Residency Review

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Oh! The Places We Will Go–After Metformin

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According to the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE), metformin is generally accepted as the initial treatment of choice for those with type 2 diabetes unless there are contraindications of severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2 as per ADA and Stages 3B, 4, and 5 chronic kidney disease (CKD) as per AACE) and acute or chronic metabolic acidosis with or without coma.[1-3] While metformin has been proven to be both effective at lowering blood glucose levels and hemoglobin A1C (A1C) values, it may also decrease cardiovascular disease risk.[1] The benefits of metformin have been proven and it continues to be the mainstay therapy in those diagnosed with type 2 diabetes (T2D). Should a patient present with a contraindication to metformin or require further glucose lowering, the ADA and the AACE provide a range of options for healthcare providers and patients. Such options include medications from the following classes: sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 (SGLT2) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist, and insulin.[1,3] This article aims to determine optimal medication options to be used in place of historically common second-line options.

Medications in the sulfonylurea class, including glipizide, glyburide, and glimepiride, are effective in lowering A1C 1% to 1.5% and are low in cost. These medications, however, cause weight gain and have a moderate risk of causing hypoglycemia.[1,4] They have also been associated with increased risk of cardiovascular disease and stroke.[5] Because of their effectiveness, low cost, and prescriber familiarity, these medications have historically been the drug of choice to add onto metformin therapy. However, recent data describing failure of sulfonylurea therapy as well as the associated adverse effects of the class, have led them to steadily fall out of favor. The sulfonylurea class exerts stress on the pancreas, particularly the beta cells, to produce insulin; within a few years of therapy, the beta cells begin to fail leading to decreased blood glucose control.[6]

Most recently, the GLP-1 receptor agonist and the DPP-4 inhibitor classes have proven to also be highly efficacious as these medications lower A1C by 1% to 1.5% and 0.5% to 1%, respectively. Both classes have a low risk of hypoglycemia and have the added benefit of weight loss with an approximate 3.3 kilogram decrease seen in the GLP-1 receptor agonist class and an approximate 1.8 kilogram decrease in the DPP-4 inhibitor class.[4] Liraglutide, exenatide, dulaglutide, and lixisenatide share a side effect profile consisting of primarily gastrointestinal issues including nausea (8% to 39%) and vomiting (4% to 16%) which often subside following the first month of treatment.[7] Because the medications in these classes are not available generically, the cost remains high as third party payers classify them as tier 2, tier 3, and tier 4, and sometimes require a prior authorization.[8-11] Further benefits of medications in the GLP-1 agonist class include beta-cell proliferation and differentiation as well as decreased cardiovascular events.[12,13] In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results: A Long Term Evaluation (LEADER) trial the cardiovascular benefits of liraglutide were determined compared to placebo and standard of care therapy.[12] To date there has not been evidence to prove if this is a class effect.

Another recent class of medications, the SGLT2 inhibitor class (empagliflozin, canagliflozin, and dapagliflozin), works by inhibiting the reabsorption of glucose in the kidneys. Due to their mechanism of action, the most common adverse effects are genitourinary events. Despite the adverse event profile, SGLT2 inhibitors have proven intermediate efficacy in T2D treatment as they lower A1C by 0.5% to 1%, carry a low hypoglycemia risk (4%), and often provide a 2 kilogram weight loss due to the excretion of glucose in the urine.[1,4] The cost, like other medication classes, can be prohibitive as third party payers classify SGLT2 inhibitors as a tier 2, tier 3, or tier 4 and some plans require a prior authorization.[8-11] Empagliflozin has been proven to reduce nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (10.5% vs. 12.1%; P=0.04; number needed to treat [NNT] 62) as well as reduce all-cause mortality (5.7% vs. 8.3%; P<0.001; NNT 38) at 3.1 years of follow-up compared to placebo in the randomized, double-blind Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.[14] However, according to the U.S. Food and Drug Administration (FDA), canagliflozin has been associated with an increased risk of leg and foot amputations.[15]

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While the ADA and AACE guidelines suggest basing drug choice, following or in addition to metformin, on patient preferences and varied patient, disease, and drug characteristics, the evidence proving efficacy and added benefits of certain medications and medication classes outweigh that of other commonly used medications, such as sulfonylureas. The primary goal of healthcare providers is patient safety. For healthcare providers caring for patients with T2D, the secondary goal is to reduce blood glucose levels while decreasing adverse effects related to medications. Newer medications, with proven efficacy, safety, and further cardiovascular benefits, will provide patients the medication necessary to aid in their disease state management and improve outcomes with a decreased burden of adverse effects.

Table from American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan[3]

Table 10
Pharmacologic Agents for T2D Treatment[a]

Monotherapy	Dual therapy	Triple therapy
	Metformin (or other first-line agent) plus	First- and second-line agent plus
Metformin	**GLP1RA**	**GLP1RA**
GLP1RA	**SGLT2I**	**SGLT2I**
SGLT2I	**DPP4I**	TZD[b]
DPP4I	TZD[b]	Basal insulin[b]
AGI	Basal insulin[b]	**DPP4I**
TZD[b]	**Colesevelam**	**Colesevelam**
SU/glinide[b]	**BCR-QR**	**BCR-QR**
	AGI	**AGI**
	SU/glinide[b]	SU/glinide[b]

Abbreviations: A1C = hemoglobin A1C; AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; DPP4I = dipeptidyl peptidase 4 inhibitors; GLP1RA = glucagon-like peptide 1 receptor agonists; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.
[a] Intensify therapy whenever A1C exceeds individualized target. Boldface denotes little or no risk of hypoglycemia or weight gain, few adverse events, and/or the possibility of benefits beyond glucose lowering.
[b] Use with caution.

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Improve Cardiovascular Outcomes in People with Type 2 Diabetes

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Type 2 diabetes mellitus (T2D) is a risk factor for cardiovascular (CV) disease. People with T2D and a history of CV disease are at an increased risk of death.[1] Most recently, two antihyperglycemic agents demonstrated improved cardiovascular outcomes and a lower risk of CV related deaths. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial may help decrease CV disease in people with type 2 diabetes.

Empagliflozin (Jardiance®) is an inhibitor of sodium-glucose co-transporter 2 (SGLT2) whose primary mechanism of action is to block glucose reabsorption in the kidney, which results in glucose excretion in the urine. The EMPA-REG OUTCOME trial demonstrated that for people with T2D at high risk of a CV event, the effects of empagliflozin on cardiovascular morbidity and mortality, nonfatal MI, or nonfatal strokes, when compared to placebo, were noninferior to the standard of care. People with T2D who were ≥ 18 years, BMI ≤45, glomerular filtration rate (GFR) at least 30 mL/min, at high risk for having CV event defined as a previous event or history of established cardiovascular disease (CVD), and had poor glucose control defined as A1C 7%-9 % if no glucose lower agents 12 weeks before randomization were taken by the patient or A1C 7%-10% receiving stable glucose-lowering therapy 12 weeks prior to randomization were included in the trial. The primary outcome was death from CV causes, nonfatal MI, or nonfatal stroke. The trial required at least 691 primary outcome events to occur in order for the test of noninferiority for the primary outcome to have 90% power; 772 events occurred collectively. The results revealed death from CV causes, nonfatal MI, or nonfatal stroke occurred in 10.5% of people on empagliflozin vs. 12.1% on placebo (hazard ratio (HR) 0.86; 95% confidence interval (CI), 0.74-0.99; superiority p=0.04, non-inferiority p<0.001; NNT 62). This implies that people with T2D, at high risk of CV events, receiving empagliflozin, compared to placebo, had a lower rate of primary CV outcome and death from any cause when added to standard of care.[1]

Liraglutide (Victoza®) is a glucagon-like peptide-1 (GLP-1) receptor agonist. It mimics the action of incretins in the gut causing the pancreas to release insulin in a glucose-dependent manner to help maintain blood glucose levels. The LEADER trial assigned people with T2D to receive once daily liraglutide injection (0.6-1.8mg) at a maximum tolerated dose or a placebo injection in addition to standard of care therapy. People with T2D who were ≥ 50 years, had at least one co-existing cardiovascular condition (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or were ≥ 60 years and had at least one CV risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or ankle-brachial index <0.9) were included. People had to have an A1C ≥ 7% at screening, be anti-diabetic drug-naïve or treated with 1 or more oral antihyperglycemic drugs or NPH, long-acting analog, or premixed insulin. The study's primary outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome occurred in fewer people in the liraglutide group (608 of 4668 [13.0%]) than in the standard of care group (694 of 4672 [14.9%]) (HR, 0.87; 95% CI, 0.78-0.97; p=0.01) and death from CV causes occurred in fewer people in the liraglutide group (219 [4.7%]) than in the standard of care group (278 [6.0%]) (HR, 0.78; 95% CI; 0.66-0.93). Additionally, death from all causes occurred in fewer people in the liraglutide group (381 [8.2%]) than in the standard of care group (447 [9.6%] (HR, 0.85; 95% CI, 0.74-0.97). The results of the study demonstrated that people on liraglutide had a lower occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke compared to the placebo group.[2]

Safety and tolerability were described in both trials. Empagliflozin shares common adverse drug reactions of its' class such as increased urinary tract infections (18%), genital infections (6.4%), and complicated urinary tract infection (1.7%). However the EMPA-REG trial revealed safety and tolerability data similar to that of the control group.[1] Liraglutide's safety and tolerability showed increased gastrointestinal complications that led to discontinuation in 4.1% of people compared to 1.2% in the placebo group.[3] Trials are ongoing and more data is expected to help guide prescribing habits.

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Drug	Primary Outcome	Primary Outcome Results	Safety and Tolerability Data	Inclusion Criteria
Empaglifozin	Time to CV mortality, nonfatal MI, or nonfatal stroke in patients with T2D taking empagliflozin compared to placebo	Empagliflozin vs. placebo (10.5% vs 12.1%) (HR, 0.86; 95% CI, 0.74-0.99; superiority p=0.04, non-inferiority p<0.001; NNT 62)	Empagliflozin vs. placebo –Drug discontinuation 17.3% vs. 19.4% (p<0.01) - Hypoglycemia 27.6% vs. 27.9% - UTI 18.0% vs. 18.1% - Complicated UTI 1.7% vs. 1.8%	- T2D - ≥18 years - BMI ≤ 45 - GFR at least 30 ml/min - High risk for CV event - A1C 7%-9 % - no glucose lower agents 12 weeks before randomization - A1c 7%-10% - on stable glucose-lowering therapy 12 weeks prior
Liraglutide	Time to cardiovascular death, or first occurrence of nonfatal myocardial infarction, or nonfatal stroke	- Occurrence of primary outcome: liraglutide vs. standard of care group (13.0% vs. 14.9%) (HR, 0.87; 95% CI, 0.78-0.97; p=0.01) - Death from CV: liraglutide vs. standard of care group (4.7% vs 6.0%) (HR, 0.78; 95% CI, 0.66-0.93) - Death from all: liraglutide vs. standard of care group (8.2% vs 9.6%) (HR, 0.85; 95% CI, 0.74-0.97)	Increased gastrointestinal complications that led to discontinuation in 4.1% compared to 1.2% in placebo group	- T2D who were: ≥ 50 years, had at least one co-existing cardiovascular condition (coronary arteria disease, cerebrovascular disease, peripheral artery disease, heart failure, or chronic kidney disease) Or were ≥ 60 years and had at least one CV risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or ankle-brachial index <0.9)

Diabetic Foot Infections In The Outpatient Setting

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Diabetic foot infections (DFI) are a relatively common and often severe consequence of living with diabetes, with the most often inciting event being some trauma leading to ulceration. DFIs represent a significant contributing factor to morbidity in many patients living with diabetes and represent one of the most common indications for amputation in Western countries.[1] Due to the common nature of DFIs in patients with diabetes, patients can commonly be exposed to antibiotics, often in an inappropriately broad or excessive manner.[2]

Appropriate antibiotic management of DFIs in the outpatient setting must take several factors into consideration, these include: likely pathogens involved, chronicity of wound, culture data and antibiotic exposure, and need for adjunctive management techniques. DFIs, particularly those that are newer in onset and less chronic in nature, are commonly caused by aerobic Gram positive cocci such as *Streptococcus* spp. and *S. aureus*.[3] More chronic wounds (especially in patients with previous antibiotic exposure) can begin to involve aerobic Gram negative bacilli such as *Enterobacteriaceae* (*E.coli, Klebsiella* spp., *Enterobacter* spp., etc.) and anaerobic bacteria such as *Bacteroides* spp.[3] *Enterococcus* spp. can frequently be isolated in DFIs, but are unlikely to be pathogens and do not need to be considered in choosing an antibiotic regimen.[3] Coverage of *P. aeruginosa*, whether empirically or based on patient specific culture data, is a controversial issue. Some investigations have shown no benefit in including pseudomonal coverage, and it is unlikely that *P. aeruginosa* is a causative pathogen in mild DFIs.[4] Culture data is likely not required in mild, previously untreated DFIs, however in many cases appropriately obtained cultures can be very helpful for providing a narrow spectrum agent to treat the causative pathogens. Current guidelines recommend the collection of tissue specimens obtained by biopsy, ulcer cutterage, or aspiration; it is important to obtain culture prior to antibiotic use, or in patients who have been treated after antibiotics have been held for 2-3 days.[3]

Many DFIs are appropriate to be managed in the outpatient setting if there are no signs of systemic infection, metabolic instability, rapidly progressive or deep tissue infection, substantial necrosis or gangrene, or presence of critical ischemia.[3] Many investigations have attempted to determine appropriate agents for DFIs, however, most studies are of low quality, unblinded, lack concealed randomization, and contain financial bias.[5] Cumulatively however, studies have shown mostly equivocal efficacy when comparing older agents to newer agents, and have shown no benefit in using bactericidal agents in comparison to those that are bacteriostatic.[5,6] An optimal duration of treatment for DFIs has been poorly elucidated, however current guidelines and expert opinion reviews suggest a duration of 1-2 weeks is appropriate for most infections in which bone is not involved.[2,3] Longer durations of treatment may expose the patient to an increased risk of treatment related adverse events, antibiotic resistant flora, and *Clostridium difficile* associated diarrhea, without providing any obvious benefit.

A table of oral options adapted from the DFI guidelines can be seen in Table 1. Many options provide reliable coverage for mild DFIs of new ulcerations; trimethoprim/sulfamethoxazole and doxycycline may provide inadequate coverage of *Streptococcus* spp. Linezolid, trimethoprim/sulfamethoxazole, and doxycycline can be used in patients who have MRSA isolated from cultures collected from DFIs, clindamycin and levofloxacin may provide coverage of MRSA, but are not reliable empiric options in this setting. Fluoroquinolones and clindamycin have high risks of causing *C. difficile* associated diarrhea, and should be used cautiously, as increasing trends of resistance have decreased the reliability of these drugs in DFIs. Ciprofloxacin should generally not be used in mild DFIs as it has limited coverage of *Streptococcus* and *Staphylococcus* spp. Furthermore, fluoroquinolones may cause dysglycemias at a higher rate than usual in patients with diabetes.[7]

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Table 1. Oral Therapy Options

Drug	Drug Class	Spectrum of Activity	Dosage	Considerations
Cephalexin	Cephalosporin (1st generation)	*Streptococcus* spp., MSSA, *Enterobacteriaceae*	500mg every 6 hours	Adjust for renal function, may not be appropriate monotherapy in chronic wounds
Cefuroxime	Cephalosporin (2nd generation)	*Streptococcus* spp., MSSA, *Enterobacteriaceae*	500mg every 12 hours	Should be taken with food, no renal adjustment
Amoxicillin/ clavulanic acid	β-Lactam/β-Lactamase Inhibitor	*Streptococcus* spp., MSSA, *Enterobacteriaceae,* anaerobes	875/125mg every 12 hours	Clavulanate can cause diarrhea, offers reliable coverage of chronic wound infections
Trimethoprim/ sulfamethoxazole	Folate synthesis inhibitor	MSSA, MRSA, *Enterobacteriaceae*	5-8mg/kg of trimethoprim (divided every 12 hours)	Offers poorer coverage of *Streptococcus* spp. than other options, can affect SCr and potassium, avoid in patients on warfarin
Levofloxacin	Fluoroquinolone	*Streptococcus* spp., MSSA, MRSA (±), *Enterobacteriaceae, P. aeruginosa*	750mg every 24 hours	Risk of *C. difficile*, reliability of Gram negative coverage is decreasing, separate administration from cation containing compounds
Moxifloxacin	Fluoroquinolone	*Streptococcus* spp., MSSA, *Enterobacteriaceae,* anaerobes	400mg every 24 hours	Risk of *C. difficile*, reliability of Gram negative coverage is decreasing, separate administration from cation containing compounds, may be costly for patient
Clindamycin	Lincosamide	*Streptococcus* spp., MSSA, MRSA	300mg every 6 hours	High risk of *C. difficile*, doses over 300mg very poorly tolerated
Linezolid	Oxazolidinones	*Streptococcus* spp., MSSA, MRSA	600mg every 12 hours	Avoid in patients on antidepressants, durations of >2 weeks should be avoided
Doxycycline	Tetracyclines	MSSA, MRSA	100mg every 12 hours	Separate administration from cation containing compounds, should be taken with a full glass of water