MetaAnalysis – Systematic Review
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. Citation: Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, Meeran K. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 17;319(15):1580-1591. doi: 10.1001/jama.2018.3024. Review. PubMed PMID: 29677303; PubMed Central PMCID: PMC5933330.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/29677303
C. First date published study available to readers:4/17/2018
D. PubMed ID: 29677303
E. Nominated By: Stephen Wilson
F. Institutional Affiliation of Nominator: UPMC St. Margaret's
G. Date Nominated: 4/18/2018
H. Identified Through: JAMA
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 5/1/2018
K. Potential PURL Review Form (PPRF) Type: Systematic Review
L. Assigned Potential PURL Reviewer: Anne Mounsey
M. Reviewer Affiliation: UNC at Chapel Hill
A. Abstract: IMPORTANCE:
The comparative clinical efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of type 2 diabetes is unknown.

OBJECTIVE:
To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors on mortality and cardiovascular end points using network meta-analysis.

DATA SOURCES:
MEDLINE, Embase, Cochrane Library Central Register of Controlled Trials, and published meta-analyses from inception through October 11, 2017.

STUDY SELECTION:
Randomized clinical trials enrolling participants with type 2 diabetes and a follow-up of at least 12 weeks were included, for which SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors were compared with either each other or placebo or no treatment.

DATA EXTRACTION AND SYNTHESIS:
Data were screened by 1 investigator and extracted in duplicate by 2 investigators. A Bayesian hierarchical network meta-analysis was performed.

MAIN OUTCOMES AND MEASURES:
The primary outcome: all-cause mortality; secondary outcomes: cardiovascular (CV) mortality, heart failure (HF) events, myocardial infarction (MI), unstable angina, and stroke; safety end points: adverse events and hypoglycemia.

RESULTS:
This network meta-analysis of 236 trials randomizing 176 310 participants found SGLT-2 inhibitors (absolute risk difference [RD], -1.0%; hazard ratio [HR], 0.80 [95% credible interval {CrI}, 0.71 to 0.89]) and GLP-1 agonists (absolute RD, -0.6%; HR, 0.88 [95% CrI, 0.81 to 0.94]) were associated with significantly lower all-cause mortality than the control groups. SGLT-2 inhibitors (absolute RD, -0.9%; HR, 0.78 [95% CrI, 0.68 to 0.90]) and GLP-1 agonists (absolute RD, -0.5%; HR, 0.86 [95% CrI, 0.77 to 0.96]) were associated with lower mortality than were DPP-4 inhibitors. DPP-4 inhibitors were not significantly associated with lower all-cause mortality (absolute RD, 0.1%; HR, 1.02 [95% CrI, 0.94 to 1.11]) than were the control groups. SGLT-2 inhibitors (absolute RD, -0.8%; HR, 0.79 [95% CrI, 0.69 to 0.91]) and GLP-1 agonists (absolute RD, -0.5%; HR, 0.85 [95% CrI, 0.77 to 0.94]) were significantly associated with lower CV mortality than were the control groups. SGLT-2 inhibitors were significantly associated with lower rates of HF events (absolute RD, -1.1%; HR, 0.62 [95% CrI, 0.54 to 0.72]) and MI (absolute RD, -0.6%; HR, 0.86 [95% CrI, 0.77 to 0.97]) than were the control groups. GLP-1 agonists were associated with a higher risk of adverse events leading to trial withdrawal than were SGLT-2 inhibitors (absolute RD, 5.8%; HR, 1.80 [95% CrI, 1.44 to 2.25]) and DPP-4 inhibitors (absolute RD, 3.1%; HR, 1.93 [95% CrI, 1.59 to 2.35]).

CONCLUSIONS AND RELEVANCE:
In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

B. Pending PURL Review Date**:** 5/23/2018

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

A. What types of studies are included in this review?
RCTs involving patients with T2DM that compared SGLT-2 inhibitors, GLP-1 agonists, and DPP4 inhibitors with one another or with a control group (placebo or no treatment) with follow up of at least 12 weeks

B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.
Key question: Are there differences in mortality and/or cardiovascular events among patients with type 2 diabetes treated with SGLT-2 inhibitors,GLP-1 agonists, DPP-4 inhibitors, and placebo/no treatment?

C. Study addresses an appropriate and clearly focused question. Well covered
Comments:

D. A description of the methodology used is included. Well covered
Comments:

E. The literature is sufficiently rigorous to identify all the relevant studies. Well covered
Comments: See Figure 1of the study and associated explanation

F. Study quality is assessed and taken into account. Well covered
Comments: Authors analyzed and described risk of bias among studies and also evaluated for evidence of publication bias.

G. There are enough similarities between selected studies to make combining them reasonable. Well covered
Comments: Due to the nature of interventions being investigated (3 different classes of medications that have been compared to one another, and to placebo/no treatment in various studies), the design of this study was a network meta-analysis.

H. Are patient oriented outcomes included? If yes, what are they?
Yes. The primary outcome (all-cause mortality) is a patient-oriented one, as were the secondary outcomes of cardiovascular mortality, heart failure events, MI/unstable angina, and stroke. Safety end points (hypoglycemia, adverse effects leading to stopping medication) were also patient-oriented.

I. Are adverse effects addressed? If so, how would they affect recommendations?
Yes- each class of medication was evaluated for hypoglycemia risk (all 3 were associated with increased risk of hypoglycemia, but not of major hypoglycemia, and there was no difference in hypoglycemic risk between drug classes). SGLT-2 inhibitors were evaluated for risk of genital infections (an increased risk was found), UTIs (no increased risk found), and lower limb amputations (no increased risk found). DPP-4 inhibitors were evaluated for pancreatitis risk (an increased risk was found). GLP-1 inhibitors were evaluated for pancreatitis risk (no increased risk found) and retinopathy (no increased risk found). SGLT-2 inhibitors were associated with a reduction in serious adverse events compared with controls. GLP-1 agonists were associated with an increased risk of adverse events leading to trial withdrawal compared to SGLT-2 inhibitors, DPP-4 inhibitors, and controls.

These adverse effects may help to individualize treatment decisions for patients as providers evaluate the risks and benefits of medications in these classes in light of the study's main findings about mortality and cardiovascular disease reduction.

J. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity?
No- Funding was from the British Heart Foundation, a non-profit in the UK that is the country's single biggest funder of cardiovascular research

K. To which patients might the findings apply? Include patients in the metaanalysis and other patients to whom the findings may be generalized.
The study's findings apply to patients with type 2 diabetes who are being treated with long-term medications in the outpatient setting. Because about half of the participants analyzed were enrolled in trials that specifically evaluated patients at higher cardiovascular risk, the findings may be slightly more generalizable to patients in that category.

L. In what care settings might the findings apply, or not apply?
Findings are applicable to longitudinal outpatient care settings for type 2 diabetes during which patients are followed for at least 3 months.

M. To which clinicians or policy makers might the findings be relevant?
The findings are relevant to clinicians managing medications in type 2 diabetic patients, in particular primary care doctors and endocrinologists. They might also be relevant to policy makers or insurance companies who are involved in determining prescription drug formularies.

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}

A. DynaMed excerpts

B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date www.DynamicMedical.com Last Updated: . Accessed

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

D. UpToDate excerpts

E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: . Accessed

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

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? 2

B. If **A** was coded 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?

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?
1 (extremely well

D. If **C** was coded 4, 5, 6, or 7, 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?
2

F. If **E** was coded as 1, 2, 3, or4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.
In choosing among SGLT-2 inhibitors, GLP-1 agnoists, and DPP-4 inhibitors to treat type 2 diabetes, clinicians should consider their patients' overall cardiovascular risk. For all type 2 diabetic patients, and particularly for those with highest cardiovascular risk, clinicians should consider treating with SGLT-2 inhibitors or GLP-1 agonists over DDP-4 inhibitors given that treatment with one of the first two agents is associated with decreased all-cause and cardiovascular mortality compared to treatment with DDP-4 inhibitors and controls. Clinicians

should weigh these benefits against the increased risk of hypoglycemia that is associated with all 3 of these mediations, the increased risk of genital infections associated with SGLT-2 inhibitors, and the increased risk of adverse effects leading to treatment discontinuation in GLP-1 agonists compared with the other two agents, to individualize treatment decisions for their patients.

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? 1 (definitely could be done in a medical care setting)

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

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? 4 (uncertain)

J. If **I** was coded 4, 5, 6, or 7,please explain why.
The cost of these medications to patients is a potential barrier, though they are increasingly being included in patient assistance programs and formularies.

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?
1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 2

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.
The study provides high-level evidence of a difference in important patient-oriented outcomes (all-cause and cardiovascular mortality) among SLGT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors. Management of type 2 diabetes with medications is a significant portion of the work that family physicians perform, and current common practice does not generally involve prioritizing one of these agents over the others. The cost of these medications and the fact that many are injectables and therefore more uncomfortable/inconvenient for patients to administer represent potential barriers to implementation. Additionally, there are some increased risks of hypoglycemia, genital infections, and poor tolerability associated with some or all of the medicines in these classes. Clinicians should continue to individualize treatment decisions based on patients' cardiovascular risk and individual biopsychosocial factors, but the information provided in this study provides useful data to assist in that process.