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Class Update: Non-insulin Antidiabetic Agents

Month/Year of Review: September 2015
Last Review: September 2014
End date of literature search: June 2015

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

Reasons for the Review:
The purpose of this review is to evaluate new evidence on each of the antidiabetic agents, and if appropriate, update therapy recommendations and therapy placement on the Oregon Health Plan (OHP) Preferred Drug List (PDL). Prior authorization criteria for each class will be reviewed and revised based on the evidence.

Research Questions:
1. Is there any new comparative evidence for non-insulin diabetes treatments pertaining to important intermediate (e.g., hemoglobin A1C [A1C]) and long-term clinical outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new evidence about comparative harms among the available non-insulin diabetes treatments?
3. Are there subpopulations of patients with diabetes mellitus for which specific therapies may be more effective or associated with less harm?

Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for type 2 diabetes mellitus (T2DM). Evidence-based recommendations in new clinical practice guidelines from the American Diabetes Association (ADA),[1] Institute for Clinical Systems Improvement (ICIS),[2] and the National Institute for Health and Care Excellence (NICE),[4] American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)[5,6] and a systematic review draft report from the Agency for Healthcare Research and Quality (AHRQ),[3] support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL) (see Appendix 2).
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a dipeptidyl peptidase-4 (DPP-4) inhibitor, or metformin plus a sodium-glucose cotransporter-2 (SGLT-2) inhibitor have similar rates of all-cause mortality based on one systematic review.[3]
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of hemoglobin A1c (A1C) based on one systematic review.

Author: Kathy Sentena Date: March 2015

- 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).[3,14]
- 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. Data from the EXAMINE and TECOS found these drugs to be non-inferior to placebo when a composite of CV outcomes were evaluated.[9,10]
- Moderate quality evidence from two meta-analyses showed a statistically significant increase in HF outcomes with DPP-4 inhibitors compared to placebo or active treatment.[10,11] Studies included in the meta-analyses were of short duration and the majority of included outcomes were limited to 2 trials only [SAVORTIMI53 (saxagliptin) and EXAMINE (alogliptin)].
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews.[3,13,14] 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).[13]
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease based on one systematic review. Evidence from this review suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2) without increased risk of lactic acidosis, based on evidence from primarily non-clinical trial data.[8] The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.[8]
- In December of 2014 liraglutide injection (Saxenda) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity.[15] Treatments for weight loss are not funded by the OHP.

Recommendations:

- Make exenatide (Byetta®) a preferred agent but subject to current prior authorization (PA) for GLP1 receptor antagonists.
- Make empagliflozin/linagliptin (Glyxambi®) non-preferred drug subject to current PA for SGLT-2 inhibitors.
- Reorganize PDL classes for non-insulin antidiabetic agents to the following:
    - DPP-4 Inhibitors
    - GLP-1 Receptor Antagonists
    - Miscellaneous Antidiabetic Agents (metformin, pramlintide, meglitinides, others).
    - SGLT-2 Inhibitors
    - Sulfonylureas
    - Thiazolidinediones
- Remove clinical PA for pramlintide due to low overall utilization and current FDA-mandated Risk Evaluation Mitigation Strategy (REMS) already in place to promote safe use through education.
- Modify SGLT-2 inhibitor clinical PA to require monitoring renal function every 6 months.
- Continue clinical PA criteria for all DPP-4 inhibitors and all GLP-1 RAs as shown in **Appendix 4**.

Previous Conclusions:

- A recent systematic review found insufficient evidence to compare health outcomes of the newer diabetes medications and combinations.[16] Intermediate endpoints, including hemoglobin A1c (A1c) and weight, found low SOE that exenatide XR weekly was superior to exenatide daily, liraglutide was superior to exenatide and sitagliptin, exenatide was superior to sitagliptin, and canagliflozin was similar in efficacy to metformin. In a comparison between metformin and dapagliflozin there was low SOE of a trend favoring dapagliflozin for HbA1c lowering, but it was not deemed clinically significant, -0.11% and -0.12%,

respectively. There was moderate SOE that metformin was superior to linagliptin, alogliptin and sitagliptin. The addition of metformin to alogliptin, linagliptin or sitagliptin resulted in greater glucose lowering than monotherapy dose comparisons.[16]

- In a phase 4, placebo-controlled, randomized trial of over 16,000 patients there was moderate evidence that saxagliptin therapy neither conferred a CV risk or benefit compared to placebo (HR 1.00 (95% CI, 0.89 to 1.12, P<0.001 for noninferiority). Hospitalization rates in patients with heart failure were found to be higher in those patients treated with saxagliptin compared to placebo (HR 1.27 [95% CI, 1.07 to 1.51, P=0.007]).[17]
- 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%]).[18] 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]).[18]
- Oral hypoglycemic scan summary from the Drug Effectiveness Review Project (DERP) found limited new evidence since the last review; no further review or research needed.[19]

Previous Recommendations:

- The current PA criteria align with the conclusions of a recent systematic review by the DERP. No changes to the PDL are recommended.
- Continue to require a prior authorization for saxagliptin therapy. No changes to the PDL are recommended.
- Evidence on SGLT2 inhibitors supports the current PA criteria. Dapagliflozin should be added to the criteria and made non-preferred. No changes to the PDL are recommended.
- There is no new evidence on the comparative efficacy/effectiveness or safety for the oral hypoglycemic PDL class. Evaluate comparative costs in executive session

Reasons for the Review:

The purpose of this review is to evaluate new evidence on each of the antidiabetic agents, and if appropriate, update therapy recommendations and therapy placement on the Oregon Health Plan (OHP) PDL. Prior authorization criteria for each class will be reviewed and revised based on the evidence.

Background:

Type 2 diabetes mellitus (T2DM) is a prevalent disease affecting an estimated 25.6 million people in the United States, based on 2013 data.[20] In Oregon, it is estimated that 287,000 adults have T2DM, in which 38,000 are estimated to be OHP members.[21] 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.[21] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[22] 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.[1,2] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and the addition of pharmacotherapy for persistent hyperglycemia.[1,2] 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.[1,2] Classes of anti-hyperglycemic agents (AHA) 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.

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 AHA therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well.[1,2] Available data for most newer drugs are limited to short-term studies, which prevents the assessment of the durability of most available AHAs to control glucose levels long-term and to compare their impact on

microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. 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) trial.[1] UKPDS data also shows reduced incidence of microvascular risk with SU therapy and insulin.

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 for Adults with Type 2 Diabetes: An Update Focused on Monotherapy and Add-On Therapy to Metformin – Draft

A report in process from the Agency for Healthcare Research and Quality (AHRQ) reviews the effectiveness and safety of monotherapy and metformin-based combination therapy for adults with T2DM.[3] Studies on therapy with metformin, SUs, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors or metformin combination therapies were included. Outcomes of interest were the following: intermediate (e.g., A1C), long-term clinical outcomes (e.g., all-cause mortality), and safety (e.g., hypoglycemia).

Two hundred twenty nine studies were included in the analysis. The correlation of microvascular disease to A1C levels makes this outcome particularly important. Metformin, SU and TZDs were shown to have similar ability to lower A1C.[3] Metformin is associated with superior A1C lowering than DPP-4 inhibitors (absolute difference of 0.4%). Monotherapy comparisons were based on high strength of evidence (SOE). Most combination therapies (metformin plus one other agent) lower A1C to the same extent, by an additional 0.7% to 1% (intermediate SOE). However, the combination of metformin plus a GLP-1 RA decreased A1C more than metformin plus a DPP-4 inhibitor. No other combination therapy comparisons demonstrated A1C changes that were either clinically meaningful or statistically significant.

Metformin use was shown to result in less weight gain with a difference of approximately 2.5 kg compared to treatment with a SU or TZD (high SOE). Use of a TZD results in a weight difference of +2.5 kg compared to use of a DPP-4 inhibitor and +3.5 kg compared to use of a GLP-1 RA. Weight loss favored metformin when compared to DPP-4 inhibitors and SU were shown to have less associated weight gain compared to TZDs. SGLT-2 inhibitors decrease weight more than metformin and DPP-4 inhibitors (moderate SOE). Metformin plus a GLP-1 RA and metformin plus a SGLT-2 inhibitor were associated with less weight gain compared to metformin plus a DPP-4 inhibitor. Metformin plus SU were shown to have less of an effect on weight compared to metformin and insulin.

There is moderate to high evidence that the SGLT-2 inhibitors and the GLP-1 RAs decrease systolic blood pressure by up to 5 mmHg and 3 mmHg, respectively.[3] All-cause mortality data are primarily based on studies lasting only 1 year or less, and many agents have insufficient data to make conclusions regarding mortality. All-cause mortality rates are similar between metformin and pioglitazone monotherapy, and for the combinations of metformin/DPP-4 inhibitor and metformin/SGLT-2 inhibitor, based on moderate to high SOE. There are limited data on CV morbidity and CV mortality for most treatments. Metformin use is associated with decreased CV morbidity and mortality compared to SU use. Metformin and pioglitazone have similar rates of CV morbidity. No conclusions on microvascular outcomes, such as retinopathy, nephropathy and neuropathy can be made due to insufficient evidence.

SU therapy is associated with more mild, moderate and total (risk of any type of) hypoglycemia compared to all other treatments. SU therapy had a1.5-fold risk for more severe hypoglycemia compared to TZDs and metformin.[3] The combination of metformin/DPP-4 inhibitor or metformin/SGLT-2 inhibitor is associated with less risk of severe hypoglycemia compared to metformin combined with a SU (moderate SOE). The DPP-4 inhibitors have little risk for severe hypoglycemia events when compared to metformin monotherapy or metformin/TZD therapy (moderate SOE). Gastrointestinal side effects are more common with metformin and GLP-1 RAs (moderate to high SOE). Congestive heart failure is more common with TZDs compared to metformin or SU (low SOE). Risk of pancreatitis is similar between metformin and the combination of metformin/DPP-4 inhibitor, although rare in both groups. Metformin plus a SGLT-2 inhibitor is associated with a 3-fold increase in genital mycotic infections compared to metformin alone, and 6-fold higher risk when compared to metformin plus a SU (high SOE).[3] The risk of urinary tract infections is similar between SGLT-2 inhibitors alone and in combination therapy when compared to metformin or metformin plus a SU (moderate to high SOE).

Metformin in Patients with Type 2 Diabetes and Kidney Disease

A meta-analysis on the risk of lactic acidosis in patients taking metformin with kidney disease included sixty-five studies on the following: pharmacokinetic/metabolic investigations, case series, cross-sectional, observational, pharmacosurveillance studies, meta-analyses and a clinical trial.[8] Metformin concentrations were found to remain in safe therapeutic levels in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2), despite reduced metformin clearance. Additionally, circulating lactate levels were normal in patients with kidney dysfunction receiving metformin. Limited data suggests that patients who developed metformin-related lactic acidosis previously had normal renal function, questioning the utility of using renal function values as a determinant for appropriate use.[8] The incidence of lactic acidosis ranges from 3 per 100,000 person-years to 10 per 100,000 person-years in patients taking metformin, which is similar to the overall diabetic population. Observational studies have shown the use of metformin in patients with renal dysfunction have improved macrovascular outcomes. However, there is insufficient evidence from randomized controlled trials in this population. The authors recommend a revised dosing strategy to metformin labeling that outlines use in patients with CKD stage 1-3B (eGFR ≥90 to 30 mL/min per 1.73 m^2).

Dipeptidyl Peptidase-4 Inhibitors and Heart Failure: A Meta-analysis of Randomized Clinical Trials

The evidence that saxagliptin increased hospitalizations due to heart failure has prompted additional research of the DPP-4 inhibitors to determine if this is a class effect.[11] The meta-analysis by Monami, et al included 84 randomized clinical trials in patients with T2DM lasting at least 24 weeks. Included treatments were the following: vildagliptin, saxagliptin, sitagliptin, alogliptin, linagliptin and dutogliptin. Of the 84 trials, 45 reported no HF events and therefore 37 trials were included in the primary analysis. Eighty-seven percent of the HF events were from SAVOR-TIMI53 (saxagliptin) and EXAMINE (alogliptin).
In placebo and active comparison studies, the risk of acute HF was higher in the DPP-4 inhibitor-treated groups (OR: 1.19 (95% CI, 1.03 to 1.37; p=0.015). When trials with and without HF events were analyzed, the incidence of HF was the same for DPP-4 inhibitors and comparators (0.9%). When individual DPP-4 inhibitors were analyzed separately, only saxagliptin demonstrated a significant increase in HF risk.

Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Outcomes: Meta-analysis of Randomized Clinical Trials with 55,141 Participants

A meta-analysis and systematic review studied the CV safety and efficacy of DPP-4 inhibitors.[12] Fifty trials with a mean follow-up of 45.3 weeks and minimal study period of 24 weeks provided data on 55,141 patients. Alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin were the included search terms. Studies meeting the inclusion criteria had to have at least one CV outcome, a minimum of 100 patients, a randomized study design and in participants with T2DM. All-cause mortality, CV mortality, acute coronary syndrome or strokes were similar for DPP-4 inhibitors and comparators (placebo and active). The incidence in heart failure outcomes was significantly higher with DPP-4 inhibitors than with comparators (RR 1.16; 95% CI, 1.01 to 1.33; p=0.04). Like with other meta-analyses, the majority of HF outcomes came from SAVORTIMI53 (66.2%) and EXAMINE (21.3%).

A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events: comparison of glyburide with other secretagogues and with insulin

This systematic review was done to investigate the hypoglycemia and cardiovascular risk of glyburide.[13] Twenty one studies lasting 1 month to 10 years were included in the analysis. Glyburide was compared with other secretagogues and with insulin, in separate analyses. In a subgroup analysis glyburide was compared to other SUs. Glyburide was found to have a higher risk of at least one episode of hypoglycemia compared to other secretagogues (RR 1.52, 95% CI 1.21 to 1.92). Results of the comparison of glyburide to other SU demonstrated similar results with a RR of 1.83 (95% CI 1.35 to 2.49). Total hypoglycemia episodes were also higher with gluyburide compared to other secretagogues, however there was high heterogeneity between the studies. Weight, A1c and cardiovascular events were not statistically different between glyburide and comparators.

Effectiveness and Safety of Glimepiride and iDPP4, Associated with Metformin in Second Line Pharmacotherapy of Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis

A systematic review and meta-analysis was done to analyze trial data on the efficacy and safety of combination of DPP-4 inhibitors/metformin compared to glimepiride/metformin as second line therapy in the treatment patients with T2DM.[14] Four studies involving 5637 patients with endpoints presented as primary variables (no composite endpoints) were included in the review. Three of the four studies were non-inferiority design. Participants were a mean age of 58 years, mean weight o f 87 kg, and mean A1c of 7.5%. Sitagliptin, vildagliptin, and linagliptin were the DPP-4 inhibitors included in the study. Comparisons favored glimepiride/metformin use compared to DPP-4 inhibitors/metformin for A1C lowering [weighted mean difference (WMD) -0.12 (CI-0.16 to -0.07). More patients taking the glimepiride combination met A1C goals <7% compared to DPP-4 inhibitors combination. Dropouts due lack of effectiveness was lower with glimepiride than DPP-4 inhibitors combinations and need for rescue treatment was 20% less in the glimepiride group. Weight loss of -0.23 to -1.4 kg was seen with DDP-4 inhibitor combinations compared to weight gain with glimepiride combinations, ranging from 0.73 to 1.76 kg. Adverse effects were high with combinations of glimepiride and DPP-4 inhibitors, 78.3% and 71.9%, respectively. The risk of hypoglycemia was higher with glimepiride combination therapy compared to DPP-4 inhibitors (OR 5.07, 95% CI 4.33 to 5.93), mostly due to mild to moderate episodes of hypoglycemia. Discontinuations due to adverse events was higher with glimepiride combinations compared to DPP-4 inhibitors (OR 1.34, 95% CI 1.17 to 1.81).

New Guidelines:

Standards of Medical Care in Diabetes – 2015: Summary of Revisions

The annual update of the *Clinical Practice Recommendations* by the ADA have been renamed *Standards of Medical Care in Diabetes.*[1] Changes relevant to our update include the inclusion of all available therapies for diabetes management. As with previous recommendations, initial treatment with metformin should be used if pharmacotherapy is warranted. Patients presenting with markedly elevated blood glucose levels, A1C or severe symptoms should be considered for insulin therapy alone or in combination with other agents. If combination therapy is required, data suggests that all non-insulin therapy combinations lower A1C

by a similar level of approximately 0.9-1.1%.[1] Suggested add-ons to metformin include: SUs, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs or basal insulin. Patients unable to take SU therapy due to irregular meal schedules or hypoglycemia may benefit from a rapid-acting secretagogue (meglitinides). Other antidiabetic agents that aren't routinely recommended due to efficacy or tolerability issues are: α-glucosidase inhibitors, colesevelam, bromocriptine, or pramlitide. A patient-centered approach is emphasized, factoring in efficacy, side effects, cost, hypoglycemia risk, weight, comorbidities and patient preferences.

Institute for Clinical Systems Improvement (ICSI) – Diagnosis and Management of Type 2 Diabetes Mellitus in Adults

In July of 2014 the Institute for Clinical Systems Improvement (ICIS) published guidance on the management of adults with T2DM.[2] Guideline recommendations are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Metformin and insulin were the only glucose lowering therapies specifically included in guidelines. Metformin is strongly recommended based on high strength of evidence as first-line therapy. Failure to obtain A1C goals with metformin should have treatment modified. No additional oral treatment recommendations are discussed. Insulin therapy for hospitalized patients is discussed but not graded.

NICE Guidance – Empagliflozin in Combination Therapy for Treating Type 2 Diabetes

The National Institute for Health and Care Excellence (NICE) reviewed the efficacy and safety data of empagliflozin use in combination with other treatments for patients with T2DM.[4] NICE recommends empagliflozin as dual therapy for patients if a SU is contraindicated or not tolerated or the person is at significant risk of hypoglycemia. The use of empagliflozin as part of a triple therapy regimen is recommended for patients taking metformin and a SU, or metformin and a TZD. Empagliflozin may also be offered as an option with insulin, with or without other antidiabetic agents. The guidance suggests that empagliflozin would be best suited for overweight patients with good renal function requiring assistance in lowering blood glucose levels and not susceptible to genitourinary infections. Meta-analysis data show the clinical effectiveness of empagliflozin was similar to other SGLT-2 inhibitors and sitagliptin.

AACE/ACE – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan – 2015

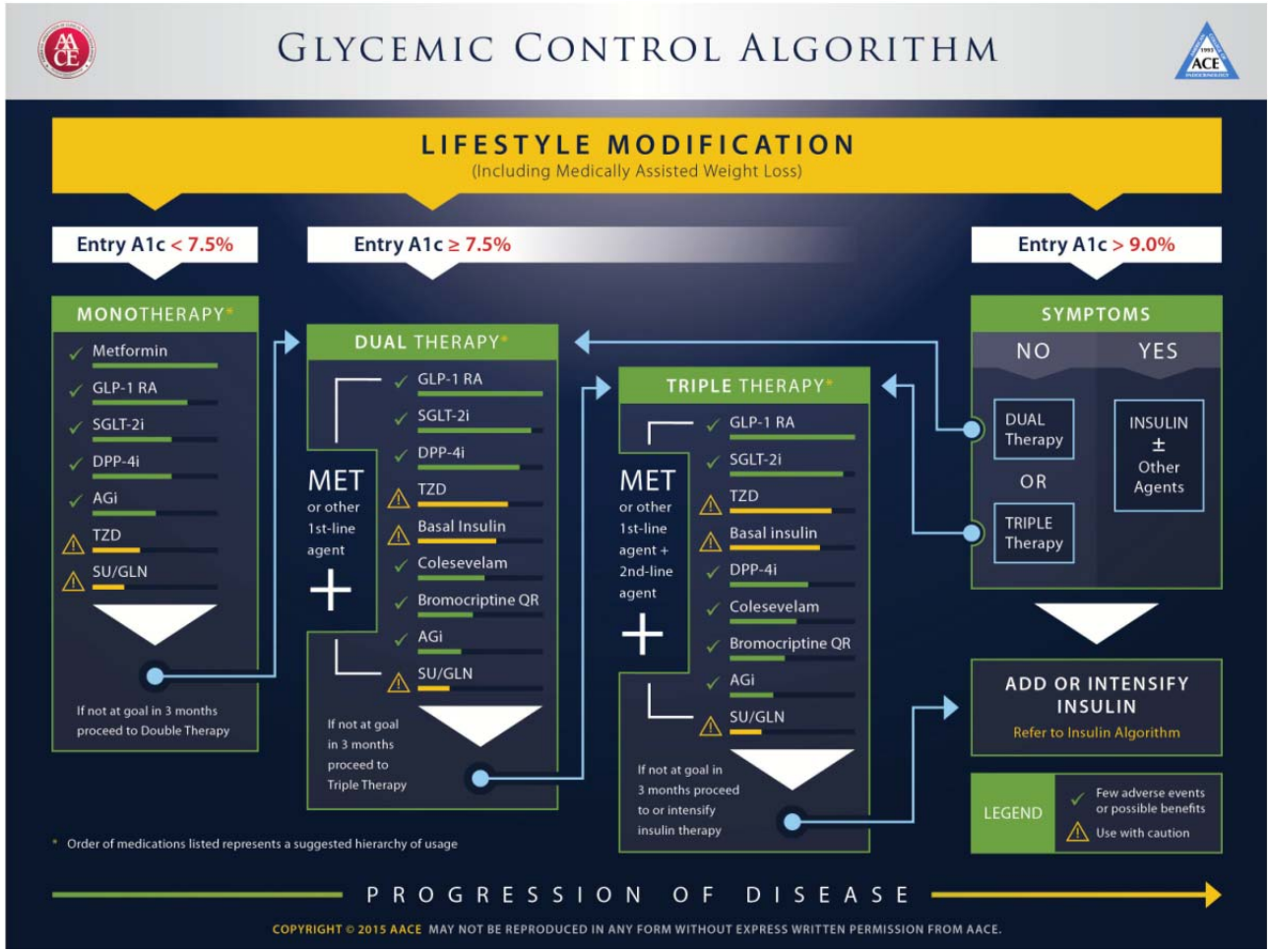
The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) updated their 2011 guidance with new recommendations for individuals with DM.[5] Guidelines development is based on expertise from AACE members integrating objective and subjective data. Evidence is graded and incorporated into recommendation grades (strong to not evidence based). New recommendations include management of comorbidities and a focus on safety as well as efficacy. A comprehensive approach to patient management is suggested, with the specific recommendations of: an education resource for the comprehensive management of patients with DM that involves all relevant practitioners, guidance on coping with issues inherent to DM care, and electronic sharing of patient information to facilitate decision making.

Blood glucose goals are recommended based on patient specific factors, with a general A1C target of ≤6.5% for most adults. Pharmacotherapy should be tailored to the patient's characteristics, such as A1C lowering, comorbidities and risk of hypoglycemia. The guidelines recommend that patients presenting with an A1C less than 7.5% be started on one of the following agents: metformin, GLP-1 RA, SGLT-2 inhibitor, DPP-4 inhibitor or an α-glucosidase inhibitor, based on a weak recommendation due to weak evidence.[5] Other options are SUs, TZDs or glinides since adverse effects may not allow these drugs to be universally recommended for everyone. Dual therapy is recommended for those with A1C greater than 7.5%. Metformin and an additional agent with low risk of hypoglycemia and weight neutral or weight negative (i.e., GLP-1 RA, SGLT-2 inhibitors, DPP-4 inhibitors) are weakly recommended based on weak evidence. TZDs and basal insulin may also be appropriate as an add-on agent. Other treatments, such as colesevelam, bromocriptine, or α-glucosidase inhibitors, have low glucose lowering ability but also low risk of adverse events, which make them appropriate for a small subset of DM patients. Intermediate evidence suggests use of SUs and glinides be monitored regularly due to the risk of hypoglycemia. Symptomatic patients with A1C greater than 9% are candidates for insulin alone or combined with metformin or another oral treatment (strongly recommended). The addition of pramlintide or a GLP-1 RA to prandial insulin is recommended to

reduce postprandial hyperglycemia and weight (intermediate evidence). Long-acting insulin is strongly recommended if non-insulin therapy is unable to control glucose levels in patients with DM. Rapid-acting insulin is recommended for elevated postprandial glucose levels based on intermediate evidence.

AACE/ACE Comprehensive Diabetes Management Algorithm 2015

The AACE algorithm serves as a quick reference guide for physicians and reiterates management described in the comprehensive care plan for DM patients as described above.[6]



Abrahmson M, Barzilay J, Blonde L, et al. AACE/ACE Comprehensive Diabetes Management Algorithm. *Endocr Prac*. *2015;21:438-447.*

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Date: September 2015

Safety Alerts:

In May of 2015, the FDA issued a warning pertaining to the use of SGLT-2 inhibitors and the risk of ketoacidosis.[23] Patients should be monitored for signs and symptoms of acidosis. The FDA is still evaluating the risk and no labeling changes have been issued at this time.

New Formulations or Indications:

GLYXAMBI® (empagliflozin and linagliptin) is a combination of an SGLT-2 inhibitor and a DPP-4 inhibitor approved in January of 2015 by the FDA to be used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when the treatment of both empagliflozin and linagliptin is appropriate.[24] The empagliflozin/linagliptin combination was approved based on one study in patients with T2DM (n=686). Patients were randomized to empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg compared to treatment with the individual components. All groups were on baseline metformin therapy. The combination of empagliflozin 10 mg or 25 mg and linagliptin 5 mg was superior at reducing A1c after 24 weeks compared to either empagliflozin or linagliptin alone.[22]

Randomized Controlled Trials:

Forty-five potentially relevant clinical trials were evaluated from the literature search. After further review, only one trial was included. Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trial is briefly described in the table below. The full abstract is included in Appendix 2.

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Primary Outcome	ARR/NNT	Quality Rating
1. Zannad, et al (EXAMINE)[9,25] RCT, DD, DB, Phase 3	1. Alogliptin (A) 25 mg PO daily* 2. Placebo (P) * Dose was 12.5 mg PO daily for eGFR 30-60 mL/min per 1.73m^2 and for eGFR <30 mL/min per 1.73m^2 the dose was 6.25 mg PO daily Treatment duration: 18 months	Demographics: Age: 61 years Male: 65% Hx of HF: 29% NYHA Class II: 56% A1C: 8.1% Key Inclusion Criteria: T2DM Currently on DM therapy (excluding GLP-1 RA and DPP-4 inhibitors) ACS event within 15-90 days before randomization A1C of 6.5 – 11% or insulin therapy Key Exclusion Criteria:	ITT: 1.2701 2.2679 PP: 1. 2128 2. 2057 Attrition: 1. 573 (21%) 2. 622 (23%)	**Composite of CV death, non-fatal MI, and non-fatal stroke:** A: 305 (11.3%) vs. P: 316 (11.8%); HR 0.96 (95% CI, ≤1.16; P= 0.315) **Composite of CV death, non-fatal MI, non-fatal stroke, and urgent revascularization due to unstable angina:** A: 344 (12.7%) vs. P: 359 (13.4%); HR 0.95 (95% CI, ≤1.16; P=0.258) **First occurrence of all-cause mortality, non-fatal MI, non-fatal stroke, urgent revascularization due to unstable angina, and hospital admission**	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Patients were randomized in a 1:1 ratio. No details on randomization methods were given. Performance: Trial was double-blind design but no details on blinding were provided. Double-dummy design masked treatment allocation. Detection: Outcome assessment was done by an independent committee, blinding was not described. Attrition: Overall attrition was 22% off the study drug at the end of the trial and similar between groups. ITT analysis was used for all data. **Applicability**: Patients: Patients were well matched except for those patients with heart failure at baseline tending to be older, female, higher BNP concentrations, and lower eGFR levels compared to those without heart failure. Intervention: Alogliptin 6.25 mg – 25 mg daily depending on renal function. Comparator: Matched placebo. Outcomes: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated

		NYHA Class IV Unstable heart disease, uncontrolled blood pressure or dialysis within 14 days of screening		**due to HF*:** A: 433 (16.0%) vs. P: 441 (16.5%); HR 0.98 (95% CI, 0.86 to 1.12; P=0.728) Hospital admission for HF*: A: 85 (3.1%) vs. P: 79 (2.9%); HR 1.07 (95% CI, 0.79 to 1.46; P=0.657) All-cause mortality*: A: 106 (3.9%) vs. P: 131 (4.9%); HR 0.80 (95% CI, 0.62 to 1.03; P=0.081) * Component of a predefined exploratory endpoint Post-hoc analysis of Hospital admission for HF: A: 106 (3.9%) vs. P: 89 (3.3%); HR 1.19 (95% CI, 0.90 to 1.58; P=0.220)	NS NS NS NS	with unacceptable levels of cardiac risk. In this study the rate of hospitalizations for heart failure, which has recently been shown to be elevated with saxagliptin, was a post-hoc analysis limiting the applicability of the findings. Setting: Forty-nine countries and 898 centers. **Analysis**: In patients with T2DM, alogliptin demonstrated a similar risk of heart failure as placebo, based on short-term data. Subgroup analysis of patients with preexisting heart failure showed no increased risk of adverse cardiac events for patients taking alogliptin compared to placebo.
1. Green, et al (TECOS)[10] RCT, DB, Phase 3	1. Sitagliptin (S) 100 mg PO daily*† 2. Placebo (P) † * Dose was 50 mg PO daily for eGFR ≥30 to <50 mL/min per 1.73m^2 † Patients also received usual care with metformin, pioglitazone, sulfonylurea or insulin Median follow-up: 3 years	Demographics: Age: 65.5 years Female: 29.3% Hx of HF: 18.0% NYHA Class 3 or higher: 2.5% A1C: 7.2% Key Inclusion Criteria: T2DM Currently on DM therapy (metformin, pioglitazone, sulfonylurea, or insulin) Established coronary artery disease A1C of 6.5 – 8.0% or insulin therapy Key Exclusion	ITT: 1.7332 2.7339 PP: 1. 5682 2. 5633 Attrition: 1. 360 (22.5%) 2. 622 (23.2%)	**Composite of CV death, non-fatal MI, and non-fatal stroke or hospitalization for unstable angina (PP population):** S: 839 (11.4%) vs. P: 851 (11.6%); HR 0.98 (95% CI 0.88 to 1.09; P<0.001 for noninferiority) Supporting analysis of ITT population: HR 0.98 (95% CI, 0.89 to 1.08; P= 0.65 for superiority) **Composite of CV death, non-fatal MI or non-fatal stroke (PP population):** S: (12.7%) vs. P: (13.4%); HR 0.99 (95% CI 0.89 to 1.11; P<0.001 for	NA NS NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized in a 1:1 ratio. Randomized via an interactive voice-response system. Performance: Trial was double-blind design but with packaging to maintain blinding. Detection: Outcome assessment was done by an independent classification committee, blinded to treatment assignment. Attrition: Overall attrition was approximately 23% in both groups. Per protocol population was used for the primary analysis and ITT analysis was done as a supporting analysis. **Applicability**: Patients: Patients with were well matched with similar usage of diabetic and cardiovascular therapies. Patients had moderately elevated A1Cs and preexisting cardiovascular disease. No patients with severe renal insufficiency were included. Intervention: Sitagliptin 50-100 mg daily depending on renal function. Comparator: Matched placebo. Outcomes: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated

		Criteria: Previous use of DPP-4 inhibitor, GLP-1 RA, or TZD (other than pioglitazone) within previous 3 months Severe hypoglycemia eGFR < 30 mL/min per 1.73 m^2		noninferiority) Supporting analysis of ITT population: HR 0.99 (95% CI, 0.89 to 1.10; P= 0.84 for superiority) Hospital admission for HF (ITT population): s: 228 (3.1%) vs. P: 229 (3.1%); HR 1.00 (95% CI, 0.83 to 1.20; P=0.98) All-cause mortality (ITT population): S: 547 (7.5%) vs. P: 537 (7.3%); HR 1.01 (95% CI, 0.90 to 1.14; P=0.88) A1C at 48 months: S: 7.20 P: 7.49 LSMD -0.29 (95% CI -0.32 to -0.27)	 NS NS NS NS	with unacceptable levels of cardiac risk. In this study the rate of hospitalizations for heart failure, which has recently been shown to be elevated with saxagliptin, was included as a secondary endpoint and therefore results could be do to chance. Setting: Thirty-eight countries and 673 centers. **Analysis**: In patients with T2DM, alogliptin demonstrated a similar risk of heart failure as placebo, based on short-term data. Subgroup analysis of patients with preexisting heart failure showed no increased risk of adverse cardiac events for patients taking alogliptin compared to placebo.
Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DD = double-dummy; eGFR = estimated glomular filtration rate; FAS = full analysis set; HF = heart failure; HR = hazard ratio; ITT = intention to treat; kg = kilogram; LSMD = least-squares mean difference; 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;						

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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	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

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	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

Diabetes, Thiazolidiniones

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

Zannad F, Cannon C, Cushman W, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a mulitcentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-76.

Background: The EXAMINE trial showed non-inferiority of the DPP-4 inhibitor alogliptin to placebo on major adverse cardiac event (MACE) rates in patients with type 2 diabetes and recent acute coronary syndromes. Concerns about excessive rates of in-hospital heart failure in another DPP-4 inhibitor trial have been reported. We therefore assessed hospital admission for heart failure in the EXAMINE trial. Methods: Patients with type 2 diabetes and an acute coronary syndrome event in the previous 15–90 days were randomly assigned alogliptin or placebo plus standard treatment for diabetes and cardiovascular disease prevention. The prespecified exploratory extended MACE endpoint was all-cause mortality, non-fatal myocardial infarction, non- fatal stroke, urgent revascularization due to unstable angina, and hospital admission for heart failure. The post-hoc analyses were of cardiovascular death and hospital admission for heart failure, assessed by history of heart failure and brain natriuretic peptide (BNP) concentration at baseline. We also assessed changes in N-terminal pro-BNP (NT-pro-BNP) from baseline to 6 months. Findings: 5380 patients were assigned to alogliptin (n=2701) or placebo (n=2679) and followed up for a median of 533 days (IQR 280–751). The exploratory extended MACE endpoint was seen in 433 (16·0%) patients assigned to alogliptin and in 441 (16·5%) assigned to placebo (hazard ratio [HR] 0·98, 95% CI 0·86–1·12). Hospital admission for heart failure was the first event in 85 (3·1%) patients taking alogliptin compared with 79 (2·9%) taking placebo (HR 1·07, 95% CI 0·79–1·46). Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the

post hoc analysis (HR 1·00, 95% CI 0·82–1·21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups. Interpretation: In patients with type 2 diabetes and recent acute coronary syndromes, alogliptin did not increase the risk of heart failure outcomes.

Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015 Jul 16;373(3):232-42.

Background: Data are lacking on the long-term effect on cardiovascular events of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease. Methods: In this randomized, double-blind study, we assigned 14,671 patients to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, aimed at reaching individually appropriate glycemic targets in all patients. To determine whether sitagliptin was noninferior to placebo, we used a relative risk of 1.3 as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Results: During a median follow-up of 3.0 years, there was a small difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, -0.29 percentage points; 95% confidence interval [CI], -0.32 to -0.27). Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98). There were no significant between-group differences in rates of acute pancreatitis (P=0.07) or pancreatic cancer (P=0.32).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to June Week 3 2015

Search Strategy:

#	Searches	Results
1	sitagliptin {No Related Terms}	807
2	alogliptin {No Related Terms}	158
3	saxagliptin {No Related Terms}	233
4	linagliptin {No Related Terms}	189
5	pramlintide {No Related Terms}	233
6	exenatide {No Related Terms}	928
7	liraglutide {No Related Terms}	603
8	albiglutide {No Related Terms}	35
9	dulaglutide {No Related Terms}	16
10	glyburide {No Related Terms}	3791
11	glipizide {No Related Terms}	532
12	glimepiride {No Related Terms}	742
13	metformin {No Related Terms}	9524
14	tolbutamide {No Related Terms}	1565
15	chlorpropamide {No Related Terms}	208
16	tolazamide {No Related Terms}	21
17	repaglinide {No Related Terms}	499
18	nateglinide {No Related Terms}	366
19	acarbose {No Related Terms}	1338
20	miglitol {No Related Terms}	151
21	dapagliflozin {No Related Terms}	145
22	canagliflozin {No Related Terms}	93
23	empagliflozin {No Related Terms}	57
24	pioglitazone {No Related Terms}	3242
25	rosiglitazone {No Related Terms}	4148
26	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	26318
27	limit 26 to (english language and yr="2014 -Current")	2029
28	limit 27 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	554

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to June Week 3 2015

Search Strategy:

#	Searches	Results
1	pramlintide.mp.	278
2	limit 1 to (english language and yr="2012 -Current")	34
3	limit 2 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	6

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 do not require a copay. • 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: *9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *TBD; 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/

Author: Kathy Sentena, Pharm.D. Date: September 2015

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 do not require PA or a copay. • 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 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.

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Date: September 2015

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: *9/15 (KS); 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *TBD; 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

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Approval Criteria		
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: *9/15 (KS); 1/15; 9/14; 9/13*
Implementation: *TBD; 2/15*

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