Diabetes Treatment Update: 
After Metformin

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Dr. Keber earned her medical degree from the State University of New York (SUNY) Downstate College of Medicine, Brooklyn, and completed her residency in family medicine at the Community Hospital of Glen Cove, New York. She has been a board-certified family physician for 35 years and currently works for Northwell Health Physician Partners Family Medicine at Glen Cove Hospital. For the past five years, the combined faculty and residency practice has had National Committee for Quality Assurance (NCQA) recognition as a Level 3 Patient-Centered Medical Home (PCMH), and Dr. Keber has been instrumental in developing the patient-centered approach and team-based care. In addition, she is the physician leader for the diabetes program in both the inpatient and ambulatory settings. She is currently the physician lead for the Enterprise Diabetes Project for the Northwell Health System, leading efforts to enhance and standardize diabetes care within the enterprise. She has lectured on topics related to diabetes care/management and team-based population health within the PCMH model of care.
Mary Muscarello, MSN, ANP-C, CDE, CRRN

Nurse Practitioner/Outpatient Diabetes Self-Management Program Coordinator/Inpatient Diabetes Educator, Glen Cove Hospital, New York

Muscarello earned her Bachelor of Science (BS) degree in nursing from Molloy College in Rockville Centre, New York, and her master’s degree in adult health from Stony Brook University, New York. For more than 17 years, she has worked for Northwell Health in various positions, including acute rehab, and as a visiting nurse. A board-certified adult nurse practitioner and certified diabetes educator, she currently works in a hospital-based family medicine clinic, specializing in the care of patients who have diabetes. She works with a socioeconomically disadvantaged population, comprised mostly of immigrants from Central America who have limited English proficiency and limited financial resources. Because many of them have never attended school, literacy and numeracy are major challenges for Muscarello's patients. She uses numerous hands-on tools to enhance her patients’ understanding of their condition and treatment. She believes that the marriage of evidence-based medicine, shared decision-making, and relationship-based care makes all the difference in successfully getting patients to goal. She has been nominated for and received several awards, including the Northwell Health President's Award for Exceptional Patient/Customer Experience for the Eastern Region.

Learning Objectives

1. Evaluate current standards of care (screening, prevention, diagnosis, treatment, management) for patients with diabetes, or who are at risk for developing diabetes, for opportunities to update standards in accordance to current research and evidence-based guidelines.

2. Apply a patient-centered approach to incorporate guideline recommendations for intensifying therapy to achieve glycemic control.

3. Use medication which allow patients to achieve their individualized metabolic targets without weight gain or increasing their risk of developing treatment emergent hypoglycemia.

4. Encourage patients to remain adherent to their prescribed behavioral and pharmacologic therapeutic interventions.
Associated Sessions

• (PBL) Diabetes Treatment Update: After Metformin

Audience Engagement System

Step 1

Step 2

Step 3
Poll Question 1

Metformin has failed to get your patient to glycemic goal. How comfortable are you with intensifying therapy?

1. Very comfortable
2. Somewhat comfortable
3. Minimally comfortable
4. Not at all comfortable
Goals of Care

- Reduce mortality
  - Cardiovascular disease (MI, CVA) is highest cause of mortality
- Enhance quality of life by reducing morbidity and other complications
  - Nephropathy, neuropathy, retinopathy, amputations other vascular complications
- Reduce patient burden

Goals of Treatment

- < 7% (ADA) for prevention of microvascular disease –level A
- < 6.5 % (ACCE) level D- but must be formulated in context of individual patient’s life expectancy, comorbid conditions
- < 8% for those elderly, chronic kidney disease, cognitive impairment, recurrent hypoglycemia, cardiovascular disease, those with short life expectancy
- Fasting glucose 80-130 mg/dl
- 2 hour PPG < 180 mg/dl
- Goals must be individualized
Evaluation of the Patient with Diabetes

- History
- Physical examination
- Labs
- Barriers to care

Patient Barriers

- Patient may be overwhelmed by new diagnosis
- Competing priorities
- Language barriers and/or limited literacy
- Issues with vision and dexterity
- Lack of perceived severity
- Limited financial resources and lack of transportation
- Cognitive impairment
- Depression and other mental health conditions
- Lack of diabetes education and training
Provider Barriers

• Time constraints
• Seemingly ever changing recommendations
• New medications continually coming on the market and patients requesting what they’ve seen on TV
• Lack of training on new medication devices
• Lack of educational support staff
• The dreaded “prior auth” for just about everything

It Takes a Team (ideal world)

• PCP-Physician/NP/PA
• Specialists-Endocrinology, Cardiology, vascular surgery, nephrology
• Podiatrist, Dentist
• CDE (Certified Diabetes Educator)
• Pharmacist
• Physical Therapist
• Registered Dietitian
• Social Worker, other behavioral health specialists
• Care Manager
• Nursing and clerical staff
Level B evidence
It Takes a Team (reality)

- PCP (Physician, NP, PA)
- Medical Assistant
- Clerical

Treatment

Lifestyle modification Always- don’t underestimate it!
- Diet with weight loss-5-10% weight loss can result in improved glucose control
- Exercise - at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. Level A evidence
- Smoking Cessation
Poll Question 2

The goal for HbA1C is:

1. Always < 7%
2. < 7% for those with renal disease, frail elderly and those with cognitive impairment
3. < 9% for patients with cardiovascular disease
4. < 6.5% for those with recurrent hypoglycemia
5. Individualize treatment goals for the patient

While the A1C is important, it only gives you the 60 - 90 day average, not the whole story

<table>
<thead>
<tr>
<th>A1c %</th>
<th>Estimated Average Glucose mg/dl</th>
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<tbody>
<tr>
<td>12</td>
<td>298</td>
</tr>
<tr>
<td>11.5</td>
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<tr>
<td>11</td>
<td>269</td>
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<td>111</td>
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<tr>
<td>5</td>
<td>97</td>
</tr>
</tbody>
</table>
Each of these patients has an A1C of 7%
So what does *average actually mean??*

- **In-Range 70-180**: 24%
- **Hyper < 180**: 18%
- **Hypo < 70 mg/dl**: 9%

**Medications**

- **Oral**
- **Injectable**
There are many paths to get to goal

- SGLT2s
- GLP1s
- DPP4s
- Meglitinides
- Basal Insulin
- Sulfonylureas
- TZDs
- Mealtime Insulin
- Metformin
- Lifestyle Changes

Which one right for your patient?

What Drives Choice of Medication?

- Insured vs uninsured
- Insurance coverage (deductibles / co-insurance)
- Risk vs benefit
- Side effect profile
- Secondary benefits (weight loss, ↓ BP)
- Patient willingness and ability to use
Uninsured Patients

Most cost effective medication:
- Metformin
- Sulfonylureas
- NPH and Regular insulin
- Mixed insulin

Don’t order expensive meds for uninsured patients

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGL
- SU/GlN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- AGL
- Colosevelom
- Bromocriptine QR
- SU/GlN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- TZD
- Basal Insulin
- DPP-4i
- Colosevelom
- Bromocriptine QR
- AGL
- SU/GlN

If not at goal in 3 months proceed to insulin therapy

SYMPTOMS
- NO
- YES

DUAL Therapy
- OR
- TRIPLE Therapy
- INSULIN or Other Agents

ADD OR INTENSIFY INSULIN

PROGRESSION OF DISEASE

ACCE 2017 from creative commons

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
Metformin First

- Inhibits glucagon release from liver and absorption of glucose by muscle
- First line- still for most patients-level A
- Lowers A1C by up to 2% points
- Then consider other options
- Low cost $, weight neutral
Metformin

- Common side effects: nausea, bloating, gas, diarrhea, metallic taste in mouth
- Better tolerated when dosing is titrated and taken with food, rather than empty stomach
- Work up to therapeutic dose of 1,000 mg BID
- Avoid TID dosing to reduce patient burden
- Extended release better tolerated but sometimes not covered by insurance. If not covered, encourage cash pay at big box store
- B12 deficiency (especially if use exceeds 10 yrs., anemia, neuropathy- level B)

Metformin Precautions/Contraindications

Avoid with Renal Dysfunction

Old recommendation: Avoid w/ SCr >1.5 in men and >1.4 in women

Newer Recommendation based on eGFR rather than SCr:

- eGFR > 45: no dose adjustment necessary; monitor renal function at least annually
- eGFR 30-45: use is not recommended for initiation of therapy; if eGFR falls to <45 mL/min/1.73m2 during therapy, consider benefits/risks of continuing therapy; can dose reduce by 50% and monitor renal function every 3 months
- eGFR <30: use is contraindicated

Glucagon-like Peptide-1 Receptor Agonists (GLP1 RA)

Injectable medication
- Increase in glucose-mediated insulin production by pancreatic β-cells - does not work if glucose level is normal
- Low incidence of hypoglycemia
- Slows gastric emptying
- Reduced glucagon secretion
- CNS actions- increased satiety → reduced intake
**Benefits GLP-1 RA**

- Weekly administration option an advantage
- Weight loss
- Reduction of A1C-1.28-1.48%
- Reduced cardiovascular events- level A
- Reduced kidney disease- level C

**Side Effects/Precautions GLP-1 RA**

**Side Effects**

- Nausea, vomiting-26%*
- Diarrhea- 6%*
- Pancreatitis (rare)
- Injection site reactions (rare)
- Medullary thyroid carcinoma (C cell)

*Usually self limited. Dose reduction can decrease incidence

**Precautions**

- Slow gastric emptying → altered absorption of oral medications
- Use with caution with medications with narrow therapeutic index or meds requiring rapid GI absorption
- Avoid in patients with gastroparesis
- Avoid with hx Medullary Thyroid carcinoma or pancreatitis
When to Choose

When metformin not tolerated or does not get patient to goal
- Insured patients only
- Need for weight loss
- Second line agent after metformin
- High cardiovascular risk- diagnosed ASCVD
- Insurance dictates which GLP1 used

GLP1 Choices

- Liraglutide (Vicotoza) taken daily
- Lixisenatide (Adlyxin) take daily
- Exenatide (Byetta) taken twice daily
- Exenatide extended release (Bydureon) taken weekly
- Dulaglutide (Trulicity) taken weekly
- Semaglutide (Ozempic) taken weekly
Patient Education

• Must receive education on pen use and injection technique as each GLP1 has a different mechanism
• Medication storage
• GI effects usually decrease after 1\textsuperscript{st} week
• Injection site reactions rare but can happen
• Report side effects

Poll Question 3

The following are all good candidates for GLP1 RA therapy EXCEPT:

1. Obese 53 yr old, HTN, A1C 7.6% on Metformin
2. Obese 36 yr old, HTN, A1C 11%, uninsured, history of pancreatitis
3. Obese 45 yr old, can’t tolerate Metformin, A1C 8%
4. 72 yr old, A1C 9%, on Lantus, e-GFR 65 ml/min
Cardiovascular Benefits for GLP1 RA

• Several studies (LEADER trial –liraglutide, SUSTAIN-6- semaglutide, ELIXA trial- lixisenatide) have shown reduced risk for MI, CVA and CV mortality and have been given additional FDA approval for this use.
• Level A use

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

Mechanism of Action

• SGLT2 is situated at the first two convoluted segments of the proximal tubule
• Reabsorbs ~90% of the filtered glucose
• Enhance urinary excretion of glucose and decreases reabsorption → lowering the glucose in the blood stream
Poll Question 4

The following are benefits of the use of SGLT2 Inhibitors:

1. Reduced hospital admissions for congestive heart failure
2. Reduced diabetic nephropathy
3. Reduce Triglycerides
4. Reduction in BP
5. All of the above
Benefits of SGLT2 Inhibitors

- Oral medication
- Can be taken anytime
- Lowers A1C 1-2%
- No hypoglycemia
- ↓ BP
- ↓ weight
- ↓ MACE, HF, CKD with some agents

Side Effects

- Polyuria → dehydration
- Hypotension, dizziness
- ↑ UTI and genital infections
- ↑ risk for DKA (rare)

Considerations

- Needs renal dose adjustment
- Expensive
- ↑ LDL-C and creatinine (transient)
- ↑ risk for amputation and fractures (canagliflozin)
SGLT2 Choices

- danagliflozin (Invokana)
- dapagliflozin (farxiga)
- empagliflozin (Jardiance)
- ertugliflozin (Steglatro)
- Many available as combination with metformin, DPP4 inhibitors

Effects of SGLT2 Inhibitors on Congestive Heart Failure

- Reduced hospitalizations for heart failure (both preserved ejection fraction and reduced ejection fraction) for 3 different SGLT2 inhibitors in 3 large studies-CANVAS, DECLARE-TIMI, CREDENCE)
- Reduced CV mortality –level A
- Level C use for nephropathy
More SGLT2 Inhibitors to Come

- May also improve the development of non-alcoholic steatohepatosis (NASH) or development to cirrhosis

- Trials currently ongoing to assess the through reductions in intra-glomerular pressure, SGLT2is attenuate albuminuria by 30-40%

Patient Education

- Advise about hygiene to reduce incidence of genital infections and UTIs
- Educate about the lowering of BP which may cause lightheadedness and to rise from lying or sitting positions slowly
- Advise of increased urination at onset of therapy which will decrease over time-need for active hydration
Sulfonylureas

**MOA:** Closes K+ ATP channels on the beta cell plasma membranes
Increases insulin secretion from beta cells

**Benefits**
- Oral medication
- Easy to administer
- Low cost $
- HbA1c reduction: 1.5%

**Side effects and considerations**
- High risk for **hypoglycemia**, especially if poor or irregular PO intake, elderly
- Long half-life, effects can last up to 72 hours
- Weight gain
- Requires renal adjustment
- Increased cardiovascular risk

DDP-4 Inhibitors

**Mechanism of Action**
- Prevents the degradation of native GLP-1
- ↑ insulin secretion
- ↓ glucagon secretion
- Is glucose dependent
### DPP-4 Inhibitors

**Benefits**
- HbA1c reduction: 0.5–0.8%
- Weight Neutral
- Glucose dependent- no hypoglycemia
- Well tolerated, oral, once daily

**Side effects and considerations**
- High cost $$$
- ↑ HF hospitalization
- Urticaria /angioedema (rare)
- Dose adjustment/avoidance for renal disease
- Potential increase risk for pancreatitis, arthralgia, URI, and bullous pemphigoid

### DPP-4 Inhibitors - Choices

- Januvia (Sitagliptin)
- Galvus (Vildagliptin)
- Onglyza (Saxagliptin)
- Tradjenta (Linagliptin)

**NOT TO BE USED IN ADDITION TO GLP1 RA**
Poll Question 5

Insulin is appropriate for all the following patients except:

1. Newly diagnosed patient with HbA1C of greater than 10% with symptoms
2. HbA1C less than 7% in patient with Type 2 diabetes
3. A morbidly obese patient treated with 3 medications and still not at goal HbA1C
4. Type 2 DM with e-GFR 20 ml/min, A1C 9%
When to Start Insulin

- Newly diagnosed, symptomatic with A1C > 10%
- Not at goal when using 3 non-insulin agents
- Uninsured, not at goal using Metformin and sulfonylurea
- Patients with renal disease that cannot tolerate other agents

Utilize Your Resources

Majority of pharmaceutical companies very willing to help
- Medical liaisons
- Certified Diabetes Educators
- Willing to come to your office
- “Train the trainer”
- Provide non-branded educational materials
Optimization of Treatment-Avoiding Clinical Inertia

- Use a patient centered approach with a team of healthcare professionals to engage the patient in caring for themselves and their diabetes
- Avoidance of medications which increase complications of hypoglycemia, weight gain, worsen renal disease or cardiac disease
- **Choose according to comorbid conditions:**
  - Obesity, Coronary artery disease- GLP1 RA
  - heart failure, renal disease, hypertension- SGLT2 inhibitor

Practice Recommendations

- Reinforce lifestyle changes and smoking cessation at EVERY visit
- Let patients know which meds will continue and which will be discontinued
- Work with what’s covered by insurance
- Use coupons and big box store pharmacies
- Discuss options with patient and allow for shared decision making
- Provide education on use of medication pens
- Educate on side effects and importance of notifying provider, not just stopping medication
- Praise ALL progress. Diabetes is a lot of work!!
- Always offer hope
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Questions
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