A Practical Update to Diabetes Management in 2020

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Disclosures

- R. Iain Pritchard: No Disclosures
Objectives

1. Explain current approaches to diabetes management based upon the American Diabetes Association (ADA) and American Association of Clinical Endocrinologist (AACE) guidelines.
2. Compare available medications for the management of diabetes, including their impact outside of glucose lowering.
3. Discuss continuous glucose monitoring and its impact on improving care for patients with diabetes.

Self Assessment Question 1

- A primary difference between the American Diabetes Association & American Association of Clinical Endocrinologist guidelines for management of patients with diabetes is which of the following?
  - A. Preferred A1C goal
  - B. Use of metformin
  - C. Holistic approach to care
  - D. Preferred second line therapy options
Self-Assessment Question 2

- Which of the following glucagon-like peptide-1 receptor agonists has been shown to decrease the risk of major adverse cardiovascular events (MACE) and has an FDA indication for this reduction?
  - A. Exenatide-ER
  - B. Lixisenatide
  - C. Semaglutide – injectable
  - D. Dulaglutide

Self Assessment Question 3

- Which of the following sodium-glucose cotransporter-2 inhibitors has a FDA indication specific to its ability to reduce hospitalization for heart failure?
  - A. Dapagliflozin
  - B. Empagliflozin
  - C. Ertugliflozin
  - D. Canagliflozin
Self Assessment Question 4

- Medicare requires that patients meet which of the following criteria to qualify for continuous glucose monitoring?
  - A. Currently testing blood glucose 4 or more times a day
  - B. Currently injecting insulin 3 or more times per day
  - C. Insulin regimen requires frequent adjustment
  - D. All of the above

Self Assessment Question 5

- The recommended blood glucose target for most patients using continuous glucose monitoring is which of the following?
  - A. 70-200 mg/dl
  - B. 63-140 mg/dl
  - C. 70-180 mg/dl
  - D. 70-140 mg/dl
Diabetes Mellitus

- American Diabetes Association
  - “Group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both”
- Four general categories
  - Type 1 diabetes
    - Immune-Mediated Diabetes
  - Type 2 diabetes
  - Gestational diabetes
  - Diabetes due to other causes

Diagnosis & Management of Diabetes in 2020

- Components of Comprehensive Management
  - Screening
  - Diagnosis
  - Goals of therapy
  - Pharmacological treatment
    - Management of hyperglycemia
    - Management of obesity
    - Management of cardiovascular disease and risk
    - Management of microvascular complications
  - Non-pharmacological treatment
    - Diabetes self-management education and support
    - Psychosocial issues
Screening, Diagnosis, & Goals

Screening for Diabetes

- When screening either a fasting plasma glucose, 2-hour oral glucose tolerance test, or A1C are appropriate
- Type 1 Diabetes
  - Widespread screening not recommended
- Type 2 Diabetes
  - Adults of any age who are overweight or obese with one additional risk factor
  - Adults over the age of 45
  - Women planning pregnancy who are overweight or obese and/or have one additional risk factor
  - In children and adolescents after the onset of puberty or after 10 year of age who are overweight or obese and have one additional risk factor
Diagnosis - Prediabetes

- Increased risk for developing diabetes and cardiovascular disease
- Criteria
  - Fasting Plasma Glucose
    - 100mg/dl – 125mg/dl (impaired fasting glucose)
  - 2-hour oral glucose tolerance test
    - 75-gram oral glucose load
    - 140 – 199 mg/dl (impaired glucose tolerance)
  - A1C
    - 5.7% - 6.4%

Diagnosis - Diabetes

- Criteria
  - Fasting Plasma Glucose
    - ≥ 126 mg/dl
  - 2-hour oral glucose tolerance test
    - 75-gram oral glucose load
    - ≥ 200 mg/dl
  - A1C
    - ≥6.5%
  - In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results
Diagnosis – A1C

- A1C should not be used to diagnose in the following conditions:
  - Sickle cell disease
  - Pregnancy
    - Second and third trimesters
  - Glucose-6-phosphate dehydrogenase deficiency
  - Hemodialysis
  - Recent blood loss
- A1C can be unreliable in the following conditions:
  - Iron-deficient anemia
  - Individuals who are post-partum

Goals of Therapy – Glycemic Control

- Standard goals
  - A1C
    - ADA: <7%
    - AACE: <6.5%
  - Preprandial plasma glucose
    - 80-130 mg/dl
  - Postprandial plasma glucose
    - <180 mg/dl
- Adjustments?
  - Consider
    - Risk of hypoglycemia
    - Disease duration
    - Life expectancy
    - Established vascular complications
    - Patient preference
    - Resources and support systems
Pharmacological Management

▪ Metformin continues to be first line therapy for patients with type 2 diabetes
  ▪ Effective
  ▪ Safe
  ▪ Inexpensive
  ▪ May reduce risk of cardiovascular events and death
▪ Then what?

Therapeutic Approach - Step 1
Therapeutic Approach – Next Steps

- Second line therapy for type 2 diabetes should be patient specific
  - Considerations
    - Risk of hypoglycemia
    - History of cardiovascular disease
    - Cost
    - Extent of A1C lowering required
    - Renal effects
    - Patient preference
- Patients may require dual or triple therapy to achieve A1C goals
- Insulin is a potential second line option

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

- Short acting
  - Exenatide
  - Liraglutide
  - Lixisenatide
  - Semaglutide
- Long acting
  - Albglutide
    - Removed from market – economic reasons
  - Dulaglutide
  - Exenatide-ER
  - Semaglutide
GLP-1s – General Characteristics

- Low risk of hypoglycemia
- Potential for cardiovascular benefit
  - No cardiovascular harm shown with any agent
- Expensive
  - No agent is currently generic
- Effective
  - Average A1C lowering potential over 1%
  - Weight loss
- Renal effects
  - Potential risk of acute kidney injury
- Side effects
  - Gastrointestinal

Exenatide

- Two formulations
  - Exenatide & exenatide-ER
- Cardiovascular risk
  - EXSCEL trial
    - No increased risk of major adverse cardiovascular events (MACE) with exenatide-ER
    - Retrospective data showing no increased risk with exenatide
- Cost
  - Exenatide - $886.53
  - Exenatide-ER - $827.26
- Efficacy
  - Exenatide-ER has demonstrated greater A1C lowering potential than exenatide
- Renal dosing considerations


Liraglutide

- Cardiovascular risk
  - LEADER trial
    - Reduction in time to first occurrence of MACE
    - FDA Indication: “Reduce the risk of MACE in adults with type 2 DM and established cardiovascular disease”
  - Cost
    - Liraglutide - $1111.35
    - Liraglutide & insulin degludec - $1245.48
- Renal Effects
  - Reduction in the development and progression of diabetic kidney disease

Lixisenatide

- Cardiovascular Risk
  - ELIXA trial
    - No increased risk of MACE
- Cost
  - Lixisenatide - $705.45
    - Rarely prescribed individually
  - Lixisenatide & insulin glargine - $849.53
- Efficacy
  - Primary effect is on post-prandial blood glucose values
Dulaglutide

- Cardiovascular risk
  - REWIND trial
    - Reduction in MACE
    - No FDA indication currently
- Cost
  - $910.07
- Efficacy
  - Less A1C lowering potential and less weight loss as compared to injectable semaglutide

Semaglutide – Injectable

- Cardiovascular risk
  - SUSTAIN-6
    - Reduction in the risk of MACE as compared to placebo
    - FDA indication: “To reduce the risk of MACE in adults with type 2 DM and established cardiovascular disease”
- Cost
  - $941.35
- Efficacy
  - Superior A1C lowering to dulaglutide, liraglutide, and exenatide-ER
Semaglutide – Oral

- Newest medication to market
- Cardiovascular risk
  - PIONEER 6
    - No increased risk
    - No FDA indication like injectable semaglutide
- Cost
  - $910.27
- Efficacy
  - Less effective than injectable semaglutide
  - Reduced side effects

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

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin
SGLT-2s – General Characteristics

- Low risk of hypoglycemia
- Potential for cardiovascular benefit
  - No cardiovascular harm shown with any agent
- Expensive
  - No agent is currently generic
  - Not as expensive as GLP-1s
- Effective
  - Average A1C lowering potential over 1%
  - Less effective as compared to GLP-1s
  - Weight loss
- Renal effects
  - Benefit seen with all agents other than ertugliflozin in the progression of diabetic kidney disease
- Side effects
  - DKA, genitourinary infections, risk of Fournier’s gangrene

Canagliflozin

- Cardiovascular risk
  - CANVAS trial
    - Reduced risk of MACE as compared to placebo
  - FDA indication: “reduce the risk of MACE in adults with type 2 DM and established CV disease”
- Cost - $601.78
- Renal effects
  - CANVAS – R
    - Reduced risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria
    - FDA indication: “reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria”
- FDA Black Box: Risk of amputation
Dapagliflozin

- Cardiovascular risk
  - DECLARE-TIMI 58
    - Did not reduce all MACE endpoints as compared to placebo
    - Reduced the risk of cardiovascular death, and hospitalization for heart failure
    - FDA indication: “reduce the risk of hospitalization for heart failure in adults with type 2 DM and established cardiovascular disease or multiple cardiovascular risk factors”
  
- Cost - $595.55

- Renal effects
  - Reduction in sustained eGFR decline, end-stage renal disease, and renal death

Empagliflozin

- Cardiovascular risk
  - EMPA-REG OUTCOME
    - Reduced the risk of MACE compared with placebo
    - FDA indication: “reduce the risk of cardiovascular death in adults patients with type 2 DM and established cardiovascular disease”
  
- Cost - $598.94

- Renal effects
  - Reduction in incident or worsening nephropathy and doubling of serum creatinine
Ertugliflozin

- Cardiovascular risk
  - VERTIS
    - Results not yet published
- Cost - $339.74
- Renal effects
  - No studies on a potential benefit found

Remaining Second-Line Therapies?

- Sulfonylureas
  - Advantages: cheap & effective
  - Disadvantages: hypoglycemia, weight gain, lack of clear cardiovascular or renal benefit, durability
- Thiazolidinediones (TZDs)
  - Advantages: cheap, effective, potential cardiovascular benefit with pioglitazone
  - Disadvantages: risk of heart failure, weight gain, other side effects
- DPP4 Inhibitors
  - Advantages: minimal side effects, low risk of hypoglycemia
  - Disadvantages: cost, limited efficacy, not additional benefits
- Insulin
  - Advantages: effective
  - Disadvantages: hypoglycemia, weight gain, cost (with most)
Insulin Therapy

- Type 2 diabetes is a progressive disease
  - Insulin should not be used as a punishment, threat, or as a sign of failure
- Basal insulin is an appropriate choice for many patients
  - Consider in those with:
    - High initial A1Cs, ≥10%
    - Using multiple oral/non-insulin therapies without achieving A1C goals
  - Many available options
    - All can get patients to A1C goals
    - Long-acting basal analogs reduce risk of symptomatic and nocturnal hypoglycemia compared to NPH insulin
      - U-100 insulin glargine & insulin detemir
    - Longer-acting basal analogs may have a lower hypoglycemia risk as compared to U-100 glargine
      - U-300 insulin glargine & insulin detemir

Insulin Therapy

- When intensifying insulin therapy two therapeutic options are now available:
  - Prandial insulin
  - Combination basal insulin & GLP-1 agonist
- Combination therapy with a GLP-1 agonist
  - Additive A1C lowering benefit
  - Less weight gain as compared to insulin intensification alone
  - Less hypoglycemia as compared to insulin intensification alone
  - Potentially more cost effective
- Prandial insulin
  - Insulin analogs and regular insulin available as therapeutic options
  - Insulin analogs have not been shown to have less hypoglycemia or improved A1C lowering over regular insulin
Putting it all together

- Both the ADA and AACE guidelines emphasize a holistic approach to patient care
- GLP-1s & SGLT-2s are preferred second line options when affordability concerns are negligible
- Use of sulfonylureas and TZDs should not be ruled out in patients with affordability concerns

But That’s Not All

- Diabetes pharmacotherapy is not limited to just control of the patient’s blood glucose values
- Other areas of pharmacotherapy include:
  - Blood pressure management
  - Lipid management
  - Antiplatelet agents
Blood Pressure Management

- ADA & AACE agree on a goal of <130/80 for some patients
  - ADA recommends a goal of <140/90 for those at low risk of cardiovascular disease
- Primary therapy with an ACE-I or ARB
- Other therapeutic options include:
  - Thiazide-like diuretics or dihydropyridine calcium channel blockers

Lipid Management - ADA

- Primary prevention
  - Aged 40-75 with no history of atherosclerotic cardiovascular disease (ASCVD)
    - Moderate intensity statin therapy
  - Aged 20-30 with ASCVD risk factors
    - Consider initiation of statin therapy
  - Patients at higher risk, i.e. multiple ASCVD risk factors or aged 50-70
    - Consider high intensity therapy over moderate intensity therapy
  - Patients with a 10-year ASCVD risk score >20%
    - Consider addition of ezetimide to reduce LDL levels by 50% or more
- Secondary prevention
  - High intensity therapy should be utilized for all patients
  - If patient is very high risk and LDL ≥70 mg/dl and patient is on statin therapy
    - Consider additional therapy such as ezetimibe or a PCSK9 inhibitor
Lipid Management - AACE

- Three patient subgroups
  - High risk: DM but no other major risk factors and/or aged <40
  - Very high risk: DM & major ASCVD risk factors
  - Extreme: DM & established CVD
- Individualized lipid targets for patients dependent on risk
  - High risk: LDL <100 mg/dl
  - Very high risk: <70 mg/dl
  - Extreme: <55 mg/dl

Lipid Management - Both

- The ADA and AACE both recommend:
  - Icosapent ethyl 4 grams/day
    - Patients with TG 135-499 mg/dl with high ASCVD risk or history of CVD
    - Based upon the results of the REDUCE-IT trial
      - Relative risk reduction of 25% compared to placebo for a composite endpoint of myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina
  - Appropriate lifestyle modifications
Antiplatelet Therapy

- Aspirin therapy is appropriate as secondary prevention
- In primary prevention only after a comprehensive discussion of the benefits and risks
  - ASCEND study
    - Prevented significant vascular events but also increased the risk of bleeding
Improving Access - Patient Assistance Programs

- All branded medications can be obtained free of charge for patients who qualify
  - Lilly Cares – lillycares.com/assistanceprograms.aspx
    - Household income under income limit for all patients
    - Household income at or below 400% of the federal poverty level
    - If Medicare Part D must have spent $1,100 on prescription medication in calendar year
  - Novocare – novocare.com/diabetes-overview/let-us-help/pap.html
    - No private prescription coverage
    - Household income at or below 400% of the federal poverty level
    - If Medicare Part D must have spent $1,000 on prescription medication in calendar year
  - Sanofi Patient Connection – sanofipatientconnection.com
    - No insurance coverage, or access to prescribed product through your insurance
    - Household income at or below 400% of the federal poverty level
    - If Medicare Part D must have spent at least 2% of your annual household income on prescription medication in calendar year

Improving Access - Patient Assistance Programs

- All branded medications can be obtained free of charge for patients who qualify
  - Boehringer-Ingelheim – Boehringer-ingelheim.us/our-responsibility/patient-assistance-program
    - No health coverage, or not enough coverage
    - No access to alternate sources of coverage
    - Meet BI’s household income guidelines
  - AstraZeneca – azandmeapp.com
    - No prescription drug coverage that helps pay for your AZ meds
    - If Medicare Part B or D must have spent 3% of your household income on prescription medications
    - Meet AZ’s household income guidelines
Improving Access – Medicare Extra Help

- Limits cost of medications to:
  - $3.60 for generics
  - $8.95 for brand name

- Who qualifies?
  - Resources limited to:
    - $14,610 for an individual or $29,160 for a married couple living together
  - Income limited to:
    - $18,735 for an individual or $25,365 for a married couple living together
      - May be able to get some help even with higher incomes

- Application:
  - [www.socialsecurity.gov/extrahelp](http://www.socialsecurity.gov/extrahelp)
  - Call social security: 1-800-772-1213
  - Local social security office

Improving Access – Other Resources

- Winchester, northern Shenandoah valley
  - Compassionate Care Pharmacy: 540-536-4102

- RxRelief Virginia
  - Connects patients with local medication access programs

- RxOutreach
  - Helps patients obtain low-cost generic medications

- Needymeds.org
  - Helps patients and providers locate information on assistance programs
Continuous Glucose Monitoring

- Four types of devices
  - Real-time CGM
  - Intermittently scanned CGM
  - Blinded (professional) CGM
  - Unblinded CGM
- When used properly CGM devices have been shown to reduce hypoglycemia in patients with type 2 diabetes using insulin therapy
- When use properly CGM devices have been shown to lower A1C and reduce hypoglycemia in patients with Type 1 diabetes
CGM – Target Ranges

- For most patients with type 1 and type 2 diabetes
  - Target range of 70-180mg/dl
- For patients with type 1 diabetes
  - Goal to spend less than 1 hour per day below target range
  - Goal to spend less than 6 hours per day above the target range
- For patients with type 2 diabetes
  - Goal to spend less than 15 minutes below 54mg/dl
  - Goal to spend less than 1.2 hours above 250mg/dl

- Glycemic targets remain personalized
  - If patient is pregnant
    - Target range of 63-140mg/dl
  - Conservative targets for patients who are older and/or are considered high risk
    - Reduce time spent <70mg/dl

Battelino T, et al "Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range" Diabetes Care 2019; DOI 10.2337/dc19-0028

Freestyle Libre

- Intermittently scanned CGM
- Has improved access to CGM devices due to in-pharmacy availability and reduced cost

- Who to consider in?
  - Commercially insured patients on insulin therapy who require additional A1C lowering or who are experiencing frequent hypoglycemia
  - Medicare patients who:
    - Checks their blood glucose 4 or more times a day
    - Takes multiple (three or more) daily injections of insulin or is on an insulin pump
    - Insulin regimen requires frequent adjustments
Other CGM devices

- **Dexcom**
  - G6 Dexcom now available for all patients
  - Medicare patients were previously required to use an older device
  - Provides real time CGM
  - Same eligibility requirements as Free Style Libre
  - Cost to patient may be substantially higher

- **Medtronic**
  - Available combined insulin pump and CGM device
  - Standalone Guardian CGM

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  - C. Holistic approach to care
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Which of the following glucagon-like peptide-1 receptor agonists has been shown to decrease the risk of major adverse cardiovascular events (MACE) and has an FDA indication for this reduction?

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Medicare requires that patients meet which of the following criteria to qualify for continuous glucose monitoring?

- A. Currently testing blood glucose 4 or more times a day
- B. Currently injecting insulin 3 or more times per day
- C. Insulin regimen requires frequent adjustment
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Self Assessment Question 5

The recommend blood glucose target for most patients using continuous glucose monitoring is which of the following?

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Questions?