Effective Health Care

GLP-1 Agonists and SGLT-2 Inhibitors in Type 2 Diabetes Patients

Results of Topic Selection Process & Next Steps

The nominator, Kaiser Permanente, is interested in a new evidence review on the comparative risks and benefits of GLP-1 agonists and SGLT-2 inhibitors in type 2 diabetes patients with and without chronic kidney disease, or with or without congestive heart failure, who have not achieved adequate glucose control on metformin. The nominator is requesting a systematic review to update their national guidelines on type 2 diabetes medications for patients with and without chronic kidney disease or with or without congestive heart failure.

We identified one review that partially addressed the scope of the nomination. Because limited original research addresses the portion of the nomination not addressed in review, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: 0832 GLP-1 Agonists and SGLT-2 Inhibitors in Type 2 Diabetes Patients

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Topic Brief Date: 3/20/2019

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

More than 30 million Americans have diabetes, and, of those, 90%-95% have type 2 diabetes[1]. Factors determining treatment choice for type 2 diabetes include age, hemoglobin A1c, body mass index, renal and cardiac morbidity, and treatment history[2]. First-line pharmacological treatment for type 2 diabetes is typically metformin, but inadequate glucose control on metformin is common and secondary medications are often required[3]. Further, due to risk of lactic acidosis, metformin may pose risks to patients with renal dysfunction[4].

Chronic kidney disease and cardiovascular disease are common comorbid conditions in patients with type 2 diabetes[5]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists for treatment of type 2 diabetes may have benefits for cardiovascular and renal outcomes[6]. Further, the 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes recently recommended SGLT-2 inhibitors for adults with type 2 diabetes with comorbid chronic kidney disease or clinical heart failure, and GLP-1 agonists or SGLT-2 inhibitors for adults with type 2 diabetes with comorbid clinical cardiovascular disease, in patients who do not have adequate glucose control with metformin alone[7].

The 2018 Consensus Report recommendations reference studies that compare GLP-1 agonists and SGLT-2 inhibitors to placebo to evaluate impact on glycemic control[7]. The nominator is interested in outcomes of head-to-head comparisons of GLP-1 agonists and SGLT-2 inhibitors to comparator medications of interest, rather than as compared to placebo. The nominator is also interested in outcomes of head-to-head comparisons of GLP-1 agonists and SGLT-2 inhibitors to comparator medications of interest in type 2 diabetes patients with comorbid chronic kidney disease or congestive heart failure.

Nominator and Stakeholder Engagement

We clarified the Key Questions and PICOS and reviewed them on a call with the nominators.

Key Questions and PICOs

The key questions for this nomination are:

1. Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality?
    a) Does the benefit vary among individuals with chronic kidney disease?
    b) Does the benefit vary among individuals with congestive heart failure?

2. Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the harms of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality?
    a. Does the harm vary among individuals with chronic kidney disease?
    b. Does the harm vary among individuals with congestive heart failure?

3. Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality?
    a. Does the benefit vary among individuals with chronic kidney disease?

    b. Does the benefit vary among individuals with congestive heart failure?

4. Does the benefit vary among individuals with congestive heart failure? Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, composite renal outcomes, congestive heart failure, cardiovascular events and all-cause mortality?
    a. Does the harm vary among individuals with chronic kidney disease?
    b. Does the harm vary among individuals with congestive heart failure?

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, and setting (PICOS) of interest (Table 1).

Table 1. Key Questions and PICOS

Key Questions	Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the benefit vary among individuals with chronic kidney disease? b) Does the benefit vary among individuals with congestive heart failure?	Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the harms of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the harm vary among individuals with chronic kidney disease? b) Does the harm vary among individuals with congestive heart failure?	Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the benefit vary among individuals with chronic kidney disease? b) Does the benefit vary among individuals with congestive heart failure?	Does the benefit vary among individuals with congestive heart failure? Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, composite renal outcomes, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the harm vary among individuals with chronic kidney disease? b) Does the harm vary among individuals with congestive heart failure?
Population	Individuals with type II diabetes on metformin with the need for additional medication for glucose control. Subpopulations of interest: Individuals with known chronic kidney	Individuals with type II diabetes on metformin with the need for additional medication for glucose control. Subpopulations of interest: Individuals with known chronic kidney	Individuals with type II diabetes on metformin with the need for additional medication for glucose control. Subpopulations of interest: Individuals with known chronic kidney	Individuals with type II diabetes on metformin with the need for additional medication for glucose control. Subpopulations of interest: Individuals with known chronic kidney

	disease; individuals with congestive heart failure	disease; individuals with congestive heart failure	disease; individuals with congestive heart failure	disease; individuals with congestive heart failure
Interventions	GLP-1 agonist as second agent	GLP-1 agonist as second agent	SGLT-2 inhibitor as second agent	SGLT-2 inhibitor as second agent
Comparators	Placebo; Sulfonylureas; DPP-4 inhibitors; Thiazolidinediones; Basal insulin	Placebo; Sulfonylureas; DPP-4 inhibitors; Thiazolidinediones; Basal insulin	Placebo; Sulfonylureas; DPP-4 inhibitors; Thiazolidinediones; Basal insulin	Placebo; Sulfonylureas; DPP-4 inhibitors; Thiazolidinediones; Basal insulin
Outcomes	Renal effects; cardiovascular events and deaths; all-cause mortality; congestive heart failure	Serious adverse events; congestive heart failure; episodes of hypoglycemia and severe hypoglycemia; retinopathy; biliary disease; acute kidney injury; renal effects; cancer; lower limb amputation; pancreatitis	Renal effects; cardiovascular events and deaths; all-cause mortality; congestive heart failure	Serious adverse events; congestive heart failure; acute kidney injury; episodes of hypoglycemia and severe hypoglycemia; severe urinary infections; genital infections; lower limb amputations; bone fractures; episodes of ketoacidosis; change in BMI

Abbreviations: GLP-1= glucagon-like peptide 1; SGLT2 = sodium–glucose cotransporter 2; DPP-4= dipeptidyl peptidase 4; BMI=body mass index

Methods

We assessed nomination GLP-1 Agonists and SGLT-2 Inhibitors in Type 2 Diabetes Patients, for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from March 2014 to March 2019. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This is an appropriate and important topic. Chronic kidney disease and cardiovascular disease are common comorbid conditions in type 2 diabetes[5]. Further, the 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes includes medication treatment recommendations for patients with type 2 diabetes and comorbid kidney and cardiovascular disease[7].

Desirability of New Review/Duplication

A new evidence review would be partially duplicative of a 2016 AHRQ systematic review[8] that evaluated comparative effectiveness and safety of medications to manage hypoglycemia in type 2 diabetes patients. The review excluded studies with a placebo or non-pharmacological comparison or without a comparison group. The review, then, included studies with head-to-head medication comparisons. The head-to-head medication comparison is important because the nominators stated an interest in head-to-head medication comparisons exclusively, in

response to the 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes guidelines that were developed from a review of studies that included comparisons of medications of interest to placebo.

The 2016 AHRQ review is partially duplicative because it includes head-to-head comparisons of the medication classes of interest, GLP-1 receptor agonists and SGLT-2, as well as medication class comparators of interest (see Table 2). The 2016 AHRQ review is not fully duplicative, as it does not focus only on people with type 2 diabetes with poor glucose control, and it does not include subpopulations of chronic kidney disease or congestive heart failure.

Table 2. Medication classes included in the current PICOS for individuals with type 2 diabetes without chronic kidney disease or congestive heart failure and in the AHRQ 2016 report

Comparator medication classes (medication classes compared to SGLT-2 inhibitors or GLP-1 agonists) in current PICOS	Medication classes additional to SGLT-2 inhibitors or GLP-1 agonists in AHRQ 2016 systematic review
1. Placebo 2. Sulfonylureas 3. DPP-4 inhibitors 4. Thiazolidinediones 5. Basal insulin	**1. Placebo-controlled studies were excluded** 2. Sulfonylureas 3. DPP-4 inhibitors 4. Thiazolidinediones 5. Basal insulin

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; DPP-4= dipeptidyl peptidase 4

Impact of a New Evidence Review

A new systematic review addressing the comparative effectiveness of GLP-1 agonists and SGLT-2 inhibitors in individuals with type 2 diabetes and comorbid chronic kidney disease or congestive heart failure may have high impact given the cost of the medications.

Feasibility of a New Evidence Review

A new evidence review is not feasible. A total of one RCT study and one clinical trial evaluating the comparative effectiveness of type 2 diabetes medications patients with congestive heart failure were identified. The RCT evaluated the comparative effects of a GLP-1 medication to a DDP-4 medication[9] and the clinical trial proposes to evaluate a SGLT-2 compared to a sulfonylurea agent[10]. We did not identify any RCTs that compared the medications of interest to comparator medications of interest in patients with type 2 diabetes and comorbid chronic kidney disease.

Table 3. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (3/2016-3/2019)	Feasibility (3/2014-3/2019)
KQ 1: Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the benefit vary among individuals with chronic kidney disease? b) Does the benefit vary among individuals with congestive heart failure?	Total number of identified systematic reviews: 1 • AHRQ EPC: 1[8]	Size/scope of review Relevant Studies Identified: 2 • RCT: 1[9]
KQ 2: Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the harms of GLP-1 agonists compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the harm vary among individuals with chronic kidney disease? b) Does the harm vary among individuals with congestive heart failure?	Total number of identified systematic reviews: 1 • AHRQ EPC: 1[8]	Size/scope of review Relevant Studies Identified: 2 • RCT: 1[9]
KQ 3: Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, congestive heart failure, cardiovascular events and all-cause mortality?	Total number of identified systematic reviews: 1 • AHRQ EPC: 1[8]	Size/scope of review Relevant Studies Identified: 1 • Clinical trial: 1[10]

Key Question	Duplication (3/2016-3/2019)	Feasibility (3/2014-3/2019)
a) Does the benefit vary among individuals with chronic kidney disease? b) Does the benefit vary among individuals with congestive heart failure?		
KQ 4: Does the benefit vary among individuals with congestive heart failure? Among people with type 2 diabetes who have not obtained adequate glucose control on metformin alone, what are the benefits of SGLT-2 inhibitors compared with placebo and other second agents on long-term outcomes such as: renal failure, composite renal outcomes, congestive heart failure, cardiovascular events and all-cause mortality? a) Does the harm vary among individuals with chronic kidney disease? b) Does the harm vary among individuals with congestive heart failure?	Total number of identified systematic reviews: 1 • AHRQ EPC: 1[8]	Size/scope of review Relevant Studies Identified: 1 • Clinical trial: 1[10]

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; GLP-1= glucagon-like peptide 1; SGLT2 = sodium–glucose cotransporter 2

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be partially duplicative of an existing product. One systematic review was identified that evaluates the comparative effectiveness of SGLT-2 inhibitors and GLP-1 agonists (as compared directly to other classes of medications for treatment of type 2 diabetes) in individuals with type 2 diabetes. The RCTs included in the review were medication-to-medication comparisons as opposed to medication to placebo comparisons. The review was not fully duplicative because it did not include medication comparisons for individuals with comorbid congestive heart failure or chronic kidney disease, and did not explicitly select studies in which participants had not achieved adequate glucose control on metformin.
- Impact: A new systematic review has likely high potential.
- Feasibility: A new review is not feasible. The evidence base is likely very small.

References

1. Type 2 Diabetes. https://www.cdc.gov/diabetes/basics/type2.html.

2. Heintjes EM, Overbeek JA, Hall GC, et al. Factors Associated with Type 2 Diabetes Mellitus Treatment Choice Across Four European Countries. *Clinical therapeutics.* 2017;39(11):2296-2310.e2214.
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *Jama.* 1999;281(21):2005-2012.
4. Tavares Bello C, Castro Fonseca R, Sousa Santos F, Sequeira Duarte J, Azinheira J, Vasconcelos C. Renal function markers and metformin eligibility. *Minerva endocrinologica.* 2018;43(3):246-252.
5. Lovre D, Shah S, Sihota A, Fonseca VA. Managing Diabetes and Cardiovascular Risk in Chronic Kidney Disease Patients. *Endocrinology and metabolism clinics of North America.* 2018;47(1):237-257.
6. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet.* 2019;393(10166):31-39.
7. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018:dci180033.
8. Bolen S, Tseng E, Hutfless S, et al. Diabetes Medications for Adults With Type 2 Diabetes: An Update. *Comparative Effectiveness Reviews.* 2016;137.
9. Arturi F, Succurro E, Miceli S, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. *Endocrine.* 2017;57(3):464-473.
10. Tanaka A, Inoue T, Kitakaze M, et al. Rationale and design of a randomized trial to test the safety and non-inferiority of canagliflozin in patients with diabetes with chronic heart failure: the CANDLE trial. *Cardiovascular diabetology.* 2016;15:57.
11. National Center for Chronic Disease Prevention and Health Promotion DoDT. Calculate What Diabetes Costs Your Business. https://www.cdc.gov/diabetes/diabetesatwork/plan/costs.html.

Appendix A. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care medication, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes. All medications of interest are available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus is on comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	More than 30 million Americans have diabetes, and, of those patients, 90%-95% have type 2 diabetes[1].
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. The nomination is in response to recent guidelines from the 2018 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes [7].
2c. Represents important uncertainty for decision makers	Yes. The nominators are interested in updating their guidelines.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes. This nomination addresses both benefits and potential harms of medication classes for type 2 diabetes.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	In the U.S., in 2017, the average medical expenditure for diabetes patients was about $16,750[11].
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	The 2016 AHRQ review[8] is partially duplicative in that it includes head-to-head comparisons of the medication classes of interest, GLP-1 receptor agonists and SGLT-2, to comparator medication classes of interest. The 2016 AHRQ review[8] is not fully duplicative, as it does not it did not include medication comparisons for individuals with comorbid congestive heart failure or chronic kidney disease, and did not explicitly select studies in which participants had not achieved adequate glucose control on metformin.
4. Impact of a New Evidence Review	

Selection Criteria	Assessment
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The standard of care for type 2 diabetes patients with chronic kidney disease or congestive heart failure is unclear. The 2018 American Diabetes Association and European Association for the Study of Diabetes Consensus Report recommendations are based, at least partially, on medication studies that compared the medication of interest to placebo, as opposed to head-to-head comparisons between medication classes.[7] The nominator is interested in the comparative effectiveness of SGLT-2 and GLP-1 to other type 2 diabetes drug classes (i.e., sulfonylureas, DPP-4 inhibitors, thiazolidinediones, basal insulin), as determined by medication-to-medication comparisons, to establish their own guidelines. Guidelines for medication treatment of type 2 diabetes patients with chronic kidney disease or congestive heart failure based on medication-to-medication studies do not exist.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. The nominator reports practice variation for medication treatment for patients with type 2 diabetes with chronic kidney disease or congestive heart failure.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	No. A total of one RCT study and one clinical trial evaluating the comparative effectiveness of type 2 diabetes medications in patients with congestive heart failure were identified. The RCT evaluated the comparative effects of a GLP-1 medication to a DDP-4 medication[9] and the clinical trial proposes to evaluate a SGLT-2 compared to a sulfonylurea agent[10]. We did not identify any RCTs that compared the medications of interest to comparator medications of interest in patients with type 2 diabetes and comorbid chronic kidney disease.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question; GLP-1= glucagon-like peptide 1; SGLT2 = sodium–glucose cotransporter 2; DPP-4= dipeptidyl peptidase 4

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/; https://www.ahrq.gov/research/findings/ta/index.html; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsrd.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
Secondary Search
AHRQ Products in development https://effectivehealthcare.ahrq.gov/
VA Products in development https://www.hsrd.research.va.gov/publications/esp/
Cochrane Protocols http://www.cochranelibrary.com/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Appendix C. Search Strategy & Results (Feasibility)

MEDLINE (PubMed) searched on: March 13, 2019	
Concept	
Type II Diabetes	(((((("Diabetes Mellitus, Type 2/medication therapy"[Mesh]) OR ((((T2DM[Title/Abstract]) OR (((diabetes[Title] OR DM[Title])) AND (two[Title] OR 2[Title] OR II[Title]))))
AND	
Metformin	(Metformin[Title/Abstract] OR glucophage[Title/Abstract])))) OR (("Metformin"[Mesh]) AND "therapeutic use"[Subheading])
AND	
Sodium-Glucose Transporter 2 Inhibitors OR Glucagon-Like Peptide 1	((((("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2 Inhibitors"[Pharmacological Action])) OR (((SGLT-2[Title/Abstract]) OR sodium glucose transporter 2 inhibitors[Title/Abstract]) OR (canagliflozin[Title/Abstract] OR invokana[Title/Abstract] OR dapagliflozin[Title/Abstract] OR farxiga[Title/Abstract] OR empagliflozin[Title/Abstract] OR jardance[Title/Abstract])))) OR (((("Glucagon-Like Peptide 1"[Mesh] OR "Glucagon-Like Peptide-1 Receptor"[Mesh])) OR (((GLP 1[Title/Abstract]) OR glucagon like peptide 1[Title/Abstract]) OR (exenatide[Title/Abstract] OR byetta[Title/Abstract] OR bydureon[Title/Abstract] OR liraglutide[Title/Abstract] OR victoza[Title/Abstract] OR saxenda[Title/Abstract] OR lixisenatide[Title/Abstract] OR lyxumia[Title/Abstract] OR albiglutide[Title/Abstract] OR tanzeum[Title/Abstract] OR dulaglutide[Title/Abstract] OR trulicity[Title/Abstract] OR semaglutide[Title/Abstract] OR ozempic[Title/Abstract])))
Limits	published in the last 5 years, Humans, English, Adult: 19+ years.
Chronic Kidney Disease	("Renal Insufficiency, Chronic"[Mesh]) OR (("chronic kidney failure"[Title/Abstract]) OR CKF[Title/Abstract])
Congestive Heart Failure	("Heart Failure"[Mesh]) OR (("congestive heart failure"[Title/Abstract]) OR CHF[Title/Abstract])
Systematic Reviews	Systematic[sb]
Randomized Controlled Trials	(((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (medication therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])
CKD & CHF SR 0	
CKD & CHF RCT 0	
CKD & CHF Other 0	

MEDLINE (PubMed) searched on: March 13, 2019	
CKD SR 0	
CKD RCT 2	
CKD Other 0	
CHF SR 0	
CHF RCT 5	
CHF Other 0	
Neither SR 7	
Neither RCT 365	
Neither Other 0	
ClinicalTrials.gov	121 Studies found for: chronic kidney disease OR congestive heart failure | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Type2 Diabetes | Adult, Older Adult | First posted from 03/13/2014 to 03/13/2019