An Update on Guidelines and Evidence of the Treatment of Type 2 Diabetes Mellitus

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Update to Guidelines and Evidence Regarding the Clinical Management of Type 2 Diabetes

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Objectives

- Guidelines Regarding Target Hgb A1C
  - What brought us to this point?
    - Review history of T2DM treatment targets
  - Where are we going?
    - Understand evidence behind the recommendations
  - How do we get there?
    - Select pharmacotherapies with patient oriented outcomes
- Evaluate Top 15 Practice Influencing Studies

T2DM Management - A Brief History

- 1921 – Insulin therapy discovered
- 1923 – Commercial production of insulin
- 1940 – ADA founded
- 1947 – Blood sugar control measure with urine
- 1955 – First oral medication (sulfonylureas)
- 1970 – First glucose meter
- 1976 – First insulin pumps
- 1977 – Hemoglobin A1C test developed
- 1978 – Pirart’s study links BG and complications
- 1989 – ADA’s first Standards of Care guide

New Guideline from ACP on Target A1c

- ADA (2018) – <7%, ≤ 6.5% or higher
- AACE (2018) – ≤ 6.5% optimal, or individualized
- ICSI (2014) – <7% to <8%
- NICE (2015) – ≤ 6.5% or ≤ 7%
- SIGN (2018) – ≤ 6.5% or ≤ 7%
- VA/DoD – 6-7% or 7-8.5% or 8-9%

How Does this Differ from Others?

- ACCORD (goal <6.5% vs 7-7.9%)
  - Excess mortality in intensive group (NNTH = 90)
- ADVANCE (goal 6.5% vs 7.5%)
  - No reduction in CV events
  - Less progression to proteinuria (NNT = 100)
- VADT (goal <6.0% vs <9.0%)
  - No difference in CV or microvascular complications
  - Underpowered for main hypothesis test
- UKPDS (Follow-up)
  - 7.1-7.3% yields macro/microvascular benefit compared to 8%
- Meta-analysis of 5 studies showed intensive BG control
  - Reduced non-fatal MI and all-cardiac mortality
  - No effect on all-cause mortality

AAFP Statement

- Support for 2016 ACP CPG
  - Hgb A1c level <7% for many but not all patients
- No endorsement of the 2018 ACP guideline
- Supports individualized targets
- Shared decision-making balancing harms/benefits
- Not “one size fits all” approach
- Not all <6.5% should be de-intensified
Choosing a Target for My Patient

- Hgb A1c level <7% for many but not all patients
- Hgb A1c level ≤6.5% can be considered
- Not all ≤6.5% should be de-intensified
- Individualize targets based on risks
- There is no “one size fits all” approach
- Remember who the Expert really is
- Remember that target A1C is just part of the guideline

Cardiovascular Outcomes with the Diabetes Drug Canagliflozin

- Two industry sponsored RCT's each with 10k pts
  - Mean age 63, A1C 8.2%
  - On metformin, SU, or drug combinations
- Canaglifozin vs placebo over average 3.6 years
  - Benefits
    - Decrease non-fatal MI/CVA, CV-related death (NNT = 224)
    - Decrease composite renal endpoint (NNT = 288)
  - Harms
    - Lower-extremity amputation (NNTH = 347)
    - Fractures (NNTH = 290)
    - Male genital infections (NNTH = 43)
    - Yeast vaginitis (NNTH = 20)

Glycemic Control in Diabetic Patients with Chronic Kidney Disease

- Cohort study of 6,165 diabetic adults with CKD
  - Mean age 70, eGFR <60mL/min/1.73m²
  - On insulin or oral drugs
- Followed for 2.3 years
  - 3% progressed to ESRD
  - 16% died
- U-shaped relation between HbA1c and mortality
  - HbA1c 6-6.9% reference standard
  - HbA1c <6.0% and >9% had higher mortality
  - HbA1c 7-8.9% no difference

Liraglutide and Renal Outcomes in Patients with Longstanding T2DM

- Renal outcomes for industry-sponsored LEADER trial
  - Mean age 64, A1c 8.7%, eGFR 80mL/min/1.73m²
- Liraglutide vs placebo over 4 years decreased
  - Combined renal endpoint (NNT = 60)
  - Size of eGFR decline for baseline 30-60mL/min/1.73m²
- Caveats
  - Decreased new-onset macroalbuminuria carried data
  - No effect on ESRD
  - Cost of liraglutide approx $10k/yr

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes

- Industry-sponsored RCT to establish CV safety
- 15k patients, mean age 62, mean A1C 8%
  - At baseline 70% had prior CV events
- Exenatide vs placebo over 3 years
  - A1c decrease (0.5% vs no change)
  - Primary CV outcome (11.4% vs 12.2%)
    - Found to be non-inferior
    - Not found to be superior

Pioglitazone vs. Sulfonylurea as Add-On Treatment for Type 2 Diabetes

- RCT 3k metformin-treated T2DM patients
  - Mean age 62, mean duration of T2DM 8yrs
  - Mean HbA1c 7.7% and 11% had known CVD
  - Excluded those with Cr > 1.5mg/dL
- Pioglitazone vs Glimepiride/Gliclazide for 5 yrs
  - Composite primary CV outcomes identical (7%)
  - HbA1c similar (approx 7.3%)
  - New HF in 1% of both groups
  - Unspecified “adverse events” > with pioglitazone
  - Hypoglycemia more likely with SU
Canagliflozin as Primary & Secondary Prevention in Patients with T2DM
• Reanalysis of industry funded CANVAS Program
  ▫ Previously demonstrated decreased CV/renal events in patients with T2DM and elevated CV risk
  ▫ RCT 10k patients treated with Canaglifozin for 3.6yrs
• Divided into primary/secondary prevention groups
  ▫ Secondary prevention had higher rate of CV composite outcome
  ▫ Rate of CV composite outcome still lower with Canaglifozin (NNT = 206)
  ▫ Also reduced renal complications
  ▫ No evidence of heterogeneity between groups

Intensive vs. Individualized Type 2 Diabetes Control
• Economic analysis of diabetes management
  ▫ Individualized glycemic control led to
    ▪ Lifetime cost-savings of $13k per person
    ▪ Decreased life-years (36 days)
    ▪ Increased QALY (36 days)
    ▪ Increased lifetime risk for diabetes complications 1%
    ▪ Decreased risk for severe hypoglycemia 1%

Refining the Use of Ezetimibe: Results of an IMPROVE-IT Reanalysis
• Re-analysis of IMPROVE-IT results for T2DM
  ▫ 4,933 study participants had diabetes (27%)
  ▫ Were more likely to be
    ▪ Older, female, have prior MI or CABG
    ▫ Also less likely to meet lab targets
  ▫ LDL goal <70mg/dL, and hs-CRP <2mg/L
  ▫ Ezetimibe reduced primary composite CV endpoint in
    ▪ Patients with T2DM (NNT = 18)
    ▪ Patients w/o T2DM with highest CV risk (NNT = 13)

CV Outcomes with Canagliflozin vs. Non-SGLT2i Antidiabetes Drugs
• Retrospective cohort study comparing CV outcomes with SGLT-2i vs other medications
  ▫ Canagliflozin had lower risk for HF admission over 30 month period than
    ▪ DPP-4 (HR, 0.7)
    ▪ GLP-1 RA (HR, 0.6)
    ▪ SU (HR, 0.5)
  ▫ No difference in composite CV endpoint
  ▫ AMI, ischemic stroke, hemorrhagic stroke

How Broad Are the Benefits of SGLT-2 Inhibitors?
• Industry-funded, multinational, retrospective observational CVD-REAL 2 study
  ▫ 400k patients from 6 nations
  ▫ 27% had established CVD
  ▫ 45% were women
  ▫ Treatment with SGLT-2i reduced risk for
    ▪ Death (HR, 0.51)
    ▪ HF hospitalization (HR, 0.64)
    ▪ MI (HR, 0.81)
    ▪ Stroke (HR, 0.68)

Monotherapy with Metformin vs. SU’s for T2DM w/ Impaired Renal Function
• Cohort study of 175k veterans with T2DM & CKD
  ▫ Pts initiated metformin or SU as monotherapy 2004-09
  ▫ 5k deaths occurred during follow-up
  ▫ Metformin compared to SU had 36% lower mortality risk
  ▫ Associated with fewer deaths per 1000 person-years by following eGFR rates as well (mL/min/1.73m²)
    ▪ >90: 3.0
    ▪ 60-89: 4.3
    ▪ 45-59: 3.4
    ▪ 30-44: 12.1

SGLT-2i and GLP-1 RA Confer Survival Benefit in Patients with T2DM
• Meta-analysis of 236 RCT’s (176k patients)
• Evaluated survival benefits of 3 medications
• Lower absolute mortality risk with
  ▫ SGLT-2 inhibitors 1.0% (NNT = 100)
  ▫ GLP-1 agonists - 0.6% (NNT = 166)
  ▫ No significant difference between these two
• No mortality benefit with DPP-4 inhibitors
• Annual cost to prevent one event > $1 million

Metformin Isn’t Associated with Acidosis in Diabetic Patients with Moderate Kidney Disease
• Cohort study comparing risks for acidosis-related hospitalization with metformin use
  ▫ 75k patients with T2DM, mean age 60
  ▫ No increased risk if eGFR ≥30mL/min
  ▫ Risk doubled if eGFR <30mL/min (NNTH = 85)
Diagnosing Diabetes Using a Single Blood Sample

- Prospective cohort study of 13k patients over 20 yrs
- Among 978 patients with elevated FBG or HbA1c
  - Combined elevation noted in same sample in 40%
    - 98% specific for T2DM dx in 5 years (LR+, 29)
    - Poor sensitivity at 55% (LR-, 0.5)
  - Combined elevation also predicted over 25 years
    - PAD (HR, 2.5)
    - CVD (HR, 1.5)
    - CKD (HR, 1.5)
    - All-cause mortality (HR, 1.5)

How Do Glargine and Detemir Compare with NPH Insulin in a Real-World Setting?

- Retrospective study of patients taking insulin analogs (glargine or detemir) vs NPH insulin
  - 25k pts, mean age 60, started basal insulin 2006-14
  - 92% of patients on NPH insulin; 8% on analogs
  - Over average follow-up of 1.7 years no significant difference between
    - Hypoglycemia-related admissions and ED visits
    - Mean HbA1c levels

Review of Objectives

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How Do Glargine and Detemir Compare with NPH Insulin in a Real-World Setting?

- Benefits of adding canagliflozin to statin therapy on cardiovascular outcomes and safety in patients with vs. without diabetes: Results from IMPROVE-IT. Circulation 2017 Dec 20; [e-pub].

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- Association of initiation of basal insulin analogs vs neutral protamine Hagedorn insulin with hyperglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. JAMA 2018 Jul 3; 320:153.