Update in Outpatient Medicine
November 9, 2019

Robert A. Gluckman MD, MACP
Chief Medical Officer Providence Health Plans

Disclosures

- Stock Holdings
  - Abbott Labs
  - Abbvie
  - Bristol Myers Squibb
  - Proctor and Gamble
  - Walgreens
Topics

- Diabetes mellitus
- Dose de-escalation
- Guideline changes
- New agents
- Benefits beyond glycemic control
- Lipid lowering beyond statins in high risk patients
- Cost Effectiveness of Statins in Primary Prevention
- OTC Meds and DOACs
- Colorectal Cancer Screening in Younger patients and Surveillance in patients with low risk adenomas

Approach to Individualization of Glycemic Targets

Less stringent controls (<8%) in some patients may be appropriate Grade B

Diabetes Care 2019;42(Suppl 1)S61-70
Use and Discontinuation of Insulin Among Adults Aged 75-79 with Type 2 Diabetes

- Longitudinal cohort study of 21,531 patients with Type 2 DM from Kaiser Permanente Northern California aged 75 and followed for 4 years
- Assessed presence of co-morbidities and functional status
- Baseline insulin use 18.9%
  - Mean duration of insulin 7.9 years

Mortality rate in cohort during follow-up
- 7.4%
- 21.4%
- 52.4%
Insulin Use and Discontinuation in the Elderly

- Current guidelines recommend individualized glycemic targets based on health status.
- This cohort study demonstrates greater use of insulin in patients with poor health status.
- This cohort study demonstrates less discontinuation of insulin in those patients with tight control and poorer health status compared to those in good health.
- Insulin is costly and carries the risk of hypoglycemia in the elderly.
- There is an opportunity to consider appropriateness of current regimens, based on health status, in the elderly.
Implementation of Health Plan Switch From Insulin Analogs to Human Insulin

- 14,635 patients managed by CareMore changed insulin regimens
- Ideal candidates were using 2 or more insulin injections/day, receiving basal and prandial injections, > 50 units/day, history of non-adherence and no recurrent hypoglycemia
- Recommended initial dose of human insulin was 80% of prior total insulin dose of either 70/30 pre-mixed insulin or NPH
  - If using 70/30- 2/3 of daily dose before breakfast and 1/3 before dinner

JAMA 2019; 321(4):374-384

Increase HgBA1C of 0.14% likely not clinically significant in Medicare age patients

No increase in hypoglycemic or hyperglycemic events

NS increase in mortality in non-switch group (likely confounders)
Lifestyle Modification and Long Term Clinical Outcomes with Diabetes

- Real world study of 19,293 patients care for in large Boston based academic health system
- Reviewed electronic health record documentation of diet, exercise or weight loss counseling using natural language processing
- Treatment assessment for 2 years after cohort entry
  - Mean follow up 5.4 years after the treatment assessment period
- Primary outcome-time to first CV event
- HgA1C decreased 1.8% in patients receiving at least monthly counseling vs. 0.7% in patients with less frequent counseling

Diabetes Care published online 8/1/19
https://doi.org/10.2337/dc19-0629

ARR at 10 years 5%
NNT 20

Implementation is resource intensive
Potential for group visits, telehealth
Pharmacologic Approaches to Glycemic Treatment

- GLP-1 receptor agonists preferred over insulin for most type 2 diabetics (i.e. HbA1C < 11%)
  - GRADE B recommendation
- SGLT-2 inhibitors or GLP-1 receptor agonists recommended for type 2 diabetics with known CVD
  - GRADE A recommendation
- SGLT-2 inhibitors recommended for type 2 diabetics with CVD and high risk for CHF
  - GRADE C recommendation
- SGLT-2 inhibitors or GLP-1 receptor agonists recommended for type 2 diabetics with CKD

Diabetes Care 2019;42(Suppl 1)

Association of Second-line Anti-diabetic Medications with CV Events in Type 2 DM

- Retrospective cohort study of 132,737 insured adults with Type 2 DM who started second line ADM therapy with a second line ADM with or without metformin.
  - Study conducted from April 2011-September 2015
  - 5.5% of patients had a history of CVD prior to starting second line ADM
- Primary outcome based on time to first cardiac event
  - Defined as hospitalization for CAD, CHF, CVA, PAD

Oral Semaglutide vs. SQ Liraglutide and Placebo in Type 2 DM (PIONEER4)

- 711 patients randomized to oral semaglutide, SQ liraglutide or placebo
- HbA1c 7-9.5% on stable dose of metformin with or without and SGLT-2
- Exclusions: eGFR < 60 ml/min, proliferative retinopathy requiring treatment, pancreatitis, non-protocol DM/obesity meds
- Oral semaglutide 3 mg x 4 weeks, 7 mg x 4 weeks, then 14 mg
- Must be taken fasting with up to 4 ounces of water, no food or beverage for at least 30 minutes, as food impairs absorption of oral semaglutide
- Primary outcome: Change in HbA1c at 26 weeks
- Secondary outcomes: Change in bodyweight at 26 weeks, change ion HbA1c at 52 weeks, change is FBG 26-52 weeks, % reaching HbA1c of < 7%, weight loss of 5% or 10%

Lancet 2019;394:39-50
Glycemic control

Proportion of patients HbA1c < 7%

Weight Loss
- Oral semaglutide more effective than SQ liraglutide in lowering HbA1c at 52 weeks
- Oral semaglutide more effective than SQ liraglutide at 26 and 52 weeks for weight loss
- Important to instruct patients on how to take medication correctly
- Rates of adverse events for oral semaglutide
  - Nausea 20%
  - Diarrhea 15%
  - Nasopharyngitis 14%
- Rates of discontinuation 11% oral semaglutide vs. 9% SQ liraglutide vs. 4% placebo

Efficacy and safety of once weekly semaglutide vs. daily canagliflozin added to metformin
SUSTAIN 8 Trial
- 788 patients aged 18 or older with type 2 DM and HbA1c 7-10.5% on at least 1500 mg metformin randomized to semaglutide 1 mg SQ once weekly vs. canagliflozin 300 mg once daily
- Primary endpoint was change in HbA1c at 52 weeks
- Secondary endpoint was change in bodyweight at 52 weeks

Lancet Diabetes Endocrinol published online 9/17/19
<table>
<thead>
<tr>
<th></th>
<th>Semaglutide</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 7%</td>
<td>66%</td>
<td>45%</td>
</tr>
<tr>
<td>HbA1c &lt; 6.5%</td>
<td>53%</td>
<td>24%</td>
</tr>
<tr>
<td>Weight loss 10% of greater</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>Discontinuation of treatment</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Use of SGLT2 inhibitors and risk of major CV events and CHF: Scandinavian register based cohort study

- Cohort study from registry data from Denmark, Norway, and Sweden
- 25,988 eligible new users of SGLT2 Inhibitors and 94,411 new users of DPP4 inhibitors
- Median follow up 1.4 years
- Primary outcomes-major CV events (MI, CVA, CC death) CHF event (hospitalization or death)
- Secondary outcome-all cause mortality and individual components of major CV events.

BMJ 2019;366:l4772

Meta-analysis demonstrated benefit (HR 0.86) in patients with established ASCVD
81% of cohort without ASCVD
Intention to treat an analysis demonstrated reduction in CHF and all cause mortality, but not major ASCVD event.

As treated analysis demonstrated larger HF and mortality benefit and a reduction in major ASCVD event.

Summary - Diabetes Mellitus Update

- Oral semaglutide now approved by FDA and will be on the market soon
- Expensive, similar to injectable GLP-1 agonist
- GLP-1 agonist now recommended for most Type 2 diabetics before insulin
  - Expensive
  - Human insulin less expensive and for most Type 2 diabetics as effective without increased adverse events
- Patients taking SGLT-2 inhibitors have lower CHF risk
  - Less impact on glycemic control than GLP-1 agonists
- Sulfonylureas have cost benefits but some increased risk for CV events
Effect of Simvastatin-Ezetimibe Compared with Simvastatin Monotherapy after ACS in Patients ≥ 75 Secondary Analysis IMPROVE-IT Trial

- 18,144 patients randomized within 10 days of ACS to simvastatin 40 mg monotherapy - vs. simvastatin 40 mg plus ezetimibe
- LDL 50-125 mg/dL without history of lipid lowering or 50-100 mg/dL if on Rx
- Primary endpoint- CVD death or major adverse cardiac event defined as non-fatal MI, unstable angina leading to hospitalization, revascularization 30 days after index ACS, non-fatal CVA.

JAMA Cardiol 2019;4(9):846-854
Effect of PCSK9 Inhibitor Evolocumab on Total CV Events in Patients with CVD
A Prespecified Analysis from the FOURIER Trial

- 27,564 patients aged 40-85 with prior MI, CVA, or PAD
  - LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL while taking optimized statin therapy
  - Randomized to SQ evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo
  - Primary endpoint time to composite CV death, MI, CVA, hospitalization for unstable angina
    - Secondary endpoint- above minus unstable angina
  - Median follow up 2.2 years

JAMA Cardiol. 2019;4(7):613-619
89.5% of trial patients had no events
5.7% had a single event
3.5% had two events
1.4% had 3 or more events

For every 1000 patient treated for 3 years
- 22 First events prevented
- 52 Total events prevented
Updated Cost-effectiveness Analysis of Evolocumab in Patients with Very High-risk ASCVD as defined by the 2018 ACC/AHA Guideline

- Updated cost-effectiveness analysis based on 60% price reduction in October 2018
- Patients had very high risk ASCVD with LDL ≥ 70 mg/dL despite maximally tolerated statin therapy
  - Only 5-6% patients received ezetimibe
- Modeled different scenarios considering baseline risk
  - 4.4 events per 100 patient years based on FOURIER clinical trial patients at VHR
  - 6.4 events per 100 patient years based on patients in usual clinical practice
  - 12.3 events per 100 patient years representing the usual clinical practice rate multiplies by the 2 fold risk since in VHR patients in the FOURIER Trial

JAMA Cardiol 2019;4(7):691-695

ACC/AHA Guideline VHR Criteria

- History of multiple ASCVD events (recent ACS, History of MI or ischemic stroke, symptomatic PAD)
- 1 major ASCVD event and multiple high risk conditions
  - Age 65 or greater
  - Current smoking
  - Familial hypercholesterolemia
  - CHF
  - DM
  - HTN
  - CKD
  - Prior revascularization (CABG or stent)
  - LDL greater than 100 mg/dL despite maximal therapy
Ezetimibe is generic and inexpensive and should be used first in VHR patients with persistently elevated cholesterol.

- FOURIER Trial enrolled few patients with ezetimibe added to a statin.
- Patients with persistently elevated cholesterol and VHR probably benefit from adding a PCSK9 Inhibitor.
- Cost effectiveness has significant variation based on risk estimates.
Cost Effectiveness of LDL Cholesterol Level Guided Statin Therapy in Patients with Borderline CV Risk

- Microsimulation model of 4 statin treatment strategies
  - Treat all patients with 10 year absolute risk ≥ 7.5%, diabetes, or LDL ≥ 190 mg/dL
  - Treat patients with 10 year absolute risk 5.0-7.4% and LDL 160-189 mg/dL
  - Treat patients with 10 year absolute risk 5.0-7.4% and LDL 130-159 mg/dL
  - Treat all patients with 10 year absolute risk ≥ 5.0%
- Modeled treatment with moderate intensity statin for borderline risk patients
- Modeled lifetime treatment in 100 simulated cohorts of 1 million patients aged 40 at baseline

JAMA Cardiol. 2019;4(10):969-977
Treating patients with borderline risk and LDL ≥ 160 is likely cost saving
Treating patients with borderline risk and LDL 130-159 may be cost saving in men and likely cost effective in women
Assumes 50% adherence and 0.5%/year development of diabetes
Long time horizon for cost savings to develop
Unclear if CAC scoring would increase efficiency
Need patient centered approach

Prevalence and Knowledge of Potential Interactions Between OTC Products and Apixaban
Surveyed patients treated at UCLA and UCSF who were taking apixaban
34% of patients reported daily or almost daily use of at least one OTC product with potential interaction with a DOAC
27.2% additional patients reported some use of OTC meds with potential risk
Increasing use of DOACs
Emphasizes the need to question about use of OTC meds

Colorectal Cancer Screening for Average Risk Patients-2018 Update from the ACS

- Qualified recommendation to start screening at age 45
- Stool based test or structural exam
- Incidence 45-49 31.4/100,000
- Incidence in 50-54 58.4/100,000

Doi:10.3322/caac.21457 Available online at cacancerjournal.com
Colorectal Cancer Screening- ACS Guideline

- Colon cancer rates increasing in younger patients, but still much less common than patients > 50
- Significant decrease in CRC rates in older patients likely related to screening
- ACA mandate to fully cover cost of CRC screening is based on USPTF (age ≥ 50)
- Colonoscopy first strategy in younger patients costly to patients
- Models show similar impact in mortality reduction for colonoscopy first vs. FIT
- FIT first offers less opportunity to reduce CRC incidence
- Cost of universal screening with a mix of colonoscopy and FIT at an estimated cost $250 per screen- estimated $5.5 billion or $6.1 million per death averted
Long Term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps

- Follow up of 3 large cohort studies including 122,899 who underwent removal of conventional adenomas
- Median follow-up 10 years

https://doi.org/10.1053/j.gastro.2019.06.039

Questions?