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OHSU Drug Effectiveness Review Project Summary Report: Newer Diabetes Drugs and Cardiovascular Disease Outcomes

Date of Review: August 2020

Date of Last Review: GLP-1 Receptor Agonists (March 2019)
DPP-4 inhibitors (July 2018)
SGLT-2 inhibitors (July 2018)
Literature Search: 1/01/2018 - 4/09/2020

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. In adults with type 2 diabetes mellitus (T2DM), what is the evidence for cardiovascular (CV) benefit for newer diabetes drugs, including mortality?
2. In adults with T2DM, what harms are associated with newer diabetes drugs that have led to treatment discontinuation or determined to be a severe adverse event that has been prespecified as a severe adverse event of interest (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection)?
3. Does the effectiveness differ in patients with or without prior cardiovascular disease (CVD)?

Conclusions:
- A 2020 Drug Effectiveness Review Project (DERP) report and one randomized controlled trial provided evidence for the review.
- The DERP report serves as the main evidence for this review. All studies in the report included patients with T2DM and a majority of patients were at high risk for CV disease or established CV disease.
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (exenatide extended release (ER), liraglutide and sematglutide) demonstrated a small risk reduction in all-cause mortality (absolute risk reduction [ARR] of 1.0% to 1.4% and number needed to treat [NNT] of 71-100) in patients with T2DM based on moderate evidence (median study durations from 2.1 to 3.8 years).[1] There was a neutral effect on risk of hospitalizations for heart failure (HF) in comparisons between GLP-1 RAs and placebo based on moderate quality of evidence.
- Dipeptidyl peptidase-4 (DPP-4) inhibitors were reported as having a neutral effect on all CV outcomes (all-cause mortality, stroke, myocardial infarction [MI], hospitalization for heart failure) based on low to moderate quality of evidence.[1] There was an increased risk of hospitalizations for HF based on low quality of evidence from one saxagliptin trial (ARR 0.7%; number needed to treat [NNT] 143).
- Sodium-glucose transport protein 2 (SGLT-2) inhibitors significantly reduced the risk of hospitalization due to HF.[1]
    - Canagliflozin, dapagliflozin, empagliflozin were reported to have a reduced risk of hospitalizations due to heart failure (NNT 42-80) in studies lasting 2.6 to 3.1 years based on moderate quality of evidence.[1]
    - Empagliflozin reduced all-cause mortality compared to placebo, 5.7% vs. 8.3% (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001; ARR 2.6%/NNT 38 over a median follow up of 3.1 years).[1]

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- Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).[1]
- In patients, with and without T2DM (41% with diabetes), and a history of HF and reduced injection fraction, dapagliflozin reduced the composite outcome of worsening heart failure or CV death, 16.3% vs. 21.2% (HR 0.74; 95% CI, 0.65 to 0.85; P<0.001; ARR 4.9%/NNT 20 over a median of 18.2 months).[2]

Recommendations:

- Recommend that newer diabetic therapies (DPP-4 inhibitors, GLP-1 RAs and SGLT-2 inhibitors) be second-line treatment options. Remove requirement for step therapy other than metformin.
- Recommend removing step therapy requiring sulfonylurea trial in prior authorization (PA) criteria for DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors.
- After executive session, recommend making saxagliptan, dulaglutide, dapagliflozin, empagliflozin, and canagliflozin preferred.

Summary of Prior Reviews and Current Policy

- Review of the evidence for GLP-1 receptor agonists in March of 2019 resulted in changes in the PA criteria to allow use of basal insulin with GLP-1 receptor agonists and auto-PA preferred products for patients with claims for metformin use in the previous 40 days. After executive session exenatide vials (Bydureon®) and liraglutide (Victoza® 2 and 3 Pak) were added to the Practitioner-Managed Prescription Drug Plan (PMPDP).
- No changes were made after presentation of newer diabetes medications. The requirement of trial of amylin analogs was removed from the SGLT-2 criteria. Semaglutide injection and ertugliflozin were maintained as non-preferred on the PMPDP.
- Evidence supporting current Oregon Health Administration (OHA) Fee-for-Service (FFS) policy came from the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) which recommends metformin as first-line therapy and consideration of sulfonylureas as an option for second-line therapy.
- Prior review of CV outcomes for newer diabetes drugs have demonstrated a neutral or small benefit over placebo with a major limitation of evidence is studies only in patients with CV disease or at high risk for CV disease.
- Current Oregon Health Plan (OHP) fee-for-service policy for newer diabetes treatment allows for the use of the GLP-1 RAs, Bydureon® and Victoza®, without prior authorization (PA) if prescribed in conjunction with, or record of prior use as described above, with metformin. DPP-4 inhibitors require a PA with a requirement of a trial of metformin and a sulfonylurea, or contraindications to these drugs, as outlined in the PA criteria in **Appendix 1**. The DPP-4 inhibitor, sitagliptin, is also a preferred drug but requires that patients meet specific clinical PA criteria. SGLT2 inhibitors are available as last-line therapy as described in the clinical PA criteria.
- Prescriber alignment with preferred agents is 41% for the GLP-1 RA class, 81% for the DPP-4 class and there are no preferred products designated in the SGLT-2 class.

Methods:

The 2020 drug class report on Newer Diabetes Drugs and Cardiovascular Disease Outcomes by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

The focus of a recent review performed by the DERP was CV outcomes associated with newer diabetes drugs.[1] Adults with T2DM who received a SGLT-2 inhibitor, DPP-4 inhibitor or GLP-1 RA were included (**Table 1**). All patients were allowed standard of care for glucose control and CV risk management. Eligible studies included randomized clinical trials and prospective and retrospective cohort studies (≥10,000 patients) that were published from January 1, 2017 to October 2, 2019.[1] Sixteen randomized, controlled trials were identified, 15 of which were placebo-controlled and one active control that compared linagliptin to glimepiride.[1] Important outcomes studied were mortality (all-cause and CV), CV outcomes (fatal or nonfatal myocardial infarction [MI], fatal or nonfatal stroke, hospitalization for heart failure), serious adverse events and pre-specified adverse reactions (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection). Serious adverse events were investigator determined events related to study treatment causing permanent discontinuation and one of the adverse events of interest (e.g., pancreatitis, hypoglycemia, neoplasm, allergic reaction, genital infection).

Table 1. Newer Diabetes Drugs Eligible for Inclusion in DERP Cardiovascular Outcomes Report[1]

Class	Generic Names	Brand Names
SGLT-2 inhibitors	Ertugliflozin Empagliflozin Dapagliflozin Canagliflozin	Steglatro* Jardiance Farxiga Invokana
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
SGLT-2 inhibitor with DPP-4 inhibitor	Dapagliflozin-saxagliptin Empagliflozin-linagliptin	Qtern* Glyxambi*
SGLT-2 inhibitor with metformin	Ertugliflozin-metformin Empagliflozin-metformin ER Canagliflozin-metformin ER Empagliflozin-metformin Dapagliflozin-metformin ER Canagliflozin-metformin	Segluromet* Synjardy XR* Invokamet XR* Synjardy* Xigduo XR* Invokamet*
DPP-4 inhibitor with TZD	Alogliptin-pioglitazone	Oseni*
DPP-4 inhibitor with metformin	Linagliptin-metformin ER Alogliptin-metformin Sitagliptin-metformin ER Linagliptin-metformin	Jentadueto XR* Kazano* Janumet XR* Jentadueto*

	Saxagliptin-metformin ER Sitagliptin-metformin	Kombiglyze XR* Janumet*
GLP-1 agonists	Oral semaglutide Semaglutide Lixisenatide Dulaglutide Albiglutide Exenatide ER Liraglutide Exenatide	Rybelsus Ozempic Adlyxin Trulicity Tanzeum Bydureon Victoza Byetta
GLP-1 agonist with long-acting insulin	Liraglutide-insulin degludec U100/3.6 mg Lixisenatide-insulin glargine U100/33 mg	Xultophy* Soliqua*
Abbreviations: DPP-4 = dipeptidyl peptidase 4; ER = extended release; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; XR = extended release Key: * No studies met inclusion criteria		

The results for the effectiveness and harms data from the DERP report are divided by therapeutic class and presented in **Table 2**. The GLP-1 RAs were the only drug class that demonstrated a risk reduction in all-cause mortality, with about a 1% absolute difference between active treatment and placebo.[1] Moderate level of evidence found the risk of hospitalization for heart failure was not associated with risk or benefit for the GLP-1 RA class compared to placebo. Lack of precision amongst the class weakens the conclusions of these results.

GLP-1 RA:

All-cause mortality:

- Exenatide extended release [ER] = 6.9% vs. placebo = 7.9% (hazard ratio [HR] 0.86; 95% CI, 0.77 to 0.97; P=0.02; ARR 1%/NNT 100 over a median of 3.2 years).[1]
- Liraglutide = 8.2% vs. placebo = 9.6% (HR 0.85; 95% CI, 0.74 to 0.97; P=0.02; 1.4%/NNT 71 over a median of 3.8 years).[1]
- Semaglutide = 1.4% vs. placebo = 2.8% (HR 0.49; 95% CI, 0.27 to 0.92; ARR 1.4%/ NNT 71 over a median of 2.1 years).[1]

Stroke:

- Dulaglutide = 3.2% vs. placebo = 4.1% (HR 0.76; 95% CI, 0.62 to 0.94; P=0.01; ARR 0.9%/NNT 90 over a median of 5.4 years).[1]

Myocardial infarction:

- Albiglutide 4.0% vs. placebo = 5.0% (HR 0.75; 95% CI, 0.61 to 0.90; P=0.003; ARR 1%/NNT 100 over a median of 1.6 years).[1]
- Liraglutide = 6.3% vs. placebo = 7.3% (HR 0.86; 95% CI, 0.73 to 1.00; P=0.05; ARR 1%/NNT 100 over a median of 3.8 years).[1]

Major Adverse Cardiovascular Events (MACE):

- Patients treated with liraglutide with single vascular disease at baseline demonstrated a risk reduction for MACE over patients without cardiovascular disease (CVD) at baseline (HR 0.82; 95% CI, 0.71 to 0.95); however, there was no effect in patients with polyvascular disease (HR 0.82; 95% CI, 0.66 to 1.02).[1]

- Risk of CV death was reduced with liraglutide in patients with single vascular disease at baseline compared to patients without single vascular disease (HR 0.67; 95% CI, 0.53 to 0.85); no effect was seen in patients with polyvascular disease.[1]
- Exenatide ER reduced all-cause mortality in patients without heart failure at baseline (HR 0.79; 95% CI, 0.69 to 0.92) but no reduction was seen in patients with preexisting heart failure.[1]
- Low quality evidence found a reduced risk of severe adverse reactions compared to placebo (driven by albiglutide, dulaglutide, semaglutide, and oral semaglutide.

DPP-4 Inhibitors:

Hospitalizations for Heart Failure:

- Saxagliptin increased risk of hospitalizations for heart failure compared to placebo (3.5% vs. 2.8%; HR 1.27, 95% CI, 1.07 to 1.51; P=0.007; ARR 0.7%/number needed to harm [NNH] 143 with a median follow up of 2.1 years).[1]

Severe Adverse Events:

- Saxagliptin = 41.4% vs. placebo = 39.6% (RR 1.05; 95% CI, 1.01 to 1.09; P=0.02; ARR 1.8%/NNH 56 with a median follow up of 2.1 years).[1]

MACE:

- No significant differences were found with any of the DPP-4 inhibitors.

SGLT-2 Inhibitors:

All-cause mortality:

- Empagliflozin = 5.7% vs. placebo = 8.3% (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001; ARR 2.6%/NNT 38 over a median follow up of 3.1 years).[1]

Hospitalizations for Heart Failure:

- Canagliflozin = 5.5/1000 patient-years vs. placebo 8.7/1000 patient-years (HR 0.67; 95% CI, 0.52 to 0.87 with a median follow up of 295 weeks)(CANVAS).[1]
- Canagliflozin = 4.0% vs. placebo = 6.4% (HR 0.61; 95% CI, 0.47 to 0.80; P<0.001; ARR 2.4%/NNT 42 over a median follow up of 2.62 years)(CREDENCE).[1]
- Dapagliflozin = 2.5% vs. placebo = 3.3% (HR 0.73; 95% CI, 0.61 to 0.88; ARR 0.8%/NNT 80 over a median follow up of 4.2 years).[1]
- Empagliflozin = 2.7% vs. placebo = 4.1% (HR 0.65; 95% CI, 0.50 to 0.85; P=0.002: ARR 1.4%/NNT 71 over a median follow up of 3.1 years).[1]

Severe Adverse Events:

- Canagliflozin = 33.5% vs. placebo = 36.7% (RR 0.91; 95% CI, 0.84 to 0.99; P=0.03).[1]
- Dapaliflozin = 34.1% vs. placebo 36.2% (RR 0.94; 95% CI, 0.91 to 0.98; P=0.005).[1]
- Empagliflozin = 38.2% vs. placebo 42.3% (RR 0.90; 95% CI, 0.85 to 0.96; P = 0.0007).[1]

MACE:

- Non-CV death was reduced in patients taking dapagliflozin who also had a history of heart failure (HR 0.50; 95% CI, 0.29 to 0.86; P=0.03).[1]
- Dapagliflozin reduced risk of CV death (HR 0.83; 95% CI, 0.73 to 0.95; P= 0.005; ARR 0.9%; NNT 111) and hospitalizations for heart failure (HR 0.73; 95% CI, 0.61 to 0.88; p-value not reported; ARR 0.8%; NNT 125) in patients with a history of heart failure and reduced ejection fraction.
- Dapagliflozin reduced MACE in patients with history of MI (HR 0.84; 95% CI, 0.72 to 0.99; P=0.04).
- Dapagliflozin reduced recurrent MI in patients with history of MI (HR 0.78; 95% CI, 0.63 to 0.95).[1]
- Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).[1]

There was insufficient evidence of efficacy and harms outcomes to compare monotherapy with combination therapy of newer diabetes drugs. This review was limited by the lack of head-to-head comparisons between drugs in different classes. Trials also may not have been long enough to sufficiently capture CV outcomes. Differences in standard of care may have also influenced the results. External validity may be reduced by the inclusion of patients with a 10 year or more history of diabetes with established CVD or at high risk of CVD. There is insufficient evidence on the CV implications of these therapies in patients who are not at high risk.

Table 2. Cardiovascular Outcomes for Newer Diabetes Medications Vs. Placebo[1]

Outcome	All-Cause Mortality	Stroke	Myocardial Infarction	Hospitalization for Heart Failure	Serious Adverse Events	Comments
Drug Class						
GLP-1 RA *7 trials*	*Small risk reduction* (moderate quality of evidence) Benefit: - Exenatide ER - Liraglutide - Semaglutide oral Neutral: - Albiglutide - Dulaglutide - Lixisenatide - Semaglutide inj	*No effect* (low quality of evidence) Benefit: - Dulaglutide Neutral: - Albiglutide - Exenatide ER - Liraglutide - Lixisenatide - Semaglutide oral No evidence: - Semaglutide inj	*No conclusion* (very low quality of evidence) Benefit: - Albiglutide - Liraglutide Neutral: - Dulaglutide - Exenatide ER - Lixisenatide - Semaglutide oral No evidence: - Semaglutide inj	*No effect* (moderate quality of evidence) Neutral: - Dulaglutide - Exenatide ER - Liraglutide - Lixisenatide - Semaglutide (oral and inj) No evidence: - Albiglutide	*Reduced risk* (low quality of evidence) Benefit: - Albiglutide - Dulaglutide - Semaglutide (oral and inj) No evidence: - Exenatide ER - Liraglutide - Lixisenatide	Only patients with an eGFR < 60 mL reported reductions in MACE with liraglutide (HR, 0.69; 95% CI, 0.57 to 0.85; P= 0.01)
DPP-4 Inhibitors *5 trials*	*No effect* *(moderate quality of evidence)* Neutral: - Alogliptin - Saxagliptin - Sitagliptin - Linagliptin	*No effect* *(moderate quality of evidence)* Neutral: - Saxagliptin - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(low quality of evidence)* Neutral: - Saxagliptin - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(low quality of evidence)* Harm: - saxagliptin Neutral: - Sitagliptin - Linagliptin No evidence: - Alogliptin	*No effect* *(moderate quality of evidence)* Harm: - Saxagliptin Neutral: - Alogliptin - Sitagliptin - Linagliptin	

SGLT-2 Inhibitors *4 trials*	*No effect (moderate quality of evidence)* Benefit: - Empagliflozin Neutral: - Canagliflozin - Dapagliflozin	*No effect (low quality of evidence)* Neutral: - Canagliflozin - Dapagliflozin - Empagliflozin	*No effect (moderate quality of evidence)* Neutral: - Canagliflozin - Dapagliflozin - Empagliflozin	*Significant risk reduction (moderate quality of evidence)* Benefit: - Canagliflozin - Dapagliflozin - Empagliflozin	*Significant risk reduction (moderate quality of evidence)* Benefit: - Dapagliflozin - Empagliflozin Neutral or benefit: (conflicting results) - Canagliflozin	Canagliflozin decreased risk of stroke in patients with an eGFR < 45 mL (HR 0.32; 95% CI, 0.11 to 0.96).
Abbreviations: DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; ER = extended release; GLP-1 = glucagon-like peptide 1; MACE = major adverse cardiovascular events; SGLT-2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones; XR = extended release						

Randomized Controlled Trials:

A total of 134 citations were manually reviewed from the initial literature search. After further review, 133 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
McMurray, et al[2] Phase 3, PC, RCT	Dapagliflozin 10 mg daily Vs. Placebo (n=2373)	Patients with or without diabetes with NYHA class II, III, or IV HF and an ejection fraction of 40% or less	Composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death	Dapagliflozin: 386 (16.3%) Placebo: 502 (21.2%) HR 0.74 (95% CI, 0.65 to 0.85) P<0.001 ARR 4.9%/NNT 20 over a median of 18.2 months

Abbreviations: ARR – absolute risk reduction; CV – cardiovascular; HF – heart failure; HR – hazard ratio; NNT – number needed to treat; NYHA – New York Heart Association; PC – placebo-controlled; RCT – randomized controlled trial.

References

1. Drug Effectiveness Review Project. Newer Diabetes Drugs and Cardiovascular Disease Outcomes: Update. February 2020.

2. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303.

Appendix 1: Current Preferred Drug List

DPP-4 Inhibitors

Generic	Brand	Form	PDL
sitagliptin phos/metformin HCl	JANUMET	TABLET	Y
sitagliptin phosphate	JANUVIA	TABLET	Y
alogliptin benz/metformin HCl	ALOGLIPTIN-METFORMIN	TABLET	N
alogliptin benz/metformin HCl	KAZANO	TABLET	N
alogliptin benz/pioglitazone	ALOGLIPTIN-PIOGLITAZONE	TABLET	N
alogliptin benz/pioglitazone	OSENI	TABLET	N
alogliptin benzoate	ALOGLIPTIN	TABLET	N
alogliptin benzoate	NESINA	TABLET	N
linagliptin	TRADJENTA	TABLET	N
linagliptin/metformin HCl	JENTADUETO XR	TAB BP 24H	N
linagliptin/metformin HCl	JENTADUETO	TABLET	N
saxagliptin HCl	ONGLYZA	TABLET	N
saxagliptin HCl/metformin HCl	KOMBIGLYZE XR	TBMP 24HR	N
sitagliptin phos/metformin HCl	JANUMET XR	TBMP 24HR	N

GLP-1 receptor agonists

Generic	Brand	Form	PDL	Route
exenatide	BYETTA	PEN INJCTR	Y	SQ
exenatide microspheres	BYDUREON	VIAL	Y	SQ
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y	SQ
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y	SQ
albiglutide	TANZEUM	PEN INJCTR	N	SQ
dulaglutide	TRULICITY	PEN INJCTR	N	SQ
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N	SQ
exenatide microspheres	BYDUREON PEN	PEN INJCTR	N	SQ
lixisenatide	ADLYXIN	PEN INJCTR	N	SQ
semaglutide	OZEMPIC	PEN INJCTR	N	SQ
semaglutide	RYBELSUS	TABLET	N	PO

SGLT-2 inhibitors

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	N
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin propanediol	FARXIGA	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N

dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empagliflozin	JARDIANCE	TABLET	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Randomized Controlled Trial

A Trial to Evaluate the Effect of the Sodium-Glucose Co-Transporter 2 Inhibitor Dapagliflozin on Morbidity and Mortality in Patients With Heart Failure and Reduced Left Ventricular Ejection Fraction (DAPA-HF)

John J V McMurray, David L DeMets, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, Anna M Langkilde, Felipe A Martinez, Olof Bengtsson, Piotr Ponikowski, Marc S Sabatine, Mikaela Sjöstrand, Scott D Solomon, DAPA-HF Committees and Investigators

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce the risk of incident heart failure hospitalization in individuals with type 2 diabetes who have, or are at high risk of, cardiovascular disease. Most patients in these trials did not have heart failure at baseline and the effect of SGLT2 inhibitors on outcomes in individuals with established heart failure (with or without diabetes) is unknown.

Design and methods: The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) is an international, multicentre, parallel group, randomized, double-blind, study in patients with chronic heart failure, evaluating the effect of dapagliflozin 10 mg, compared with placebo, given once daily, in addition to standard care, on the primary composite outcome of a worsening heart failure event (hospitalization or equivalent event, i.e. an urgent heart failure visit) or cardiovascular death. Patients with and without diabetes are eligible and must have a left ventricular ejection fraction ≤ 40%, a moderately elevated N-terminal pro B-type natriuretic peptide level, and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m2 . The trial is event-driven, with a target of 844 primary outcomes. Secondary outcomes include the composite of total heart failure hospitalizations (including repeat episodes), and cardiovascular death and patient-reported outcomes. A total of 4744 patients have been randomized.

Conclusions: DAPA-HF will determine the efficacy and safety of the SGLT2 inhibitor dapagliflozin, added to conventional therapy, in a broad spectrum of patients with heart failure and reduced ejection fraction.

Appendix 3: Search Criteria

Database(s): Ovid MEDLINE(R) ALL 1946 to April 08, 2020

Search Strategy:

#	Searches	Results

1	sitagliptin.mp. or Sitagliptin Phosphate/	2437
2	alogliptin.mp.	499
3	linagliptin.mp. or Linagliptin/	753
4	saxagliptin.mp.	729
5	sitagliptin.mp. or Sitagliptin Phosphate/	2437
6	exenatide.mp. or Exenatide/	3164
7	liraglutide.mp. or Liraglutide/	2811
8	albiglutide.mp.	194
9	dulaglutide.mp.	372
10	lixisenatide.mp.	441
11	semaglutide.mp.	356
12	canagliflozin.mp. or Canagliflozin/	1106
13	dapagliflozin.mp.	1095
14	empagliflozin.mp.	1246
15	ertugliflozin.mp.	99
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	11245
17	limit 16 to (english language and humans and yr="2018 -Current")	1365
18	limit 17 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	134

Appendix 4: Prior Authorization Criteria

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):

Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All SGLT-2 inhibitors

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of T2DM?	**Yes:** Go to #6	**No:** Go to #4
4. Does the patient have a diagnosis of heart failure with reduced ejection fraction (New York Heart Association class II-IV)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for dapagliflozin 10 mg daily?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient failed, or have contraindications to, metformin or is requesting a SGLT-2 inhibitor to be used in combination with metformin? (document contraindication, if any)	**Yes:** Go to #7	**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.
7. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <30 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <30 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <45 mL/min/ 1.73 m^2 , or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *8/20 (KS), 6/20 (KS), 7/18 (KS), 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred GLP-1 receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Has the patient tried and failed metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.
5. Is the request for semaglutide or dulaglutide?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the patient currently taking prandial insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.	**No:** Approve for up to 12 months

Initiating Metformin

5.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
6.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
7.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *8/20 (KS), 6/20 (KS), 3/19 (KS), 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred DPP-4 Inhibitors. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Has the patient tried and failed metformin, or have contraindications to metformin? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

9. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
10. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
11. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
12. The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *8/20 (KS), 7/18 (KS); 9/17; 9/16; 9/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1/20; 10/13/16; 10/15; 1/15; 9/14; 1/14; 2/13*