Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Antidiabetic Agents (excluding insulins)

Month/Year of Review: September 2017 **End date of literature search:** May 22, 2017
Last Review: September 2016
PDL Classes: DPP-4 Inhibitors; GLP-1 Receptor Agonists; Oral Hypoglycemics (sulfonylureas and meglitinides); SGLT-2 Inhibitors; Thiazolidinediones; Miscellaneous Antidiabetic Agents

Current Status of PDL Class:
- See Appendix 2

Purpose of Review:
To evaluate new evidence for each non-insulin antidiabetic drug class on the Preferred Drug List (PDL) and, if appropriate, update current recommendations for placement of specific agents within these drug classes on the Oregon Health Plan (OHP) PDL and current clinical prior authorization (PA) criteria.

Research Questions:
1. Is there any new comparative evidence for non-insulin diabetes treatments on surrogate efficacy outcomes (e.g., hemoglobin A1C [A1C] less than 7%) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for non-insulin diabetes treatments on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, etc.)?
3. Are there subpopulations of patients with diabetes mellitus for which specific therapies may be more effective or associated with less harm?

Conclusions:
There were 3 systematic reviews with meta-analyses[1–3], 6 new clinical practice guidelines (American Diabetes Association [ADA], American College of Physicians [ACP], 3 from the National Institute for Health and Care Excellence [NICE], and one from the American Association of Clinical Endocrinologists/American College of Endocrinology [AACE/ACE])[4–9], 4 new safety alerts[10–13], 4 new drug formulations[14–17] and 3 new randomized controlled studies (RCTs)[18–21] that provide clinically meaningful new evidence for these drugs. The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed. Several systematic reviews and meta-analyses were not included due to poor quality or because the evidence available for the analysis was of poor quality.[22-32]

Author: Kathy Sentena, PharmD Date: September 2017

EFFICACY OUTCOMES

- *Mortality:* Head-to-head RCTs are often underpowered to detect differences in mortality. Many RCTs that have evaluated clinically meaningful effectiveness outcomes (e.g., mortality, macrovascular and microvascular outcomes) lack long-term data, do not report cardiovascular (CV) mortality, have low incidence of mortality overall, and have low or insufficient quality of evidence for these outcomes. Caution is advised in drawing strong conclusions on these outcomes subject to these limitations. **Table 1** describes evidence related to A1C lowering, CV events and harms.
    - There is low quality evidence that there are no differences in CV outcomes or all-cause mortality between antidiabetic treatments for patients with type 2 diabetes mellitus (T2DM) based on mean trial duration of 6 months.[2]
    - There is moderate evidence in patients with T2DM that metformin is associated with less CV-related mortality than sulfonylureas (SU) (absolute difference [AD] -2.9% to -0.1%; 2 RCTs).[1]
    - There is moderate evidence liraglutide lowers the risk for the composite endpoint of CV-related mortality, non-fatal myocardial infarction (MI), or non-fatal stroke compared to placebo at 36 months (Absolute risk reduction [ARR]= 1.9%; number needed to treat [NNT]= 53). Liraglutide reduced the risk of CV-related mortality (ARR= 1.3%; NNT of 77) and all-cause mortality (ARR of 1.4%; NNT 71) versus placebo over 3.5 years.[18] The ADA guideline recommends liraglutide be considered in T2DM patients with established atherosclerotic disease.[5]
    - There is moderate evidence from a double-blind, multi-center randomized controlled trial, in patients with CV disease or at high risk for CV disease, that canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo, 26.9 vs. 31.5/1000 patient-years, respectively (ARR 0.3%/NNT 333 over 3.6 years).[21] None of the component endpoints were statistically different from placebo. There was a higher risk of amputations in patients treated with canagliflozin compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75).
- *Hemoglobin A1c:*
    - There is high quality evidence to recommend metformin first for patients with T2DM requiring antidiabetic treatment to meet glucose targets. [4,5,32]
    - There is moderate to high level of evidence, based on two high quality systematic reviews and meta-analyses, that A1C lowering is similar between monotherapy antidiabetic therapies, except for DPP-4 inhibitors which were found to have less glucose lowering than metformin[1,2] or SU[1].

SAFETY OUTCOMES

- *Hypoglycemia:* There is high quality evidence that the risk of hypoglycemia is higher with SU therapy than metformin, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 RAs.[1,2]
    - Use of SU was associated with a higher incidence of severe hypoglycemia compared to metformin (absolute difference [AD] 0.8% to 14%) and higher rates of mild, moderate or total hyperglycemia when compared to GLP-1 RAs and DPP-4 inhibitors based on moderate evidence (AD 6% to 21% ; $p<0.05$).[1]
- *Heart Failure:* An update from the U.S. Food and Drug Administration (FDA) reports saxagliptin and alogliptin may increase the risk of heart failure (HF), especially in patients with preexisting heart or kidney disease.[12]
- *Weight:* There is moderate to high evidence that metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with weight loss and SUs and thiazolidinediones (TZDs) are associated with weight gain.[1,2]
    - In monotherapy comparisons, metformin was associated with a mean difference of 1.3 kg weight loss compared to a DPP-4 inhibitor ($p<0.05$). Use of a TZD was associated with a mean weight gain of 1.2 kg more than with a SU ($p<0.05$). Use of a SU was associated with a mean weight gain of 2.3 kg more than with a GLP-1 RA ($p<0.05$). Table 1 gives an overview of relative effect of each antidiabetic class on weight when compared to placebo.

- *Bladder Cancer:* The FDA has added a warning to pioglitazone labeling that it may be associated with increased risk for bladder cancer, although the risk is not fully illucidated.[10] However, data analysis shows conflicting results suggested with hazard ratios (HR) that ranged from 1.0 (95% CI, 0.59 to 1.72) to 1.63 (95% CI, 1.22 to 2.19).
- *Amputations:* An FDA black boxed warning has been added to canagliflozin labeling due to the increased risk of amputations.[11] Amputation rates were 5.9 out of every 1,000 patients treated for canagliflozin compared to 2.8 for placebo out of every 1,000 patients treated based on the CANVAS study. A second study, CANVAS-R, found the risk to be 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 patients treated with placebo. The mechanism is unknown and the applicability of this risk to the entire class is still being determined.

PLACE IN THERAPY

- Moderate quality evidence demonstrates that adding a second antidiabetic therapy to metformin results in a similar A1C lowering of 0.9 -1.1%. A SU, DPP-4 inhibitor, or pioglitazone are recommended as second-line agents in combination with metformin by NICE if monotherapy with metformin fails to get patients to their treatment goal.[8] Triple therapy regimens recommended by NICE are: 1) metformin, DPP-4 inhibitor, and a SU; 2) metformin, pioglitazone and a SU 3); metformin, pioglitazone or SU, and an SGLT-2 inhibitor; or 4) insulin-based treatment.[8] GLP-1 RAs are recommended by NICE if patients on metformin and 2 other treatments, fail to meet glucose lowering targets and meet additional criteria as described below.
- Dual therapy treatment options recommended by the ADA, in combination with metformin, are: SU, thiazolidinedione (TZD), DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA or basal insulin.[5] ACP recommends a SU, TZD, SGT-2 inhibitor, or a DPP-4 inhibitor if a second oral agent is required in addition to metformin.[4]
- There is high quality evidence from a report by CADTH that SU should be added to metformin in patients with T2DM and without established CV disease that fail to meet glucose lowering targets.[3] Moderate quality evidence recommends the use of empagliflozin for patients with T2DM and a high risk of CV disease.[3]

Table 1. Non-insulin Glucose Lowering Drugs Effectiveness and Harms Comparisons

Drug Class	Relative A1C lowering[33]	Cardiovascular Data	Safety Warnings	Effect on Weight[1,5]
Biguanides • Metformin	1% to 1.5%	• UKPDS found that metformin may reduce the risk of CV mortality[34]	• Very small risk of lactic acidosis in patients with poor renal function	• Neutral/ loss
Sulfonylureas (2nd generation) • Glyburide • Glipizide • Glimepiride	1.0% to 1.5%	• No evidence of CV risk reduction	• Risk of hypoglycemia is higher than other oral antidiabetic treatments[1]	• Gain
Thiazolidinediones • Pioglitazone • Rosiglitazone	1.0% to 1.5%	• Use in patients with pre-diabetes and history of stroke or TIA was found to decrease subsequent stroke or MI (ARR 2.8%/NNT 36) compared to placebo over 4.8 years[20]	• Pioglitazone may increase the risk of bladder cancer compared to placebo[10] • TZDs increase the risk of HF exacerbations • TZDs increase the risk of bone fractures	• Gain

		• No CV morbidity or mortality benefit when rosiglitazone was added to metformin and SU[35] • No benefit or harm on CV endpoints with the use pioglitazone compared to placebo (HR 0.90; 95% CI, 0.80 to 1.02; p=0.095)[36]		
DPP-4 Inhibitors • Sitagliptin • Saxagliptin • Alogliptin • Linagliptin	0.5% to 1.0%	• Saxagliptin and alogliptin have demonstrated increased risk in HF related hospitalizations. No difference in CV mortality was demonstrated.[37,38] • Sitagliptin was found to provide no benefit or harm to CV endpoints[40] • Linagliptin is still being evaluated	• Saxagliptin and alogliptin have been linked to increased risk of heart failure[12] • DPP-4 inhibitors may increase risk of pancreatitis • DPP-4 inhibitors may increase risk of severe joint pain	• Neutral/ loss
SGLT2 Inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin	0.5% to 1.0%	• Empagliflozin demonstrated a reduction in the composite endpoint of death from CV causes, nonfatal MI and nonfatal stroke when compared to placebo (ARR 6%/NNT 63) over 3.1 years in patients with underlying CV disease.[39] • Canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo, 26.9 vs. 31.5/1000 patient-years, in patients with CV disease or at high risk for CV disease (ARR 0.3%/NNT 333 over 3.6 years).[21]	• Canagliflozin increases risk for amputations[11] • Canagliflozin and dapagliflozin are associated with acute kidney injury • SGLT2 inhibitors are associated with ketoacidosis and serious urinary tract infections • Canagliflozin may increase the risk of reduced bone mineral density and fracture	• Loss
GLP-1 Receptor Agonists • Exenatide • Exenatide Once-weekly • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	1.0% to 1.5%	• Liraglutide was found to decrease the composite outcome of death from CV causes, nonfatal MI, nonfatal stroke compared to placebo (ARR 1.9%/ NNT 53) over 3.5 years in patients on standard therapy with a history of CV disease or at high risk of CV disease[18] • Lixisenatide demonstrated no benefit or harm when compared to placebo for the composite endpoint of death from	• GLP-1 RA class may increase the risk of pancreatitis • An increased risk of thyroid cell cancers was demonstrated in rodent models	• Loss

		CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (HR 1.02; 95% CI, 0.89 to 1.17)[41]		
Meglitinides • Repaglinide • Nateglinide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Gain
Alpha-glucosidase Inhibitors • Acarbose • Miglitol	0.5% to 1.0%	• ACE Trial is ongoing	• No major safety warnings	• Neutral
Amylin Mimetics • Pramlintide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Loss

Recommendations:

- New evidence does not require a change to the current policy.
- Add new formulations to existing PA criteria.
- No changes to the PDL are recommended based on the new evidence. Evaluate comparative costs in executive session.

Previous Conclusions

- There is insufficient comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for T2DM
- There is insufficient evidence to compare health outcomes of the newer diabetes medications and combinations.
- There is high quality evidence that monotherapy with either metformin, a TZD or a SU results in similar lowering of A1C based on one systematic review. There is moderate quality evidence that DPP-4 inhibitors lower A1C less than metformin and glimepiride based on two systematic reviews (one for each comparison).
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews. Evidence from a recent systematic review and meta-analysis found glyburide to be associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.
- Moderate quality evidence from one fair and one good quality trial suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Hospitalization rates in patients with heart failure were higher in clinical trials of saxagliptin compared to placebo.
- A systematic review and meta-analysis on SGLT2 inhibitors, including canagliflozin and dapagliflozin, demonstrated A1C lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]). The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90)] and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to7.45]).
- In patients with a history of cardiovascular (CV) disease, there is moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) can decrease risk for CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed

to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99) in patients with high cardiovascular risk. Reduction in risk is primarily driven by a 2.2% reduction in CV death (3.7% vs. 5.9%) and not non-fatal MI or non-fatal stroke.

Previous Recommendations:

- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.
- Prior authorize the GLP-1 agonists and DPP-4 inhibitors to limit use to patients who have tried and failed therapy with metformin and sulfonylureas.
- Prior authorize SGLT-2 inhibitors to limit for patients unable to tolerate or have contraindications to all other therapies proven to be safe and effective (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin).

Background:

Type 2 diabetes mellitus is a prevalent disease affecting an estimated 25.6 million people in the United States, based on 2013 data. In Oregon, it is estimated that 287,000 adults have T2DM, in which 38,000 are estimated to be OHP members.[42] OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[42] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[43] Despite a variety of treatment options, a significant number of patients fail to meet A1C goals; within 3 years of being diagnosed, 50% of patients require combination therapy to control their disease.[44,45] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and the addition of pharmacotherapy for persistent hyperglycemia.[32,33] Guidelines recommend a goal A1C of < 7% for most patients but a range of <6.5% to <8% is reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[5] Classes of non-insulin antidiabetic agents currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT-2 inhibitors, SUs, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines continue to recommend metformin a first line treatment in most patients with T2DM.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. Hemoglobin A1C is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well.[32,33] A clinically relevant change in A1C is considered to be ≥0.3%.[1] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most available antidiabetic treatments to control glucose levels long-term and to compare their impact on microvascular and macrovascular complications. However, in 2008 the Food and Drug Administration (FDA) started requiring that CV risk be evaluated. Evidence has demonstrated an increased risk of HF-related hospital admissions with alogliptin (NNH 167) and saxagliptin (NNH 143).[37,38] For GLP-1 RAs, lixisenatide demonstrated no benefit or harm in patients with a recent acute coronary syndrome (ACS).[41] The results of the liraglutide study is included in this update and also showed CV benefits. There is moderate evidence from one trial that the SGLT-2 inhibitor empagliflozin demonstrated a 1.6% absolute reduction in the composite primary endpoint of CV death, non-fatal MI, or non-fatal stroke compared to placebo (10.5% vs. 12.1%, respectively; NNT 63 over 3.1 years).[39] Available evidence suggests that metformin is likely to reduce the incidence of CV disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS).[46] UKPDS data also shows reduced incidence of microvascular risk with SU therapy and insulin.[34]

Current OHP fee-for-service policy for non-insulin antidiabetic treatment allows for metformin use without restriction which is designated as a preferred drug (Appendix 1). Therapeutic options in the SU and TZD class are also available without restriction. DPP-4 inhibitors and GLP-1 RAs are options after trials of metformin and SU or contraindications to these drugs (Appendix 4). 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.

Utilization:
The majority of non-insulin anti-diabetic treatment costs were for metformin, SU, TZDs, DPP-4 inhibitors, GLP-1 RAs and SGLT2 inhibitors. Ninety-nine percent of prescriptions dispensed were for metformin, SU or TZD. Metformin was associated with the highest utilization accounting for 78% of the prescriptions dispensed and 66% of the costs. GLP-1 RAs prescriptions accounted for 34% of the costs but < 1% of the prescriptions dispensed. SU were found to be associated with 12% of the prescriptions dispensed and 14% of the costs. Two percent of the utilization and costs were for TZD therapy. The cost for SGLT-2 class accounted < 1% of prescription volume and cost. DPP-4 inhibitors accounted for < 1% utilization and costs.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

AHRQ – Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes
A systematic review and meta-analysis was performed to determine the comparative effectiveness and safety of antidiabetic treatments used alone or in combination with metformin.[1] Studies were included if they were head-to-head monotherapy comparisons of metformin, TZDs, SU, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs; comparisons to metformin alone with a metformin-based combination; and comparisons of metformin-based combinations where the second medication was one of the monotherapies described above or a basal or premixed insulin. The Jadad scale was used to evaluate the quality of the RCTs and the Downs and Black tool was utilized for non-randomized and observational studies. One-hundred sixteen new studies were included, 81% were RCTs, for a total of 204 studies all together. Funding was provided by Agency for Healthcare Research and Quality (AHRQ) and no authors reported a conflict of interest.

The evidence was graded low or insufficient for all-cause mortality, CV morbidity and microvascular complications. There is insufficient evidence on the study of long-term outcomes.[1]

Cardiovascular mortality: metformin was found to have a lower incidence than SU (moderate evidence).

- Based on evidence from 2 RCTs that found a relative risk of CV mortality of 0.6 to 0.7 favoring metformin over SU, with an absolute difference of 0.1% to 2.9%.[1]

Hemoglobin A1C lowering: reductions were similar across all antidiabetic therapies and metformin-based combinations. The exception was DPP-4 inhibitors which had less lowering compared to metformin and SU (based on moderate to high evidence for all comparisons).[1]

- Analysis of 14 studies found no clinically meaningful difference (≥0.3%) in A1C between antidiabetic therapies.

Body weight: maintenance or reductions were seen with metformin, DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors.[1] Weight was increased with SU, TZDs, and insulin with between group differences of up to 5 kg.

- Results were significant for metformin compared to DPP-4 inhibitors where an analysis of 6 studies found a mean difference of -1.3 kg (95% CI, -1.6 to -1.0 kg; $p<0.05$) favoring metformin (high level of evidence). TZDs caused significantly more weight gain compared to SU by a mean difference of 1.2 kg (95% CI, 0.6 to 1.8 kg; $p < 0.05$) (high level of evidence). SUs increase weight by a mean difference of 2.3 kg (95% CI, 1.2 to 3.3 kg; $p<0.05$) more than GLP-1 RAs based on 4 studies (moderate level of evidence). Comparisons in which meta-analyses were not able to be conducted are presented in **Table 2** below.
- Metformin monotherapy was found to decrease weight by a mean difference of 2.2 kg (95% CI, -2.6 to -1.9 kg; $p<0.05$) when compared to metformin/TZD combination. A mean difference of -3.2 kg (95% CI, -4.6 to -1.6 kg; $p<0.05$) was found between metformin monotherapy and metformin/SU combinations, favoring monotherapy, in patients who weight 90 kg or more based on high strength of evidence. In patients weighing less than 90 kg, metformin monotherapy was associated with a mean difference in weight of -1.2 kg (95% CI, -1.6 to -0.6 kg; $p < 0.05$) based on high strength of evidence from 5 studies.

Table 2. Summary of Moderate to High Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combinations Therapy Where Meta-analyses Could Not Be Conducted for Weight.[1]

Comparison	RCTs (Participants), *n (n)*	Range in Mean Between-Group Differences	Conclusion	Strength of Evidence
SU vs. DPP-4 inhibitors	4 (1659)	0.7 to 1.8 kg	DPP-4 inhibitors favored	Moderate
DPP-4 inhibitors vs. TZD	2 (1475)	−2.3 to −2.5 kg	DPP-4 inhibitors favored	Moderate
GLP-1 receptor agonists vs. TZD	2 (1048)	Both studies: −3.5 kg	GLP-1 receptor agonists favored	Moderate
SGLT-2 inhibitors vs. Met	3 (1903)	−1.3 to −1.4 kg	SGLT-2 inhibitors favored	Moderate
SGLT-2 inhibitor vs. DPP-4 inhibitors	1 (899)	−2.5 to −2.7 kg	SGLT-2 inhibitors favored	Moderate
Met + SGLT-2 inhibitors vs. Met + DPP-4 inhibitors	5 (3423)	−1.8 to −3.6 kg	Met + SGLT-2 inhibitors favored	Moderate
Met + SU vs. Met + premixed or basal insulin	3 (894)	−1.7 to −0.6 kg	Met + SU favored	Moderate
Met + GLP-1 receptor agonists vs. Met + premixed insulin	2 (426)	−1.9 to −5.1 kg	Met + GLP-1 receptor agonists favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; RCT = randomized, controlled trial; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylureas; TZD= thiazolidinedione.

Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. Annals of Internal Medicine. 2016;164(11):740-751. doi:10.7326/M15-2650.

Hypoglycemia: SUs were most often associated with hypoglycemia as monotherapy and in combination therapy regimens (moderate to high evidence).

- In studies that compared metformin to SU, risk for severe hypoglycemia was 0.8% to 14% higher with SU ($p<0.05$). In comparisons of combination therapy, metformin/SU therapy was associated with an increased risk of severe hypoglycemia compared to metformin/DPP-4 inhibitors (OR 0.2; 95% CI, 0.1 to 0.6; $p<0.05$) (moderate evidence). Metformin/SU were also associated with a 1% to 3% increased risk of severe hypoglycemia compared to metformin/SGLT2 inhibitors.
- SU as monotherapy or in combination therapy was associated with a higher rate of mild, moderate, or total hyperglycemia versus GLP-1 RA, DPP-4 inhibitors, and metformin (OR 2.0 to 3.8; $P < 0.05$).

Gastrointestinal Adverse Events: GI adverse events are defined as diarrhea, nausea and vomiting for this endpoint. There was moderate to high strength of evidence that metformin and GLP-1 RAs, as monotherapy and in combination with other antidiabetic treatments, were associated with the highest incidence of adverse GI events.[1] In comparisons between GLP-1 RAs and SU, GLP-1 RAs were associated with a 3% to 9% increased risk of adverse GI events. Combination therapy of metformin/GLP-1 RA had a 0% to 23% higher risk for adverse GI events compared to metformin/DPP-4 inhibitor ($p<0.05$). Metformin/GLP-1 RA combination were also associated with 8% to 19% more adverse GI events than metformin/TZDs ($p<0.05$). No difference was found in the risk of GI adverse events between TZDs and SU and the combination of metformin/SU and metformin/TZD.

Genital Mycotic Infections: There was moderate to high strength of evidence that risk of genital mycotic infections was higher with SGLT2 inhibitors compared to placebo and active treatments. When metformin was compared to metformin/SGLT2 inhibitor, the risk of genital mycotic infections was up to 9.9% higher for the combination therapy (OR 3.0; 95% CI, 1.2 to 7.2 for women and OR 2.7; 95% CI, 0.8 to 9.0 for men). In a comparison between metformin/GLP-1 RA and metformin/SU combinations, there was a 7.1% to 17.4% $P < 0.05$) increase in genital mycotic infections with metformin/SGLT2 ($p<0.05$). In a comparison between SGLT2s and metformin, SGLT2s were associated with increased risk of genital mycotic infections by -0.04% to 15.7% ($p<0.05$). A comparison between metformin/SGLT2 inhibitor and metformin/DPP-4 inhibitor combinations found a -2.8% to 8.8% increase in genital mycotic infections with metformin/SGLT2.

In summary, the new evidence that was identified since the 2015 AHRQ review supports the current guideline recommendations. Metformin remains the first-line treatment in patients with T2DM who require therapy to reduce glucose levels. The optimal second-line agent to add to metformin to in most patients is not clear and dependent upon patient specific characteristics. With lack of long-term outcomes, practitioners must balance adverse events, costs, comorbidities and administration concerns when choosing a second antidiabetic agent.

Palmer, et al. – Clinical Outcomes and Adverse Events of Glucose-Lowering Drugs

In a systematic review and meta-analysis, the efficacy and safety of drugs used to treat T2DM were compared. Three-hundred and one RCTs that were at least 24 weeks (median 6 months) in duration that compared two individual glucose lowering therapies were included.[2] Classes included in the review were: metformin, SU, DPP-4 inhibitors, GLP-1 RA, SGLT-2 inhibitors, basal insulin, meglitinide, and alpha-glucosidase inhibitors. Insulin therapies of basal-bolus and prandial insulin were included if they were compared to previous drug classes already mentioned, placebo or standard therapy. Monotherapy (n=177 studies), drugs added to metformin (n=109 studies) and drugs added to metformin and a SU (n=29 studies) were identified. Patients included had a baseline A1C of 8.2%-8.4% and mean duration of diabetes of 5.7 years. The Cochrane risk of bias tool was used to determine study quality. Depending on the domain, the risk of bias ranged from 31.9%-93.4%. Trials were excluded (n=1035) on a methodological basis for non-parallel study design and lack of reporting of meta-analysis outcomes. The primary outcome was CV mortality. Secondary outcomes were all-cause mortality, serious adverse events, MI, stroke, change in A1C, treatment failure, hypoglycemia and body weight. Several authors had received funding from industry. Funding for the analysis was provided by the Royal Society of New Zealand.

The incidence of CV and all-cause mortality outcomes between antidiabetic treatment when compared as monotherapy (n=25 studies), dual therapy (with metformin) (n=26 trials) and triple therapy (with metformin and SU) were not statistically significantly different.[2]

Monotherapy Comparisons: No evidence was available for GLP-1 RAs and basal insulin for monotherapy comparisons. All monotherapy antidiabetic treatment comparisons were more effective than placebo with an A1C standard mean difference (SMD) of -0.66% to -1.11%. In metformin comparisons, metformin resulted in lower A1C than alpha-glucosidase inhibitors, DPP-4 inhibitors, SU and TZDs (SMD 0.16% to 0.35%). SGLT-2 inhibitors, basal insulins, GLP-1 RA and meglitinides were not statistically significantly different from metformin. Treatment failure was highest with placebo (11%; 95% CI, 8 to 14%), followed by meglitinides (5%; 95% CI, 1 to 9%) and DPP-4 inhibitors (3%; 95% CI, 1 to 6%).[2] Compared to metformin SGLT2 inhibitors were associated with the lower risk of treatment failure by a difference of -0.3% (95% CI, -4% to 3%), which is unlikely to be clinically significant. The two treatments most commonly associated with hypoglycemia, based on placebo and active treatment comparisons, were basal insulin (AD 10%; 95% CI 0.08% to 20%) and SU (AD 10%; 95% CI, 7% to 13%). When compared to metformin, GLP-1 RAs were associated with the lower body weight with a SMD of -0.28 kg. SU and TZDs were associated with 0.19 kg to 0.24 kg higher body weight than metformin.[2] Differences in body weight were small suggesting the clinical significance is low.

Dual Therapy Comparisons with Metformin: Metformin/DPP-4 inhibitor combination therapy was associated with lower risk of stroke when compared to metformin/SU (AD -0.2%; 95% CI -0.4% to -0.04%).[2] Differences were small and unlikely to be clinically significant. For all other dual combination therapy comparisons with metformin, the outcomes of serious adverse events, MI or stroke were not significantly different. Similar levels of A1C lowering were seen with all dual combination comparisons; however, there was substantial heterogeneity in the comparison making conclusions difficult. In comparisons of dual combination therapy, metformin/SGLT-2 inhibitor therapy was associated with 3% lower rate of treatment failure compared to metformin/SU (95% CI; -6% to -0.8%).[2] Metformin/alpha-glucosidase inhibitor, followed by metformin/DPP-4 inhibitor, were associated with the highest treatment failure rates compared to other metformin combinations. Hypoglycemia rates were higher with metformin/SU. The difference in risk of hypoglycemia was -4% to -22% lower with other combinations compared to metformin/SU. Metformin combined with a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 RA resulted in a mean weight decrease of -0.58 kg to -1.05 kg when compared to metformin/SU combination therapy.

Triple Combination with Metformin and SU: No differences were found between any comparisons for all-cause mortality or serious adverse event outcomes. There was insufficient evidence for MI and stroke. The combination of metformin/SU plus TZD or basal insulin were associated with greatest A1C reduction. Metformin/SU plus an alpha-glucosidase inhibitor had the least A1C lowering when compared to or metformin/SU plus TZD, GLP-1 RA, or basal insulin.[2] Treatment failure rates were lowest with metformin/SU plus basal insulin and highest with metformin/SU plus DPP-4 inhibitor. A GLP-1 RA added to metformin and SU resulted in the lowest risk of hypoglycemia of all triple therapy studied. The largest difference in hypoglycemia rates were seen when GLP-1 RAs were compared to TZDs combined with metformin and SU which demonstrated a 10% difference between the groups (95% CI, -18 to 2) favoring GLP-1 RAs; however, this was not statistically significant. Changes in body weight were significantly lower for SGLT2 inhibitors (SMD -0.33 kg), which is unlikely to be clinically significant.

In summary, monotherapy comparisons with metformin found DPP-4 inhibitors and alpha-glucosidase inhibitors resulted in 0.33% to 0.35% lower mean A1C values. Compared to metformin, SU and basal insulin had clinically significant increases in hypoglycemia rates. GLP-1 RAs were associated with the least changes in body weight with a mean decrease in body weight of 0.28 kg. For dual therapy comparisons, there is no clear difference in glucose lowering. SU therapy, alone or in combination, is consistently associated with a higher risk of hypoglycemia. TZDs were consistently associated with the most weight gain. There were no significant correlations between the degree of A1C lowering, hypoglycemia and body weight and characteristics at baseline based on a network meta-regression analyses. Cardiovascular and mortality outcomes remain imprecise, primarily due to short trial durations, lack of reporting CV mortality and low incidence of mortality in studies.

<u>CADTH – New Drugs for Type 2 Diabetes: Second-line Therapy</u>

A recently published CADTH report provides recommendations for second-line therapy for patients with T2DM.[3] This report updates a 2013 version and includes evidence on new drugs and new drug classes that have become available since that time. A systematic review of oral and injectable antidiabetic agents was performed which identified 166 RCTs for inclusion in the review. Classes included were the following: SU, SGLT2 inhibitors, DPP-4 inhibitors, TZDs, GLP-1 RAs, alpha-glucosidase inhibitors, meglitinides and biphasic insulin.

The report provides two new recommendations.

1. **In patients with T2DM without established CV disease it is recommended that a SU be added to metformin for adults who are inadequately controlled on metformin alone.[3] Additional evidence is presented in Table 3.**

a. A meta-analysis was preformed to support this recommendation which found A1C lowering of -0.58% to -0.94%.[3] There was no evidence of superiority of other classes to SU for safety or efficacy outcomes. Limitations to the review were a lack of evidence for long-term outcomes (e.g., CV events). Overall the evidence was defined as robust by the authors. Clinically significant hypoglycemia events were rare across all classes studied, including the incidence of severe hypoglycemia. SU were associated with a small increase in weight, approximately 2 kg.
b. Evidence suggests that SU should be used with caution in elderly patients.

Table 3. Evidence Analysis for Recommendation 1[3]

Outcome	Evidence
Body Weight	When compared to metformin basal insulin and SU were associated with the most weight gain ranging from 2.1 kg to 2.8 kg. Statistically significant reductions in weight were found for GLP-1 RAs and SGLT2 inhibitors (-1.4 to -2.2 kg) when compared to metformin. Antidiabetic agents (non-insulin) added to metformin were associated with less weight gain compared to SU with a range of -1.9 to -4.3 kg. Compared to DPP-4 inhibitors both GLP1-RAs and SGLT2 inhibitors were found to reduce weight to a greater extent ($p < 0.05$).
Blood Pressure	When compared to metformin monotherapy all antidiabetic treatments lowered blood pressure diastolic blood pressure compared to baseline values except for SU ($p < 0.05$). The mean difference in diastolic blood pressure lowering was more for SGLT2 inhibitors combined with metformin compared to SU and DPP-4 inhibitors ($p < 0.05$).
Hypoglycemia	Severe hypoglycemia was more common with SU compared to metformin (OR 6.4%; 95% CI, 2.24 to 17.51). Comparisons between the classes demonstrated a reduced risk of severe hypoglycemia with GLP-1 RAs, SGLT2 inhibitors and DDP-4 inhibitors compared to SU. In metformin monotherapy comparisons, all antidiabetic treatments had a lower rate of nonsevere hypoglycemia compared to SU and basal and biphasic insulin. Biphasic insulin was associated with a higher rate of nonsevere hypoglycemia compared to basal insulin.
Mortality	Due to low event rates the meta-analysis for all-cause mortality and CV mortality were not robust. In an analysis of DPP-4 inhibitors compared to SU there was no difference in all-cause mortality (OR 1.19; 95% CI, 0.65 to 2.17) or CV mortality (OR 1.84; 95% CI, 0.66 to 5.12).
Adverse Events	In comparison to metformin no antidiabetic class was associated with a statistically significant increase or decrease in serious adverse events. Withdrawals were higher with SU, DPP-4 inhibitors, basal insulin, GLP-1 RAs when combined with metformin compared to metformin alone ($p < 0.05$). The total number of adverse events were higher with GLP-1 RAs, basal insulin and biphasic insulin compared to metformin.
Cholesterol	SGLT2 inhibitors increased low-density lipoprotein (LDL) cholesterol in comparison to metformin and DPP-4 inhibitors. Combinations of metformin and SGLT2 inhibitors were associated with an increase in high-density lipoprotein (HDL) cholesterol compared to metformin alone, SU, DPP-4 inhibitors, and GLP-1 RAs.
Heart Failure	Low events prevented strong conclusions on HF. Comparison of SU to DPP-4 inhibitors found no difference in HF rates (OR 1.35; 95% CI, 0.48 to 3.82).
Stroke and TIA	Low event rates prevented strong conclusions. No significant differences were found between metformin and SU, SGLT-2 and DPP-4 inhibitors.
Pancreatitis	Meta-analysis results were inconclusive due to low event rates.
Urogenital Adverse Events	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased urogenital adverse events.

Fractures	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased fracture rates (data not available for GLP-1 RAs).
Unstable Angina	No significant differences were found in comparisons of metformin to combinations of metformin and SU or SGLT2 inhibitors or DPP-4 inhibitors.

2. **In patients with T2DM and CV disease, therapy should be considered which has been has been specifically studied for this indication and recommendations have been previously provided by CADTH.[3] Additional evidence is presented in Table 4.**
    a. There is not enough evidence to support a recommendation for a specific drug class at this time based on 17 RCTs. All trials allowed patients to continue on varying regimens of background therapies.
    b. Previous reviews of the evidence recommend the use of empagliflozin for patients at high risk of CV events.

Table 4. Evidence Analysis for Recommendation 2 (Cardiovascular trials only)[3]

Outcome	Evidence
Major Adverse Cardiovascular Events	Evidence from 5 RCTs provided insufficient data to conclude that any antidiabetic class lowered the risk of MACE (composite endpoint of CV mortality, nonfatal MI, and nonfatal stroke).
Mortality	SGLT2 inhibitors reduced the risk of all-cause mortality when compared to placebo (OR 0.67; 95% CI, 0.47 to 0.95) or DPP-4 inhibitors (OR 0.66; 95% credible interval [CrI], 045 to 99). No other comparisons were available
Cardiovascular Mortality	None of the classes significantly lowered CV mortality when compared to placebo or to other antidiabetic classes.
Hospitalizations Due to Heart Failure	Data was insufficient to draw conclusions.
Adverse Events	None of the classes significantly increased or decreased the risk of adverse events, severe adverse events or withdrawals due to adverse events
Hypoglycemia	In comparisons of TZDs to existing therapies, TZDs were found to have the greatest risk of severe hypoglycemia (OR 2.05; 95% CI, 1.11 to 3.98); however, data was not available for SU or metformin.
Cancer	Compared to placebo TZDs significantly decreased pancreatic cancer based on 3 RCTS. In class comparisons TZDs also decreased the risk of pancreatic cancer when compared to GLP-1 RAs (OR 0.13; 95% CI, 0.01 to 0.75). Placebo and class comparisons found no increase in the risk of bladder cancer.
Pancreatitis	The risk of pancreatitis was not increased with DPP-4 inhibitors (OR 1.60; 95% CI, 0.97 to 2.66) or GLP-1 RAs (OR 0.73; 95% CI, 0.37 to 1.39) when compared to placebo or each other.
Fractures	No classes significantly increased or decreased fracture rates in comparison to each other or placebo based on 3 RCTs.

New Guidelines:

The American Diabetes Association – Standards of Medical Care 2017

The ADA updates their standards of care in diabetes each year.[5] The 2017 standards contain comprehensive recommendations for managing all aspects of patients with diabetes. ADA makes recommendations based on a systematic review or other review of the published literature and grading of the evidence. Recommendations are given a rating of A, B, C and E (**Table 5**). Statement of extensive literature search is included but specific methods are not described. Updates pertaining to the pharmacology of diabetes and treatment goals will be included in this review.

Table 5. ADA Evidence-grading System[5]

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
B	Supportive evidence from well-conducted cohort studies
C	Supportive evidence from poorly controlled or uncontrolled studies
E	Expert consensus or clinical experience

Recommendations:

Hemoglobin A1C goals – A goal of <7% is recommended for most patients based on level A evidence. A lower goal of <6.5% may be appropriate for those that are candidates for more intensive management without experiencing significant hypoglycemia (level C evidence). Patients with limited life expectancy, history of severe hypoglycemia and advanced complications may be more appropriately managed with a higher goal of <8% (level B evidence).[5]

Pharmacological Management of T2DM – Metformin is recommended first-line in patients without contraindications based on level A evidence.[5] Newly diagnosed patients presenting with an A1C of ≥10% or a blood glucose of ≥300 mg/dL should be considered candidates for insulin based on expert opinion (level E evidence). Dual therapy may be considered in patients presenting with A1C levels of ≥9%. If noninsulin monotherapy at maximal tolerated doses fails to control glucose levels to target ranges after 3 months, then an additional oral agent, basal insulin or a GLP-1 RA should be added (evidence level A). The most appropriate treatment to add to metformin is not clearly defined.[5] A meta-analysis found that newer classes of noninsulin therapies lowered A1C to a similar level of approximately 0.9-1.1%. If goal glycemic levels are not obtained with metformin monotherapy, a treatment from one of the following classes should be considered: SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 RA or basal insulin. If after 3 months the goal A1C is still not achieved, a third agent should be initiated. If triple therapy fails to get a patient to target A1C after an additional 3 months, then combination injectable treatment should be considered. The guidelines do not recommend one medication class over another after metformin. Treatments should be determined by patient-specific factors, such as risk for hypoglycemia, weight changes, adverse effects, and cost (evidence level E). Insulin therapy should not be delayed in patients who are not obtaining glycemic treatment goals (evidence level B). Empagliflozin or liraglutide should be considered for patients with a long history of diabetes who are not meeting glucose targets and have established atherosclerotic disease (evidence B) since both agents have shown to decrease cardiovascular and all-cause mortality when added to standard care in patients with preexisting cardiovascular disease.

American College of Physicians – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus

A 2017 update from the ACP evaluated oral treatment options for patients with T2DM and updated recommendations from 2012.[4] The recommendations were based on the AHRQ evidence review of oral agents for the treatment of T2DM (presented above). Evidence from randomized and observational studies were

included. Study quality was assessed and evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Classes included in the review were TZDs, SUs, DPP-4 inhibitors and SGLT2 inhibitors and metformin.

Evidence was low or insufficient for clinical outcomes of mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy and neuropathy, based on data from 65 new studies.[4] Most antidiabetic therapies had similar efficacy in their ability to lower A1C.
ACP updated 2 recommendations:

1. Metformin should be prescribed to patients requiring glucose lowering therapy (strong recommendation; moderate-quality of evidence).[4]
2. If a second oral agent is required then either a SU, TZD, an SGLT2 inhibitor, or a DPP-4 inhibitor should be considered in addition to metformin (weak recommendation; moderate quality of evidence). Treatment selection should be made after a discussion of benefits, adverse effects and costs.[4]

<u>NICE – Type 2 Diabetes in Adults</u>
NICE updated several recommendations to its 2015 guidance on the management of T2DM.[8] Recommendations include a target A1C of 7.0% or less. If target A1C is not met with diet, lifestyle and adherence reinforcement, drug treatment should be considered. Metformin is recommended first-line in adults with T2DM. Metformin is not recommended in patients with an estimate glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2. Alternatives to metformin, if contraindicated or not tolerated, are: DDP-4 inhibitor, pioglitazone or SU. SGLT2 inhibitors are recommended instead of a DPP-4 inhibitors if SU or pioglitazone is not appropriate. Pioglitazone is not recommended in patients with HF, hepatic impairment, diabetic ketoacidosis, current or history of bladder cancer or uninvestigated macroscopic hematuria. In patients with symptoms of hyperglycemia, SU or insulin therapy should be considered.

Drug therapy intensification is also recommended in patients on monotherapy with an A1C above 7.5%.[8] Specific drug treatments should be based on efficacy, safety, comorbidities, polypharmacy, patient's preferences and needs and cost. Recommended combinations are: metformin and DPP-4 inhibitor, metformin and pioglitazone, metformin and a SU, or metformin and a SGLT2 inhibitor. In patients who are unable to take metformin, the following combinations are recommended: DPP-4 inhibitor and pioglitazone, DPP-4 inhibitor and a SU or pioglitazone and a SU.

The following triple therapies are recommended if needed: 1) metformin, DPP-4 inhibitor and SU 2) metformin, pioglitazone and SU 3) metformin, SGLT2 inhibitor, and pioglitazone or SU 4) insulin-based treatment.[8] If metformin and 2 other antidiabetic treatments fail to lower glucose levels to goal, are not tolerated or are contraindicated then metformin, a SU and GLP-1 RA should be considered in patients who have the following characteristics:1) a BMI of 35 kg/m2 or greater and psychological or other medical problems associated with obesity 2) a BMI of less than 35 kg/m^2 and who insulin therapy would have significant occupational implications 3) weight loss would benefit other significant obesity-related comorbidities. Use of GLP-1 RA should be monitored and only continued if there is at least a 1% reduction in A1C and at least a 3% weight loss within 6 months. In patients who are candidates for insulin, metformin therapy should be continued unless contraindicated or not tolerated. NPH insulin is recommended with or without short-acting insulin; however, this practice is less common in the United States (US). Insulin detemir or insulin glargine is recommended in patients who require assistance in insulin administration, experience lifestyle altering hypoglycemia, or the patient would require NPH and additional oral antidiabetic treatments.[8] Pre-mixed (biphasic) insulin analogues are recommended if injecting immediately before a meal, hypoglycemia is an issue or postprandial hyperglycemia is a concern. Patients who start on NPH insulin may need to be switched to insulin detemir or insulin glargine if target A1C levels are not reached due to hypoglycemia, or if the patient experiences significant hypoglycemia, has problems operating the NPH insulin device (not available in the US), or who require assistance in insulin administration.

Suggested intervals for monitoring A1C to assess goal attainment and response to therapy is every 3 months until A1C and treatment is stable, after that every 6 months is sufficient.

NICE – Recommendations for Dapagliflozin Triple Therapy in T2DM

In 2016 NICE updated guidance on the use of dapagliflozin in triple therapy regimens for adult patients with T2DM.[6] The guidance recommends dapagliflozin as one option as a triple therapy regimen in combination with metformin and a sulfonylurea (see below). Previous appraisals focus on the use of dapagliflozin as part of a dual therapy regimen. NICE recommends metformin first-line, followed by combination therapy if glucose targets are not obtained.

NICE – Canagliflozin, Dapagliflozin and Empagliflozin as Monotherapies for Treating Type 2 Diabetes

Based on an evidence review, NICE recently updated guidance for the use of 3 SGLT-2 inhibitors.[7] The guidance recommends canagliflozin, dapagliflozin or empagliflozin as an option in adult patients with T2DM that are unable to take metformin and diet and exercise fail to lower blood glucose levels to target after the following have been met:

- A DDP-4 inhibitor would otherwise be prescribed and
- A SU or pioglitazone is not appropriate

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm

An updated consensus statement was released by the AACE/ACE in 2017.[9] Recommendations are based on evaluating the evidence by giving the evidence a rating and evaluating the risk of bias. They also include a subjective factor impact and two-thirds expert consensus in the overall recommendation grade, which allows for high bias in recommendation development. Several authors have associations with industry that could influence recommendations. The strength of the recommendations were provided in a visual format based on a colored line but were not assigned an alphabetical recommendation grade which limits interpretation of the guidance.

Target A1C values of ≤ 6.5% are recommended if it can be reached safely and affordably. Pharmacotherapy recommendations are based on initial A1C level (**Table 6**).[9] Hemoglobin A1C should be reassessed every 3 months. Patients on monotherapy that are not meeting glucose targets after 3 months should be considered for dual therapy (**Table 6**). Patients who are not at goal using dual therapy are recommended to go to triple therapy (**Table 6**).

Table 6. AACE/ACE Glycemic Control Recommendations[9]

Entry A1C	Recommendations (in order of suggested hierarchy of usage)	
< 7.5%	1. Metformin 3. SGLT2 Inhibitors 5. TZD‡ 7. SU/GLN‡	2. GLP-1 RA 4. DPP-4 inhibitors 6. AGi
Dual Therapy: ≥ 7.5%* * In combination with metformin or other first-line agent	1. GLP-1 RA 3. DPP-4 inhibitors 5. Basal insulin‡ 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. TZD‡ 6. Colesevelam 8. AGi

Triple Therapy: ≥ 7.5%† † In combination with metformin or other first-line agent + second-line agent	1. GLP-1 RA 3. TZD‡ 5. DPP-4 inhibitor 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. Basal insulin‡ 6. Colesevelam 8. AGi 10. Add or intensify insulin therapy
< 9%	Symptoms: Insulin ± other agents No symptoms: Dual therapy or triple therapy	
‡ These treatments are recommended to be used with caution due to adverse effects. Abbreviations: AGi = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase 4; GLP-1 RA = glucagon-like peptide receptor agonist; SGLT2 = sodium glucose cotransporter 2; TZD = thiazolidinedione		

Safety Alerts:

The FDA reviewed the risk of heart failure associated with the use of the DPP-4 inhibitors, saxagliptin and alogliptin, in February 2014.[12] In April 2016, they concluded that saxagliptin and alogliptin may increase the risk of heart failure, especially in patients with preexisting heart or kidney disease and. The FDA requested the manufacturers to update warning labeling for these drugs. The recommendation came from review of clinical trial data that demonstrated increased risk of hospitalizations in patients who received saxagliptin or alogliptin compared to placebo. The risk was 35 out of 1,000 patients for saxagliptin compared to 28 out of 1,000 for placebo. The risk was 39 out of 1,000 for alogliptin compared to 33 out of 1,000 for placebo. Therefore, the risk is approximately increased by 6-7 patients per 1000 with saxagliptin and alogliptin compared to placebo.

Pioglitazone may be associated with an increased risk of bladder cancer according to an updated review by the FDA in December of 2016.[10] The possible association of pioglitazone and bladder cancer was first identified in 2010 based on epidemiological data. Since then, additional studies have yielded conflicting results. One study found a trend towards higher risk with increased duration of use but results were not statistically significant (HR 1.06; 95% CI, 0.89 to 1.26). A second study found the risk of bladder cancer with pioglitazone, compared to placebo, was higher during the treatment period (RR 2.83; 95% CI, 1.02 to 7.85); however, during the 12.8 years of follow-up (trial and observational period) there was no increased risk identified (HR 1.0; 95% CI, 0.59 to 1.72). A retrospective cohort trial found the risk of bladder cancer with pioglitazone use was higher compared to no TZD use (HR of 1.63; 95% CI, 1.22 to 2.19). The FDA concluded that pioglitazone may increase the risk of bladder cancer and the label has been updated.

Labeling changes were required by the FDA for metformin-containing products in April of 2016.[13] The changes expanded the use of metformin for patients with diabetes with mild to moderate renal impairment when previously metformin was note recommended to be used in these patients. Recommendations were also added that eGFR be monitored annually. Metformin is still contraindicated in patients with an eGFR of less than 30 mL/min/1.73 m^2 and not recommended in patients with an eGFR of 30-45 mL/min/1.73 m^2.

A 2016 review found interim trial data that suggested canagliflozin may be associated with an increased risk of leg and foot amputations in patients with T2DM.[11] The suggested mechanism for this risk is unknown and the risk with other SGLT2 inhibitors has not been determined. Recent data released in May 2017 found that canagliflozin was associated with an increased risk of amputations based on analyses of two large clinical trials, the Canagliflozin Cardiovascular

Assessment Study (CANVAS) and A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R). The incidence of amputations was 2-times higher in patients treated with canagliflozin compared to placebo. In the CANVAS study, the risk was 5.9 out of every 1,000 patients treated with canagliflozin compared to 2.8 out of every 1,000 patients treated with placebo. In the CANVAS-R study, the risk was 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 treated with placebo. Amputations were most common in the toe and middle of the foot. More extensive amputations involving the leg, below and above the knee have also occurred. Canagliflozin labeling has been updated with a black box warning to this effect.

New Formulations:

Insulin glargine/lixisenatide (Soliqua™ 100/33)

A combination formulation of the previously reviewed lixisenatide and insulin glargine was approved in 2016 as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM who are not controlled on basal insulin (less than 60 units daily) or lixisenatide.[14] The starting dose for patients that remain uncontrolled on 30 units or less of basal insulin or on lixisenatide is 15 units of the combination product (15 units of glargine/5 mcg lixisenatide) subcutaneously (SC) once daily. For patients using 30-60 units of basal insulin daily, who remain uncontrolled, the starting dose is 30 units (30 units of insulin glargine/10 mcg lixisenatide) given SC once daily. The maximum daily dose is 60 units (60 units of insulin glargine/20 mcg lixisenatide) SC daily. Injection should be administered one hour prior to the first meal of the day.

Insulin glargine/lixisenatide was approved based on one open-label, 30-week, active-controlled, multicenter, RCT in patients with T2DM.[14] Insulin glargine/lixisenatide 100/33 was compared to insulin glargine 100 units/mL in 736 patients. Patients with a 12-year history of diabetes were followed for 30 weeks after a 6-week run-in and stabilization phase. Insulin glargine/lixisenatide treated patients had lower A1C levels compared to insulin glargine alone (6.9% vs. 7.5%, respectively; MD -0.5%; 95% CI, -0.6 to -0.4%: $p<0.01$). The dose of insulin glargine was capped at 60 units to determine the efficacy of the GLP-1 RA component. The doses of insulin glargine at the end of the trial were similar between groups.

Dapagliflozin/saxagliptin (Qtern®)

The combination product of the SGLT-2 inhibitor, dapagliflozin, and the DPP-4 inhibitor, saxagliptin, was approved for the treatment of patients with T2DM as an adjunct to diet and exercise who have inadequate glycemic control with dapagliflozin or are already being treated with dapagliflozin and saxagliptin.[15] The combination tablet of dapagliflozin 10 mg and saxagliptin 5 mg should be taken once daily in the morning.

The dapagliflozin/saxagliptin combination was approved based on one 24-week, double-blind, placebo-controlled trial in 315 patients with T2DM. Patients who were on dapagliflozin and metformin and remained uncontrolled were randomized to saxagliptin or placebo.[15] At week 24, patients receiving dapagliflozin, metformin and saxagliptin had greater A1c lowering compared to patients taking dapagliflozin, metformin and placebo (MD -0.4%; 95% CI, -0.4 to -0.2; $p<0.0001$).

Insulin degludec/liraglutide (Xultophy® 100/3.6)

A combination formulation insulin degludec, a long-acting insulin, and liraglutide, a GLP-1 RA, was approved in 2016.[16] The combination product is approved as an adjunct to diet and exercise in patients with T2DM who have hyperglycemia despite basal insulin (less than 50 units a day) or liraglutide (less than or equal to 1.8 mg daily). The recommended starting dose is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given SC once daily with a maximal dose of 50 units (50 units insulin degludec and 1.8 mg liraglutide).

Three RCTs were used for the approval of insulin degludec/liraglutide. All trials had a duration of 26 weeks in a total of 1393 patients with T2DM.[16] In an open-label comparison between insulin degludec/liraglutide versus liraglutide 1.8 mg in patients on stable oral antidiabetic treatments, insulin degludec/liraglutide resulted in an A1C reduction of -1.31% compared to -0.36% in the liraglutide group (MD -0.95%, 95% CI, -1.15 to -0.75%; p<0.001). A second double-blind trial evaluated insulin degludec/liraglutide compared to insulin degludec once daily in patients taking metformin. Insulin degludec/liraglutide decreased A1C by 1.95% compared to a decrease of 1.05% for insulin degludec at week 26 (MD -0.89% (95% CI, -1.10 to -0.68%). Insulin degludec doses were kept to a similar level to determine contribution of liraglutide to the combination; therefore, the clinical effect of insulin degludec may have been diminished by titration restrictions. The last trial was an open-label comparison of insulin degludec/liraglutide versus insulin glargine in patients with T2DM who were on metformin. At 26 weeks, A1C decreased by 1.67% in patients taking insulin degludec/liraglutide compared to 1.16% in patients taking insulin glargine. Insulin degludec/liraglutide was found to be non-inferior to insulin glargine (MD -0.51%, 95% CI, -0.67 to -0.34; p<0.01).[16]

Canagliflozin/metformin ER (Invokamet XR)

A new combination product of canagliflozin and metformin ER was approved in 2016 for the treatment of patients with T2DM as an adjunct to diet and exercise in adults with T2DM.[17] Canagliflozin/metformin ER is available 4 different strengths: canagliflozin 50 mg with metformin ER 500 mg or 1000 mg and canagliflozin 150 mg with metformin ER 500 mg or 1000 mg. Maximum recommended dose is canagliflozin 300 mg daily/metformin ER 2000 mg daily. Approval of canagliflozin/metformin ER was based on previous study data that compared canagliflozin and metformin to other active treatments.

New Indications:

In August of this year liraglutide (Victoza®) labeling was changed to include the indication for reduction in the risk of major adverse CV events in adults with T2DM and established CV disease. The evidence was based on the results of the study by Marso, et al (Table 7) which found a reduction in the composite endpoint of CV death, non-fatal MI and non-fatal stroke at 36 months in patients taking liraglutide compared to placebo for an average of 3.5 years (ARR 1.9%/NNT 53).

Randomized Controlled Trials:

One thousand fifty-two potentially relevant clinical trials were evaluated from the literature search. After further review, only 4 trials were included (**Table 7**). Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trials are briefly described in the table below. The full abstracts are included in Appendix 2.

Table 7. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Outcomes	ARR/NNT	Quality Rating
1. Marso, et al (LEADER)[18] RCT, DB, MC, Phase 3	1. Liraglutide 1.8 mg SC (L)* ‡ 2. Placebo SC (P)* * In addition to standard care	Demographics: Age: 64 years Male: 64% A1C: 8.7% DM duration: 13 yrs. Established CV disease: 81.3% CKD: 72.4%	ITT: 1.4668 2.4672 PP: 1. 4529 2. 4513 Attrition:	**Composite of CV death, non-fatal MI, and non-fatal stroke at 36 months:** L: 608 (13.0%) P: 694 (14.9%) HR 0.87 (95% CI, 0.78 to 0.97; P<0.001 for noninferiority and P=0.01 for superiority)	ARR 1.9/53	**Internal Validity (Risk of Bias)**: Selection: (low) Patients were randomized in a 1:1 ratio by interactive voice/web response system. Performance: (unclear) Trial was double-blind design but no details on blinding were provided. Detection: (low) Outcome assessment was adjudicated in a blinded fashion by an external, independent, event-adjudication committee. Attrition: (low) Overall attrition was low and similar between groups. ITT analysis was used for all data. Discontinuations without an outcome

	‡ or the maximum tolerated dose 3.5 years	Any antidiabetic mediations: 88% Metformin use: 76% SU use: 50% <u>Key Inclusion Criteria</u>: - T2DM - A1C ≥ 7% - Currently on DM therapy or naïve to treatment - ≥ 50 yo + ≥1 CV coexisting condition or ≥ 60 years + ≥1 CV risk factor <u>Key Exclusion Criteria</u>: - T1DM - Use of GLP-1 RA, DPP-4 inhibitor, pramlintide, or rapid-acting insulin - MEC or medullary thyroid cancer - Acute coronary event or CV event within 14 days of screening and randomization	1. 139 (3.0%) 2. 159 (3.4%)	**Death from CV causes:** L: 219 (4.7%) vs. P: 278 (6.0%) HR 0.78 (95% CI, 0.66 to 0.93; P=0.007) **Death from any cause:** L: 381 (8.2%) vs. P: 447 (9.6%) HR 0.85 (95% CI, 0.74 to 0.97; P=0.02) **<u>Secondary Outcomes</u>** **Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or heart failure:** L: 948 (20.3%) vs. P: 1062 (22.7%) HR 0.88 (0.81 to 0.96; P=0.005) **Renal and retinal microvascular outcome:** L: 355 (7.6%) vs. P: 416 (8.9%) HR 0.84 (95% CI, 0.73 to 0.97; P= 0.02)	ARR 1.3/77 ARR 1.4/71 ARR 2.4/42 ARR 1.3/77	were censored from the day of last visit and any future outcomes were not included. <u>Publication:</u> (high) The study was funded by Novo Nordisk, the manufacturer of liraglutide, and the National Institutes of Health. **Applicability**: <u>Patients</u>: Patients were well matched at baseline for most characteristics. There were more patients in the placebo group that received SU, TZDs and insulin which may negatively influence cardiac effects which may bias results in favor of liraglutide. Patients were most likely older than the majority of patients with Medicaid. <u>Intervention</u>: FDA approved dose of liraglutide. Median daily study dose was 1.78 mg. <u>Comparator</u>: Matched placebo. <u>Outcomes</u>: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated with unacceptable levels of cardiac risk. <u>Setting</u>: Thirty-two countries and 410 centers. Thirty percent of patients were enrolled in North American treatment centers. **Analysis**: In patients with T2DM liraglutide was more effective at reducing the risk of death and death from CV causes in patients on standard therapy and had a history of CV disease. Subgroup analysis found that patients with an eGFR of < 60 ml/min/1.73 m^2 may be most likely to benefit from liraglutide.
2. Gadde, et al (DURATION-NEO-2)[19] RCT, OL, MC, Phase 3	1. Exenatide QWS-AI 2 mg SC (E) 2. sitagliptin 100 mg PO daily (S) 3. Placebo SC (P) 28 weeks	<u>Demographics</u>: Age: 53 years Male: 55% A1C: 8.5% DM duration: 8.4 yrs. White: 81% Body mass index: 31.7 kg/m2 <u>Key Inclusion Criteria</u>: - T2DM - A1C ≥ 7.1 -11.0%	<u>mITT</u> E: 181 S: 122 P: 61 Attrition: E: 26 (14%) S: 13 (11%) P: 14 (23%)	**Change in A1C at 28 weeks:** E: -1.13% S: -0.75% P: -0.40% E vs. S: LSM -0.38 (95% CI, -0.70 to -0.06) P = 0.021 E vs. P:	NA NA	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized in a 3:2:1 ratio by interactive web response system and stratified by A1C level. <u>Performance</u>: (high) Trial was open-label design. All staff, providers and patients were blinded to placebo or sitagliptin randomization. <u>Detection</u>: (low) Outcome assessment performed in a blinded manner. <u>Attrition</u>: (high) Attrition varied between groups and was substantial in the placebo group. <u>Publication:</u> Study funded by the manufacturer. **Applicability**:

		- FPG < 280 mg/dL - Currently on metformin ≥ 1500 mg for at least 2 months - BMI ≤ 45 kg/m2 <u>Key Exclusion Criteria</u>: - eGFR < 30 mL/min/1.73 m^2 - Use of GLP-1 RA, DPP-4 inhibitor, SU, TZD or weight loss medications within 3 months of screening - ≥ 2 episodes of severe hypoglycemia within previous 6 months		LSM -0.72 (95% CI, -1.15 to -0.30) P = 0.001 **<u>Secondary Outcomes</u>** **A1C < 7%:** E: 43.1% S: 32% P: 24.6% P < 0.05 for both comparisons (no CI provided) **Body weight:** E: -1.12 kg S: -1.19 kg P: 0.15 kg E vs. S: LSM 0.1 kg (95% CI, -0.70 to 0.9) P = 0.863 E vs. P: LSM -1.3 (95% CI, -2.3 to -0.2) P = 0.20	 E vs. S: ARR 11.1/9 E vs. P: ARR 18.5/5 NS NS	<u>Patients</u>: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. <u>Intervention</u>: FDA approved dose of exenatide weekly. <u>Comparator</u>: Sitagliptin 100 mg and placebo comparison appropriate. <u>Outcomes</u>: A1C is an accepted surrogate end point used for evaluating the efficacy of glucose lower therapy. Health outcomes, such as mortality, macrovascular and microvascular effects would be more helpful. <u>Setting</u>: Eighty-one treatment centers in the US. **Analysis**: In patients with T2DM exenatide used once weekly was more effective than sitagliptin and placebo w/ similar effect on weight. A majority of patients experienced anti-exenatide antibodies which reduced effect on A1C in patients w/ high levels.
3. Kernan, et al (IRIS)[20] RCT, DB, MC, Phase 3	1. Pioglitazone 45 mg daily (PZ) 2. Placebo (P) 4.8 years	<u>Demographics</u>: Age: 63 years Male: 66% Fasting glucose: 98 mg/dL (pre-diabetic) Stroke: 87% HTN: 71% <u>Key Inclusion Criteria</u>: - ≥ 40 years	<u>ITT</u> PZ: 1939 P: 1937 Attrition: PZ: 175 (9%) P: 151 (8%)	**Fatal or non-fatal stroke or MI:** PZ: 175 (9.0%) P: 228 (11.8%) HR 0.76; 95% CI, 0.62 to 0.93 P = 0.007 **<u>Secondary Outcomes</u>**	 ARR 2.8/36	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized in a 1:1 ratio by random permuted block design. <u>Performance</u>: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. <u>Detection</u>: (unclear) Endpoints will be assessed and adjudicated by three separate review committees for stroke, MI/CV and diabetes. Blinding was not described. <u>Attrition</u>: (low) Attrition was low in both groups. ITT was used for data analysis. <u>Publication:</u> (high) Authors had ties to industry. Funding provided by a grant from the National Institute of Neurological Disorders and Stroke.

		- Ischemic stroke or TIA - HOMA IR ≥3.0 <u>Key Exclusion Criteria</u>: - Diabetes diagnosis - NYHA Class III or IV - Liver disease - Pitting edema - Risk of bladder cancer		**All-cause mortality:** PZ: 136 (7%) P: 146 (7.5%) HR 0.93; 95% CI, 0.73 to 1.17 P = 0.53 **Fractures:** PZ: 99 (5.1%) P: 62 (3.2%) P = 0.003 **Diabetes Developed:** PZ: 73 (3.8%) P: 149 (7.7%) HR 0.48; 95% CI 0.33 to 0.69 P < 0.001	NS ARR 1.9/53 ARR 3.9/26	**Applicability**: <u>Patients</u>: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. <u>Intervention</u>: FDA approved dose of pioglitazone. <u>Comparator</u>: Placebo comparison appropriate in this population. <u>Outcomes</u>: Stroke is an important health outcome. <u>Setting</u>: Sixty-seven percent were from treatment centers in the US. **Analysis**: The results of this study shows a reduced risk of stroke in patients with pre-diabetes and history of stroke or TIA. The incidence of patients developing diabetes was low so applicability to patients with a diabetes diagnosis is low; however, due to lack of data in this area, the findings are still of clinical value.
3. Neal, et al (CANVAS Program)[21] RCT, DB, MC, Phase 3	1. Canagliflozin 100 mg and 300 mg daily*ł (C) 3. Placebo* (P) * Background antidiabetic therapy was permitted ł Results are a combination of two trials 188 weeks follow-up	<u>Demographics</u>: Age: 63 years Male: 64% Diabetes history: 13.5 years CV disease: 65.6% White: 78% Baseline A1C: 8.2% <u>Key Inclusion Criteria</u>: - Type 2 diabetes - A1C ≥ 7% or ≤ 10.5% - ≥ 30 years with symptomatic atherosclerotic CV disease OR ≥ 50 years with 2 or more CV risk factors - eGFR of > 30 ml/min/1.73 m^2 <u>Key Exclusion Criteria</u>: - T1DM - Fasting glucose > 270 mg/dL	<u>ITT</u> C: 5795 P: 4347 Attrition: C: 224 (3.9%) P: 184 (4.2%)	**Composite of CV death, non-fatal MI, and non-fatal stroke:** C: 585 (10.1%) P: 426 (9.8%) HR 0.86; 95% CI, 0.75 to 0.97 P < 0.001 for non-inferiority P=0.0158 for superiority **<u>Secondary Outcomes</u>** **All-cause mortality:** C: 400 (6.9%) P: 281 (6.5%) HR 0.87 (95% CI, 0.74 to 1.01) P = 0.24 **Death from CV causes:** C: 268 (4.6%) P: 185 (4.3%) HR 0.87 (95% CI, 0.72 to 1.06) P = NS	ARR 0.3%/333 NS NS	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized thru an interactive web-based response system with the use of a computer-generated randomization schedule. <u>Performance</u>: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. <u>Detection</u>: (low) Endpoints were assessed and adjudicated by separate review committees for all major cardiac evens, hospitalizations for heart failure, renal outcomes, and death who were blinded to treatment assignment. <u>Attrition</u>: (low) Attrition was low in both groups. ITT was used for data analysis. <u>Publication:</u> (low) Industry funded study. Endpoints were reported as prespecified. **Applicability**: <u>Patients</u>: A majority (71.4%) of patients took canagliflozin 300 mg in CANVAS-R and 55% in CANVAS Program were randomized to 300 mg of canagliflozin. Sixty-five percent of patients had a history of symptomatic atherosclerotic CV disease and 35% had a least 2 risk factors for CV disease. A majority of patients were on other antidiabetic and cardioprotective treatments at baseline. <u>Intervention</u>: FDA approved dose of canagliflozin. <u>Comparator</u>: Placebo comparison appropriate in this population. <u>Outcomes</u>: CV outcomes are more common in this population compared to patients without diabetes therefore, the CV impact of antidiabetic treatments are of particular importance. <u>Setting</u>: Thirty countries and 667 centers.

		- Fasting glucose <110 mg/dL and taking insulin or a SU at baseline - History of ≥1 severe hypoglycemia episode in the last 6 months - eGFR < 30 mL/min/1.73 m^2 -NYHA Class IV cardiac disease, MI, unstable angina or planned revascularization		**Progression to albuminuria:** C: 1341 (26%) P: 1114 (29.0%) (HR 0.73; 95% CI, 0.67 to 0.79)	NS	Safety Warning: A higher number of patients who received canagliflozin had amputations compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75) (ARR not provided). **Analysis**: In patients with CV disease or who are high risk of CV disease, canagliflozin reduced the composite of CV endpoints. Patients at high risk of CV disease who are also on cardioprotective medications (e.g., ACE inhibitors) may receive cardiovascular benefit from canagliflozin but also have a higher risk of amputations.

Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; CKD = chronic kidney disease; CV = cardiovascular; DB = double-blind; DD = double-dummy; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; FAS = full analysis set; FPG = fasting plasma glucose; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance index; HR = hazard ratio; HTN = hypertension; ITT = intention to treat; kg = kilogram; LSMD = least-squares mean difference; MEC = multiple endocrine neoplasia; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; NYHA = New York Heart Association; PO = by mouth; PP = per protocol; QWS-AI = once-weekly suspension for autoinjection; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; yo = years old.

References:

1. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. *Annals of Internal Medicine*. 2016;164(11):740-751. doi:10.7326/M15-2650.

2. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA*. 2016;316(3):313-324. doi:10.1001/jama.2016.9400.

3. New Drugs for Type 2 Diabetes: Second-Line Therapy – Recommendations Report - TR0012_T2DM_Final_Recommendations.pdf. https://www.cadth.ca/sites/default/files/pdf/TR0012_T2DM_Final_Recommendations.pdf. Accessed June 21, 2017.

4. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017;166(4):279-290. doi:10.7326/M16-1860.

5. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment. Sec 8. In Standards of Medical Care in Diabetes - 2017. *Diabetes Care*. 2017;40(Suppl 1):S64-S74. doi:10.2337/dc17-S011.

6. Dapagliflozin in triple therapy for treating type 2 diabetes. Technology Appraisal Guidance. November, 2016. Available at: https://www.nice.org.uk/guidance/ta418. Accessed May 3, 2017.

7. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. Technology Appraisal Guidance. May 2016. Available at: https://www.nice.org.uk/guidance/TA390/chapter/1-Recommendations. Accessed May 3, 2017.

8. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Clinical Guideline Update. December 2015. Available at: https://www.nice.org.uk/guidance/ng28. Accessed May 15, 2017.

9. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement By The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. *Endocr Pract*. 2017;23(2):207-238. doi:10.4158/EP161682.CS.

10. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

11. FDA Drug Safety Communication. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). https://www.fda.gov/drugs/drugsafety/ucm557507.htm. Accessed May 16, 2017.

12. FDA Drug Safety Communication. FDA announced that a safety review has found type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure. https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm497914.htm. Accessed May 15, 2017.

Author: K. Sentena Date: September 2017

13. Metformin-containing Drugs: Drug Safety Communication - Revised Warnings for Certain Patients With Reduced Kidney Function. https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm494829.htm. Accessed May 3, 2017.

14. Soliqua Prescribing Information. Sanofi-aventis U.S. LLC; Bridgewater, NJ; 2016.

15. Qtern Prescribing Information. AstraZeneca Pharmaceuticals LP; 2017.

16. Xultrophy Prescribing Information. NovoNordisk Inc. Plainsboro, NJ; 2016.

17. Invokamet XR Prescribing Information. Janssen Pharmaceuticals, Inc. Titusville, NJ; 2016.

18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *Journal of Medicine*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.

19. Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P, on behalf of the DURATION-NEO-2 study investigators. Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study. *Diabetes Obes Metab*. March 2017:n/a-n/a. doi:10.1111/dom.12908.

20. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. *Journal of Medicine*. 2016;374(14):1321-1331. doi:10.1056/NEJMoa1506930.

21. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. June 2017. doi:10.1056/NEJMoa1611925.

22. Vos RC, van Avendonk MJ, Jansen H, et al. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2016. doi:10.1002/14651858.CD006992.pub2.

23. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2017. doi:10.1002/14651858.CD011967.pub2.

24. Lo C, Jun M, Badve SV, et al. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2017. doi:10.1002/14651858.CD009966.pub2.

25. Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments: A Systematic Review and Network Meta-analysis. [Review]. *Annals of Internal Medicine*. 2016;164(2):102-113. doi:10.7326/M15-1432.

26. Monami M, Dicembrini I, Mannucci E. Effects of SGLT-2 inhibitors on mortality and cardiovascular events: a comprehensive meta-analysis of randomized controlled trials. [Review][Erratum appears in Acta Diabetol. 2017 Jan;54(1):37-38; PMID: 27730308]. *Acta Diabetologica*. 2017;54(1):19-36. doi:10.1007/s00592-016-0892-7.

27. Tang H, Li D, Zhang J, et al. Sodium-glucose co-transporter-2 inhibitors and risk of adverse renal outcomes among patients with type 2 diabetes: A network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. March 2017:n/a-n/a. doi:10.1111/dom.12917.

28. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19(4):524-536. doi:10.1111/dom.12849.

29. Lee M, Saver JL, Liao H-W, Lin C-H, Ovbiagele B. Pioglitazone for Secondary Stroke Prevention: A Systematic Review and Meta-Analysis. [Review]. *Stroke*. 2017;48(2):388-393. doi:10.1161/STROKEAHA.116.013977.

30. Rehman MB, Tudrej BV, Soustre J, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: Meta-analysis of placebo-controlled randomized clinical trials. *Diabetes & Metabolism*. 2017;43(1):48-58. doi:10.1016/j.diabet.2016.09.005.

31. Kongwatcharapong J, Dilokthornsakul P, Nathisuwan S, Phrommintikul A, Chaiyakunapruk N. Effect of dipeptidyl peptidase-4 inhibitors on heart failure: A meta-analysis of randomized clinical trials. [Review]. *Journal of Cardiology*. May 2016:88-95. doi:10.1016/j.ijcard.2016.02.146.

32. Tang HL, Li DD, Zhang JJ, et al. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2016;18(12):1199-1206. doi:10.1111/dom.12742

33. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149. doi:10.2337/dc14-2441.

34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854-865.

35. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373(9681):2125-2135. doi:10.1016/S0140-6736(09)60953-3.

36. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279-1289. doi:10.1016/S0140-6736(05)67528-9.

37. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.

38. White W, Cannon C, Heller S. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-1335.

39. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720.

40. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232-242. doi:10.1056/NEJMoa1501352.

41. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225.

42. Oregon Health Authorit. Oreogn Diabetes Report - A report on the burden of diabetes in Oregon and progress on the 2009 strategic plan to slow the rate of diabetes. January 2015. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf.

43. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. 2010. http://www.cdc.gov/media/pressrel/2010/r101022.html. Accessed July 23, 2013.

44. Standards of medical care in diabetes--2015: summary of revisions. *Diabetes Care*. 2015;38 Suppl:S4. doi:10.2337/dc15-S003.

45. Redmon B, Caccamo D, Flavin P. Diagnosis and management of type 2 diabetes mellitus in adults. *Institute for Clincal Systems Improvement*. July 2014. https://www.icis.org/_asset/3rrm36/Diabetes.pdf.

46. American Diabetes Association. Standards of Medical Care in Diabetes—2015: Summary of Revisions. *Dia Care*. 2015;38(Supplement 1):S4-S4. doi:10.2337/dc15-S003.

Appendix 1: Current Status on Preferred Drug List

Diabetes, Dipeptidyl Peptidase-4 Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**JANUMET**	**SITAGLIPTIN PHOS/METFORMIN HCL**	**Y**
ORAL	**TABLET**	**JANUVIA**	**SITAGLIPTIN PHOSPHATE**	**Y**
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN /METFORMIN HCL	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN MONOHYDRATE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N

Diabetes, GLP-1 Receptor Agonists & Amylin Analogs

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN INJCTR	SYMLINPEN 120	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	SYMLINPEN 60	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	BYETTA	EXENATIDE	N
SUB-Q	PEN INJCTR	VICTOZA 2-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	XULTROPHY	INSULIN DEGLUDEC/LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-Q	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-Q	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-Q	PEN INJCTR	TRULICITY	DULAGLUTIDE	N
SUB-Q	PEN INJCTR	ADLYXIN	LIXISENATIDE	N
SUB-Q	PEN INJCTR	SOLIQUA	INSULIN GLARGINE/LIXISENATIDE	N

Diabetes, Oral Hypoglycemic

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**DIABETA**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLYBURIDE**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLIPIZIDE**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**GLUCOTROL**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**AMARYL**	**GLIMEPIRIDE**	**Y**
ORAL	**TABLET**	**GLIMEPIRIDE**	**GLIMEPIRIDE**	**Y**
ORAL	**TAB ER 24H**	**GLUCOPHAGE XR**	**METFORMIN HCL**	**Y**
ORAL	**TAB ER 24H**	**METFORMIN HCL ER**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**GLUCOPHAGE**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**METFORMIN HCL**	**METFORMIN HCL**	**Y**
ORAL	TABLET	TOLBUTAMIDE	TOLBUTAMIDE	N
ORAL	TABLET	CHLORPROPAMIDE	CHLORPROPAMIDE	N
ORAL	TABLET	TOLAZAMIDE	TOLAZAMIDE	N
ORAL	TAB ER 24	GLIPIZIDE ER	GLIPIZIDE	N
ORAL	TAB ER 24	GLIPIZIDE XL	GLIPIZIDE	N
ORAL	TAB ER 24	GLUCOTROL XL	GLIPIZIDE	N
ORAL	TABLET	GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	GLYNASE	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	PRANDIN	REPAGLINIDE	N
ORAL	TABLET	REPAGLINIDE	REPAGLINIDE	N
ORAL	TABLET	NATEGLINIDE	NATEGLINIDE	N
ORAL	TABLET	STARLIX	NATEGLINIDE	N
ORAL	SOLUTION	RIOMET	METFORMIN HCL	N
ORAL	TAB ER 24	FORTAMET	METFORMIN HCL	N
ORAL	TAB ER 24	METFORMIN HCL ER	METFORMIN HCL	N
ORAL	TABERGR24H	GLUMETZA	METFORMIN HCL	N
ORAL	TABLET	ACARBOSE	ACARBOSE	N
ORAL	TABLET	PRECOSE	ACARBOSE	N
ORAL	TABLET	GLYSET	MIGLITOL	N
ORAL	TABLET	GLUCOVANCE	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLYBURIDE-METFORMIN	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	N
ORAL	TABLET	PRANDIMET	REPAGLINIDE/METFORMIN HCL	N

Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	QTERN	DAPAGLIFLOZIN/SAXAGLIPTIN	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY	EMPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN HCL	N

Diabetes, Thiazolidinediones

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**PIOGLITAZONE HCL**	**PIOGLITAZONE HCL**	**Y**
ORAL	TABLET	AVANDIA	ROSIGLITAZONE MALEATE	N
ORAL	TABLET	AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	N
ORAL	TABLET	DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	N
ORAL	TABLET	PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	N
ORAL	TBMP 24HR	ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	N

Appendix 2: Abstracts of Clinical Trials

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators.

BACKGROUND:

The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS:

In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS:

A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS:

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.).

Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study.

Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P; DURATION-NEO-2 study investigators.

AIMS:

Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors treat type 2 diabetes through incretin-signaling pathways. This study compared the efficacy and safety of the glucagon-like peptide-1 receptor agonist exenatide once-weekly (Miglyol) suspension for autoinjection (QWS-AI) with the dipeptidyl peptidase-4 inhibitor sitagliptin or placebo.

MATERIALS AND METHODS:

In this open-label, multicentre study of patients with type 2 diabetes who had suboptimal glycaemic control on metformin monotherapy, 365 patients were randomized to receive exenatide 2.0 mg QWS-AI, sitagliptin 100 mg once daily or oral placebo (3:2:1 ratio). The primary endpoint was change in glycated hemoglobin (HbA1c) from baseline to 28 weeks.

RESULTS:
At 28 weeks, exenatide QWS-AI significantly reduced HbA1c from baseline compared to sitagliptin (-1.13% vs -0.75% [baseline values, 8.42% and 8.50%, respectively]; P = .02) and placebo (-0.40% [baseline value, 8.50%]; P = .001). More exenatide QWS-AI-treated patients achieved HbA1c <7.0% than did sitagliptin- or placebo-treated patients (43.1% vs 32.0% and 24.6%; both P < .05). Exenatide QWS-AI and sitagliptin reduced fasting plasma glucose from baseline to 28 weeks (-21.3 and -11.3 mg/dL) vs placebo (+9.6 mg/dL), with no significant difference between the 2 active treatments. Body weight decreased with both active treatments (-1.12 and -1.19 kg), but not with placebo (+0.15 kg). No improvement in blood pressure was observed in any group. The most common adverse events with exenatide QWS-AI were gastrointestinal events and injection-site reactions.
CONCLUSIONS:
This study demonstrated that exenatide QWS-AI reduced HbA1c more than sitagliptin or placebo and was well tolerated.

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack.
Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR; IRIS Trial Investigators.
Abstract
BACKGROUND:
Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.
METHODS:
In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.
RESULTS:
By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).
CONCLUSIONS:
In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2017
Search Strategy:

#	Searches	Results
1	Sitagliptin Phosphate/	970
2	alogliptin.mp.	264
3	saxagliptin.mp.	380
4	linagliptin.mp. or Linagliptin/	342
5	pramlintide.mp.	303
6	exenatide.mp.	2168
7	liraglutide.mp. or Liraglutide/	1214
8	albiglutide.mp.	68
9	dulaglutide.mp.	79
10	glyburide.mp. or Glyburide/	4041
11	glipizide.mp. or Glipizide/	602
12	glimepiride.mp.	964
13	Metformin/ or metformin.mp.	12206
14	tolbutamide.mp. or Tolbutamide/	1662
15	chlorpropamide.mp. or Chlorpropamide/	218
16	tolazamide.mp. or Tolazamide/	22
17	repaglinide.mp.	633
18	nateglinide.mp.	473
19	acarbose.mp. or Acarbose/	1595
20	miglitol.mp.	195
21	dapagliflozin.mp.	285
22	canagliflozin.mp. or Canagliflozin/	286
23	empagliflozin.mp.	277
24	pioglitazone.mp.	4165
25	rosiglitazone.mp.	5289
26	lixisenatide.mp.	133
27	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 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	31226

Author: K. Sentena Date: September 2017

28	limit 27 to (english language and humans and yr="2015 -Current")	3214
29	limit 28 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	1052

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 DPP-4 inhibitors

Covered Alternatives:
- Preferred alternatives 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. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #4	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. 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: 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 as doses advanced, 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/DUR Review: *7/17 (KS), 9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *1/15; 9/14; 1/14; 2/13*

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 GLP-1 receptor agonists

Covered Alternatives:

- Preferred alternatives 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 and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the patient currently taking insulin?	Yes: Go to #6	No: Approve for up to 12 months
6. Is the patient requesting exenatide, liraglutide, ~~or~~ albiglutide, dulaglutide or lixisenatide (including combination products) and using basal insulin?	Yes: Approve for up to 12 months	No: Go to #7
7. Is the patient requesting dulaglutide and using prandial insulin?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.

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 as doses advanced, 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/DUR Review: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *2/15; 1/14*

Sodium-Glucose Co-Transporter-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:
- Preferred alternatives 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 Type 2 diabetes mellitus?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #6
6. Has the patient tried and failed all of the following drugs, or have contraindications to these drugs? • Insulin • Thiazolidinedione • DPP-4 inhibitor • GLP-1 agonist • Amylin analog	Yes: Approve for up to 6 months.	No: Pass to RPh; deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for up to 6 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/DUR Review: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13*
Implementation: *2/15*