥45 percent (median LVEF 60 percent), NYHA class II to IV HF symptoms, and an elevated NT-proBNP level were randomly assigned to treatment with dapagliflozin or placebo [17]. After 12 weeks of observation, patients assigned to dapagliflozin had a greater change in the Kansas City Cardiomyopathy clinical summary score than did patients assigned to placebo (6-point difference; 95% CI 2-9 points) and a greater increase in six-minute walk distance (20-meter difference; 95% CI 5.6-34.7 meters). The proportion of patients with an LVEF <50 percent (ie, not meeting the criterion for HFpEF) was not reported.

E. UpToDate citation
Treatment and prognosis of heart failure with preserved ejection fraction. Borlaug B, et al. In: Basow DS 2022. Available at www.uptodate.com. Last updated: 2/2022. Access date: 03/21/2022.. Accessed

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

Prefer to use these as first line for HFpEF.

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

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

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?

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

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

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. HFpEF treatment is not as robust as HFrEF treatment, this seems to show that hospitalizations will be reduced.

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**.
Easy to prescribe, accessible, can be done in hospital or clinic.

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? Yes

J. If **I** was coded "Other, explain or No", please explain why.

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. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.