Chronic Care Roundtable Meeting

Medication Care Paths for Type 2 Diabetes and Advanced Complications

November 13, 2019
John W. Kennedy, M.D.
President, AMGA Foundation
Chief Medical Officer, AMGA
Thank You
ADA Diabetes Guidelines Algorithm
Implementing an algorithm or care path for use of SGLT-2i for Patients with Type 2 Diabetes and CKD despite ACEI/ARB

Evan Norfolk MD
Chair Nephrology, Geisinger
November 13, 2019
The Science
The Government
Geisinger
Guidelines
Population Health Tools
  – Computers
  – Communication
  – Staff
Developing a Care pathway
Average Clinic Patient

63 yo male w/ hx of CAD, GERD, PVD, Obesity, HTN. Hx of DM 2 x 9 years has known retinopathy, and neuropathy. At least one trip to the cath lab
Presents to nephrology in 2016
No hx of NSAIDS/ No fx renal disease
Meds Atorvastatin, Gabapentin, Lasix, Lisinopril, Hydralazine Amlodipine, Insulin glargine, and insulin Aspart, ASA

Labs:

<table>
<thead>
<tr>
<th>Year</th>
<th>CR</th>
<th>eGFR</th>
<th>ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>1.0</td>
<td>&gt;60</td>
<td>600</td>
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<tr>
<td>2015</td>
<td>1.3</td>
<td>58</td>
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<tr>
<td><strong>2016</strong></td>
<td>2.4</td>
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<tr>
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Medicare Spending on ESRD

1% Medicare population
$35.4 Billion dollars 2016
7% Medicare FFS Costs

Epidemiology and Dx

DM 2 is 7th leading cause of mortality in US

DKD - Leading cause of CKD-> ESRD

50% of cases of ESRD

Diabetic w/ risk of developing DKD

– 33% type I  50% type II

Mortality:

– DKD  3-12 x increased beyond that of DM
– 90% die before ESRD

Diagnosis

– ACR > 30 mg/g
– Albuminuria > 30 mg/ day
– Decreased GFR
Sodium Glucose Co-Transporter
SGLT-2 Inhibitor – Renal Protection Against Hyperfiltration

SGLT-2 blocks Na/Glucose -> natriuretic response -> TGF-> Afferent vasoconstriction -> Decreased Intraglomerular Hypertension
  – Decreased hyperfiltration / Improved dynamics
  – Decreased albuminuria

Ace/arb -> efferent vasodilation

Combination-  – Combined impact on intraglomerular pressure
  Initial drop in GFR which plateaus over time
SGLT2i - Renal protective Effect
SGLT2i - Renal protective Effect w Ace-I
Benefits of SGLT2 Inhibitors

Wt loss
- Glucosuria: loss of 60-100g glucose/day
- 5 to 7 lbs after 3 months
- plateaus after 6 months

Renal protective  (normalization of hyperfiltration)
- Decreased albuminuria
- Decreased Hyperfiltration

Blood pressure decrease  5 mm Hg/ 2 mm Hg
- Empagliflozin, dapagliflozin, canagliflozin (class effect)
- Empagliflozin only agent with decreased nocturnal SBP
- Mechanism: improved endothelial fx, vascular compliance by blocking oxidative stress
# SGLT-2 Inhibitor Effect On Serum Glucose

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Effect on A1C</th>
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<tr>
<td>Normal Renal Fx:</td>
<td>Hba1c decreased by 1%</td>
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<tr>
<td>eGFR 60-90</td>
<td>Decreased A1C 0.7% (Empagliflozin)</td>
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<tr>
<td>eGFR 30-60</td>
<td>Decreased A1C by 0.4%</td>
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SGLT-2 inhibitors in DKD – Benefits

Decrease serum uric acid
Decreased SNS

Hyperglycemia
  – Decreased fasting and post prandial hyperglycemia
    • enhanced B Cell function
    • decreased insulin sensitivity

Effect on A1C
  – Normal Renal Fx → decreased 1%
  – Decreased eGFR → blunted effect
  – Renal protective effects not due to improved glycemic control

Diuretic effect → Natriuresis
SGLT-2 Adverse Effects

Genital Candida Infections  Most common adverse effect  
  – Equally M=F

Canagliflozin  
  – Increased bone fractures  
  – Increased incidence LE amputations (Legs/ Feet/ Toes)  
  – Not seen with empagliflozin/ dapagliflozin
SGLT-2 Adverse Effects

Urinary Infections
Polyuria
Postural Hypotension
DKA – Canagliflozin - 73 cases of DKA/ Ketosis – March 2013- May 2015; Not seen in large clinical trials; FDA Warning
AKI- Canagliflozin, Dapagliflozin
Fournier gangrene
– Necrotizing fasciitis 12 cases over 5 years in 1.7 million patients
What to tell patients about the agent?

Concern for DKA
- Mainly in insulin or sulfonylureas if decrease or discontinued
- Increased risk if volume depletion

Watch for groin infections
Current SGLT-2i on the Market

First approved for use in approx. 2013-14

Dapagliflozin  Farxiga
Empagliflozin  Jardiance
Canagliflozin  Invokana
Ertugliflozin  Steglatro
### SGLT2i Use and eGFR Recommendations 2019

<table>
<thead>
<tr>
<th>Medication</th>
<th>eGFR &lt; 30</th>
<th>eGFR 30-60</th>
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<tr>
<td>Dapagliflozin</td>
<td>Avoid Starting</td>
<td>Not Recommended</td>
<td>Discontinue</td>
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<tr>
<td></td>
<td>eGFR &lt; 60</td>
<td>30-60</td>
<td>&gt; 60</td>
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<tr>
<td>Empagliflozin</td>
<td>No renal dosing</td>
<td>Stop if</td>
<td>Contraindicated</td>
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<tr>
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<td>&lt;45</td>
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<td>Do not start if</td>
<td>Stop if</td>
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<td>eGFR 45-60</td>
<td>30-45</td>
<td>&lt;45 Persistently</td>
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<td>Ertugliflozin</td>
<td>Avoid starting</td>
<td>Not recommended if</td>
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Lack of glycemic effect
Lack renal outcomes
Lack safety data
Lower eGFR trials needed

Geisinger
<table>
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<tr>
<th>Study</th>
<th>Year of Publication</th>
<th>Powered for Renal Outcome</th>
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<td>EMPA- REG</td>
<td>2015</td>
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<td>Canvas / Canvas-R</td>
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<td>Declare-Timi58</td>
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<td>Credence Trial</td>
<td>2019</td>
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<td>Dapa CKD</td>
<td>Est. November 2020</td>
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Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Patients – Removing Excess Glucose (EMPA-REG Outcome Trial) -2015

7020 pt w/ DM 2 w/ CAD + PVD or Cerebrovascular Disease randomized to Empagliflozin 10mg, 25 mg vs Placebo
Baseline eGFR > 30
- 26% had eGFR <60
- 40% population had proteinuria
Primary endpoint- cardiovascular death, nonfatal MI, nonfatal stroke
- Sig decreased by Empagliflozin
- Early decrease risk of cardiovascular death (38%) and CHF hospitalizations (35%)
  • Not accounted for by decrease in MI or CVA as there rates were unchanged.

Terminated 3.1 years due to Empagliflozin benefits
All Cause Mortality decreased (32%)
Heart failure most sensitive outcome
Empa-Reg Endpoint (Empagliflozin) -2015

44% Risk Reduction in doubling of serum Cr
38% Risk Reduction decrease in ACR
55% Risk Reduction decreased of RRT
Empagliflozin resulted in decrease in loss of eGFR by 0.9 ml/min/yr

Significantly reduced rate of death from Cardiovascular causes, hospitalization, heart failure and death

14% reduction major adverse cardiovascular events

Increased risk genital infections
Urosepsis
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (Canvas/Canvas-R) -2017

Two trials; 10,142 patients w/ DM2 and CAD
RCT canagliflozin vs Placebo for 188 Wk (3 yr/ 7 mth)
Primary endpoint composite Cardiovascular death, nonfatal MI, nonfatal CVA.
Primary outcome lower w/ canagliflozin
Renal outcomes not statistically significant but possible benefit of canagliflozin
  • Decreased progression of albuminuria
  • Improved composite outcome of a sustained 40% decreased in eGFR, RRT, or Renal related deaths
**Adverse effects Canvas/Canvas-R**

- Increased bony fracture
- Increased risk of amputations (toes/feet/legs) doubled
  - not seen w/ empagliflozin or dapagliflozin
  - EMPA- Reg- retrospective analysis no increase in lower limb amputation
Declare TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) - 2018

17,160 Pts with T2DM, 2/3 no prior cardiovascular disease

Hypothesis DM 2 rx w/ dapagliflozin decreased endpoints
- Primary safety endpoint – MACE (cardiovascular death, myocardial infarction, or ischemic stroke)
- Primary efficacy endpoint MACE + composite cardiovascular death or Heart failure w/ hospitalization
- Secondary outcomes were a renal composite (≥40% decrease in eGFR to < 60, New ESRD, death from renal or cardiac or any cause of death.

Dapagliflozin
- No decrease in adverse cardiovascular events
- Reduced reduce the risk of CHF hospitalization
- Reduced renal composite outcome
  - 40% decrease in eGFR, ESRD, or renal death

No major safety concerns.
Declare Timi 58 (from NEJM)

Followed for 4.2 years

Results:

– Dapagliflozin was noninferior to placebo regarding MACE
– lower rate of cardiovascular death or hospitalization for heart failure

– Adverse
  • DKA more common than placebo
  • Genital infections leading to discontinuation of the agent.
Canagliflozin and renal outcomes in type 2 DM and Nephropathy (Credence Trial) 2019

4401 patients double blind RCT DM 2 w/ albuminuria to canagliflozin 100 mg vs placebo

Cohort:
- eGFR 30-90 and albuminuria (UACR > 300 mg/g) - high risk for renal failure
- All on Ace./ARB for one month prior to randomization (max labeled dose or dose not associated w/ side effect); No dual RAS blockade
- Categories of gfr 30-45; 45-60 / 60-90; gfr < 30 excluded

Primary endpoint composite Renal end pt (CKD5. ESRD, Renal tx.), doubling of cr, death from renal or cardiovascular causes

Stopped early 2.62 years
Primary Outcome

- 30% lower relative risk with canagliflozin than placebo of primary composite outcome: ESRD, doubling cr, renal or cardiovascular death
- 32% lower Relative Risk of ESRD

**NNT TO PREVENT ONE DIALYSIS = 16**

Canagliflozin also had lower risk cardiovascular death, mi, CVA, hospitalization for CHF, composite cardiovascular death, mi, or CVA (not all on RAS blockade)

No difference in amputations or fractures

- Unclear if amputation was due to different populations or protocols (they looked at feet more closely here)

Rates DKA low but higher in canagliflozin vs placebo

11/2200 vs 1/2197
Credence - Nonhemodynamic mechanisms of renal protection

Decreased inflammation – NLRP3- inflammasome in cell
Decreased oxidant stress by 60%
Blunted intrarenal angiotensinogen levels

Credence- glucose lowering is minimal in eGFR of 30-44 mL/min
September 30, 2019: Updated indication for adults w/ DKD and proteinuria

- Reduce the risk of ESRD
- Reduce risk of worsening of kidney function
- Reduce risk of cardiovascular death
- Reduce risk of hospitalization for CHF

- Only DM2 agent approved to treat DMD and decrease risk of CHF hospitalizations
A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD)

4000 pts - RTC - dapagliflozin versus placebo, to see effect on CKD, or cardiovascular or renal death.

4 year study- Start date – 2/2017

Primary Outcome first occurrence of any of the components of the composite

– ≥50% sustained decline in eGFR
– ESRD
– CV death
– renal death

Est Completion Nov 2020
4 agents approved for DM2/ CKD

Efficacy to lower a1c depends on agent
  – Greater reduction occurred w/ empagliflozin

Canagliflozin, dapagliflozin and empagliflozin decreased reduction in urine ACR compared to placebo

eGFR decrease after starting med
  – 4-5 ml/min/1.73 m2 decreased

Generally returns to baseline or when med stopped
Renal disease #9 cause of death
100,000 pts on tx waiting list
20% of Medicare dollars - $114 billion/yr are spent on kidney disease
Goals:
  – fewer patients developing ESRD (25% decrease by 2030)
  – fewer Americans receiving dialysis in dialysis centers / Increase kidneys available for transplant.
  – 80% incident ESRD patients on home modality or transplant
  – Double the number of kidneys for transplant by 2030

CMII 4 Payment models
  – goal of align incentives for providers
ESRD Treatment Choices – Mandatory model: Enroll 50% dialysis providers in new model w/ incentive to encourage home modality –
  – Payment changes on Medicare claims from January 1, 2020 through June 30, 2026.

Home modality:
  – Currently 12% home dialysis penetration
  – Target: 80% transplant or home dialysis

Transforming organ donation and transplant process
  – Reform the organ procurement and management
  – Compensate lost wages and child care expenses
  – Increase the number of available organs

Encourage prize competitions through public-private partnership

HHS will launch a public awareness campaign about kidney disease
  – 40% CKD patients are unaware
Public-private partnership between HHS, FDA, and ASN to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases. Encourage development of wearable/implantable artificial kidneys. Accelerating the development of drugs, devices, biologics and other therapies across the spectrum of kidney care. Disruptive technologies via competitive, non-dilutive funding to innovators. Coordination clearer and less expensive path to bringing products to daily care. Urgency - spotlighting immediate needs.
What is Geisinger?

Largest Rural Health Care System in the U.S.
Approximately 4.6 million people in service area
    - > 100,000 inpatient admissions/year
    - > 6.7 million outpatient encounters/year
1900+ Physicians, 1200+ Advanced Practitioners
100+ Community Practice sites
12 Hospitals
500,000 + member health plan
2 Research Centers
Medical School - Geisinger Commonwealth School of Medicine
Healthcare IT and Informatics
    - EPIC Ambulatory (1996)
    - EPIC Inpatient (2007)
Nephrology Staff

Twelve Staff Physicians
- Two transplant nephrologists
- Two clinical investigator

Four mid-level providers
Two nephrology fellows
Five case managers
Four renal pharmacists
Physician leadership drives changes in clinical practice

Culture:
- Value = Quality/Cost
- Re-engineering /Transforming Care
- Data, Metrics, Outcomes
Example of Disease Management – Anemia

Initial hypothesis – That traditional mode of care, that is ESA oversight and management primarily by physicians, was not leading to optimal care

– Appropriate interval labs were being missed
– Appropriate interval ESA adjustments were being missed
– Appropriate adjuvant therapy (IV iron) was not being optimally utilized
Fundamental Design- MTM

Pharmacist responsible for
- Obtaining insurance authorization for ESA therapy
- Ensuring timely appropriate labs and review of same
- Ensuring timely, appropriate adjustment in ESA therapy
- Arranging IV Iron therapy as indicated by protocol
- Discussion with physician, patient parameters that don’t fit into protocol

Program inception September 2003 – Since 2006 all pts with CKD 3 or greater with ESA requirements enrolled in program

Nephrology paid by system for oversight of program
Outcomes Show Improvement

- Expanded dose interval
- Average ESA dose
- Time in goal Tsat
- Site of administration
- Hemoglobin Time in goal
- Days to Goal
Pop health tools and issues

Identifying at risk patients
Protocols and pathways
EHR Alerts
Ask a Doc tools
Specialty clinic- use of
  – Pharmacists
  – Case management
Access & Affordability
At risk patients

What is problem you want to solve?
Is solution evidence based? / how strong is the evidence?
DO YOU HAVE PROVIDER AGREEMENT ON GOALS?
  – If algorithm -> will everyone use it?
  – Exclusion patients- ie: Hypertension goals, Hba1c
Can you easily identify the patients?
  – Meaningful Use
Tracking a population

Patients lists
  Manually
    - outside of electronic record
    - in electronic record

  Automatically
Identifying Patients

Data issues
- Problem list - garbage basket (shared); Is it being used?
- Diagnoses - ICD10 and sub-diagnoses
- Meds
  - Is the med list accurate?
  - Are you receiving external data feeds?
- Labs
  - Discrete data? - external papers
  - Trending of data
- Can you pull all data into one place
- NLP
When to intervene?

Reports- How long does it take to obtain data to identify the target patients?
  – Can you query system in real time?
  – Do you need an analyst to write reports? (timeframe/money)
  – Are you dependent on EHR vendor?
  – What happens when you want to tweak the report?
    • Do have consensus?

Identifying patients before the visit for labs?
Identify at visit and making an intervention?
Alerts – Point of Care

Identify care gaps during the visit to make provider aware

Who receives the alert?
- Nursing staff work on protocols - Eg: flu shot; Working to the top of license?
- Provider alerts

System alerts
- Do they appear during the correct part of the workflow?
- Is verbiage cumbersome?
- Do they provide adequate information?
- Is it actionable?
- Are you measuring provider reaction to alert? Are they ignoring alert?
  - If so why?
Populations Workflows

Clinic based workflows
  – Before clinic
  – During clinic visits
  – After clinic visits

Active patient population followed by providers

Attribution

Patient population at large
Patient has Type 2 diabetes mellitus with kidney complication, without long-term current use of insulin (E11.29) With Type 2 diabetes mellitus with stage 3 chronic kidney disease (N18.3) with persistent proteinuria (R80.1). Confirm patient is on first line therapy then consider use of Dapagliflozin, Empagliflozin, Canagliflozin, or Ertugliflozin.
Pt w/ DM CKD and Proteinuria on Metformin. Consider SLGT2i.
Pt w/ DM CKD and Proteinuria on Metformin. Consider SLGT2i.
Last Hba1c: 8.4 (8/15/19)
Last eGFR 59 (8/15/19)
Last ACR 35 (1/6/19)
Pt w/ DM CKD and Proteinuria on Metformin. Consider SLGT2i.

Last HbA1c: 8.4 (8/15/19)
Last eGFR 59 (8/15/19)
Last ACR 35 (1/6/19)

Order Empagliflozin
Order Canagliflozin
Pt w/ DM CKD and Proteinuria on Metformin. Consider SLGT2i.

Last Hba1c: 8.4  (8/15/19)
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Order Empagliflozin
Order Canagliflozin
Will not add (Enter Reason)
Order Med from Alt Class
Pt w/ DM CKD and Proteinuria on Metformin. Consider SLGT2i.
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Insurance covers Canagliflozin

Order Empagliflozin
Order Canagliflozin

Will not add (Enter Reason)
Order Med from Alt Class
American Diabetes Association Diabetes Care, 2019. Jan; 42(Supplement 1): S90-S102. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.
Electronic Health Record  DM 2 Order Set

- Nutrition Referral (lifestyle changes)
- Wellness Coach Referral (lifestyle changes)
- Metformin (First Line therapy if eGFR > 45)
  - eGFR > 60  Metformin 1000 mg po daily
  - eGFR 45-59  Metformin 500 mg po daily
- Second Line - ASPVD Main Risk- GLP-1
- Second Line - CKD/ CHF Main Risk- SGLT2i
- Second Line - Cost Constraints Sulfonylureas/ TZD
- Third Line - SGLT2i (If already on Metformin/GLP1)
- 2nd or Third Line - DPP-4 (if GLP-1 Contraindicated)
- Basal insulin
Scorecard

### Outcomes Clinic 1

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<thead>
<tr>
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<th>Jan-18</th>
<th>Feb-18</th>
<th>Mar-18</th>
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<td>Measure of urine ACR</td>
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<td>Use of ace/arb if DM microalbuminuria</td>
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<td>Blood pressure at target (140/90)</td>
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<td>30 Day readmission</td>
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<td>Outcome Measures</td>
<td>Jan-18</td>
<td>Are you reviewing the data?</td>
<td>Is the data pushed?</td>
<td>Do you need to retrieve it?</td>
<td>Do you have targets?</td>
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Dr. Smith
Scorecard

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<td>48</td>
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Admission 8 6 7
30 Day readmission 4 4 4

Why is one providers data not consistent?
- Labs scanning issue?
- Priorities to provider?
  - Overwhelmed / too many alerts
  - Doesn’t care measure
- Carrot/ Stick
Geisinger’s program to easily route questions to a specialty (35 specialties) Specialist replies in predefined time

Easy inline workflow in electronic health record

Specialist can review pt record and conveniently documents reply and route answer in patient’s chart

No need to figure out who to call

Reduce scheduling of unnecessary face-to-face consultations with specialists

Helps specialist to triage urgent cases which need to be seen urgently – right care/ right patient/ right time

> 99% completion rate
Ask a doc - Outcomes

- Decreased turnaround time between primary and specialty physicians: 6½ hours compared to traditional referrals, which could take weeks to months.
- 14% reduction in total cost of care in first month of program.
- 20% reduction in cost in 2nd month.
- 74% drop in specialist visits.
- 84% of Geisinger PCP use it routinely.
- Over 17,000 consults thus far.
- 10% of all Geisinger referrals to participating specialties.
- Opened up almost 4,000 additional face-to-face specialty slots in 2018.
Ask-A –Doc

How to best leverage this tool for use of SGLT-2?
Nephrologist Thoughts on SGLT2i Use...

Directly Ordered: yes 4  no 5  Request others order: yes 4  no 5

“I would feel wary of prescribing it in patients with diabetic foot ulcers/severe PVD, frequent UTIs, or poorly controlled diabetes/poor compliance.”

“I am not very familiar with them and I have to study more about it”

“generally uncomfortable prescribing diabetes meds since I’m not primarily responsible for DM management, worry about side effects and clear communication to other team members about changes, would favor this be driven by pharmacy in our dept”

“occasionally ask MTM/PCP to consider these; have definitely had MTM approach me about “

“The main issue is practical. DM is managed by PCP and MTM Clinic for vast majority. To start this “drug might mean we have to stop/adjust other drugs”

“Have asked PCP and MTM clinic to start.. but lot of them gets stopped for various reasons----Pre renal AKI, yeast infections, DKA etc. “

“Multiple times [have asked for them to be started].got good response from PCPs and endocrine”

“I think it is challenging to start managing a diabetic medication which is also being managed by PCP. Who takes responsibility for managing the patient’s diabetes? I also don’t think there is enough time in most clinic visits to take this on. MTM management I believe would be the best.”
we should be using them in the appropriate population. That being said, I'm not sure we should be the ones prescribing them. They are becoming the "new anti-RAAS" therapy, and for good reason.

However, a nephrologist prescribing an SGLT2i can open a can of worms in my opinion (side effects, monitoring, need for adjustment in other components of DM regimen, etc.). They SHOULD be standard of care in our department for the right group of patients, but I think utilizing the MTM pharmacist is the best way to make that happen. If we see a candidate for an SGLT2i, we should refer to MTM DM pharmacist or message them if they already follow. Same goes for Endocrine if they are following.
MTM Pharmacist - SGLT-2 Considerations

Connected EHR
- Physical location/ Modes of communication

Algorithms
Tailor meds
- SGLT2i and diuretics
- Discontinuation SGL2i

Labs
- Glycemic effect
- Follow-up cr

Education
Med interactions:
  - Sulfonylureas / insulin

Compliance
Med List Accuracy
Work w/ physician
Document in EHR
Pharmacist Salary?
Summary – Science

SGLT-2 Inhibitors are cardiorenal risk reduction agents w/ glucose lowering as side effect
Only class of drug since RAS blockers to show decreased progression of CKD
Canagliflozin now shown to further slowed CKD when combined with RAS
Glucose lowering effect is blunted w/ lower eGFR
Use only until eGFR =30
Summary - Algorithm

Consensus
- Patient population
- Provider Workflow
- System tools

Electronic pathways

MTM Pharmacist

Scorecards - Process measures
- Data review
- Attribution
- Giving providers back their data
- Improving process measures

Outcome data review

Geisinger
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A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD) https://clinicaltrials.gov/ct2/show/NCT03036150
Patients with Type 2 Diabetes and Chronic Kidney Disease

Nikita Stempniewicz
AMGA Foundation Chronic Care Roundtable
November 2019
AMGA’s Distinguished Data and Analytics Collaborator
Clinical guidelines (ADA) recommend measuring urine albumin, e.g., urine albumin to creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR) at least once per year in all patients with type 2 diabetes.

- Powerful predictors of future health care costs and utilization, and cardiovascular and kidney outcomes
- Allow providers to screen, diagnosis, and risk stratify chronic kidney disease (with a known risk relationship)
uACR and eGFR Measurement by Org. and Site of Care

- 520,000 patients aged 18 – 85, with ≥ 1 visit with a PCP in 2018, no ESRD, and a Dx for T2DM

https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3236557
uACR and eGFR Measurement by Org. and Site of Care

- 520,000 patients aged 18 – 85, with ≥ 1 visit with a PCP in 2018, no ESRD, and a Dx for T2DM

https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3236557
Quality Measures for CKD in T2DM

• Medical Attention for Nephropathy (current measure): Percentage of patients who had a nephropathy screening test or evidence of nephropathy
  – any urine protein test OR
  – diagnosis of nephropathy OR
  – visit with a nephrologist OR
  – prescribing ACE-i or ARB

• Kidney health evaluation (proposed replacement): Received a kidney health evaluation
  – eGFR AND
  – Urine Albumin-Creatinine Ratio (uACR)

Issues with Medical Attention for Nephropathy Measure

- eGFR not included, an important test for CKD detection and risk stratification
- “Topped-out” at most health systems, false sense of optimal kidney care for people with diabetes
Patients w/ uACR + eGFR – By Organization

618,000 patients aged 18-89, with ≥ 1 visit with a PCP in 2018, and a Dx for DM (T1 or T2)

No measurement
uACR+eGFR measured

Medical Attention for Nephropathy in current NCQA Comprehensive Diabetes Care group: Red lines show 25th, 50th, and 75th percentiles of performance (2018 Q4) among 90 AMGA member organizations in Together to Goal®, AMGA Foundation’s campaign to improve care for 1 million people with type 2 diabetes.
Issues with Current Medical Attention for Nephropathy Measure

- eGFR not included, an important test for CKD detection and risk stratification
- “Topped-out” at most health systems, false sense of optimal kidney care for people with diabetes
- Convoluted measure: can meet the numerator in multiple ways, which may or may not have been a deliberate attempt to address nephropathy
Background

- 685,000 patients with type 2 diabetes receiving care at 24 different health care organizations
  - patients age 18 – 75, with a diagnosis of type 2 diabetes, and ≥ 2 visits in the last 18 months with a PCP, cardiologist, endocrinologist, or nephrologist

- Urine protein measurements
  - kidney health evaluation measure: albumin to creatinine ratio only
  - medical attention for nephropathy: includes a broader set of urine protein measurements (e.g., including qualitative measurements with a dipstick)
uACR Measurement Rates

- 685,000 patients age 18 – 75 with type 2 diabetes and at least 2 visits with a PCP, cardiologist, endocrinologist, or nephrologist.
- Overall, 49% of patients (in green) had a urine albumin to creatinine test in the 12 month measurement period.
- Rates ranged from 41 – 58% across individual organizations.

![uACR Measurement Rates Graph]

- No uACR
- uACR measured
Urine Protein Test for Nephropathy Screening or Monitoring

- 685,000 patients age 18 – 75 with type 2 diabetes and at least 2 visits with a PCP, cardiologist, endocrinologist, or nephrologist.
- Overall, 15% of patients (in light green) had a urine protein test in the 12 month measurement period other than uACR.
- Rates ranged from 7 – 31% across individual organizations.
Overall, 6% of patients (in teal) had a diagnosis for nephropathy, treatment for nephropathy, or a visit with a nephrologist, and no urine protein test.

Rates ranged from 3 – 8% across individual organizations.
ACE or ARB Prescriptions

- Overall, 15% of patients (in orange) had an ACE or ARB prescription and no urine protein test, nephropathy Dx, nephropathy treatment, or visit with a nephrologist.
- Rates ranged from 12 – 19% across individual organizations.
Pushback on Including ACE/ARBs

• While the evidence shows that ACE/ARBs are beneficial among patients with T2DM and albuminuria, the medical attention to nephropathy measure only requires a prescription, with or without evidence of albuminuria

• ~ 15% of patients met the measure for use of ACE-i/ARB only
  – < 1% of patients who met the measure solely on ACE-i/ARBs use had a Dx for microalbuminuria
  – ~ 75% had a diagnosis for cardiovascular disease (e.g., hypertension)

• “Use of these medications does not obviate the need for a nephropathy screening in diabetics. Inclusion of these medications as numerator compliance leads to overreporting and may contribute to underscreening of a population at risk.”

Key Points

• Most patients with T2DM have eGFR measured, consistent with guideline recommendations.

• uACR measurement rates were moderate and variable across organizations.

• Measurement rates varied widely within organizations, many with one or more site of care among the highest and lowest performers across sites at all organizations.

• Current medical attention for nephropathy may be giving false sense of optimal kidney care for people with T2DM.

• Proposed kidney health evaluation measure helps identify opportunities for improvement at all organizations, which would likely stimulate more consistent use of evidence-based therapy and more accurate risk prediction, reducing complications in this high-risk population.
Next Steps

• Working with NKF and NCQA to evaluate the kidney health evaluation measure, to replace the medical attention for nephropathy measure in NCQA’s Comprehensive Diabetes Care measure set
  – Examine performance and disparities
  – Describe association of evidence based interventions with meeting quality measure
    • Use of kidney protective drugs, nephrology consultation, Statin therapy, diabetes and blood pressure control
  – Compare to same for current medical attention to nephropathy measure
  – Goal: NQF endorsement of new measure

• Working with AMGA members to understand trends and barriers in measurement for uACR and eGFR among patients with type 2 diabetes
Breakout Groups

- Group 1 – Curie Room
- Group 2 – Edison G
- Group 3 – Edison EF (Stay here)
Together 2 Goal® Innovator Track

- Cardiovascular Disease Cohort
  - Concluded June 2019
- Eye Care Cohort
  - Concluded September 2019
- 12 month programs
CVD Cohort

12 groups
~ 4,000 FTE Physicians
190,000+ T2D Patients
CVD Cohort Measures

• 1: Non-Tobacco User

• 2a: Daily aspirin for $2^\circ$ prevention
• 2b: Daily aspirin for $1^\circ$ prevention

• 3a: Any statin
• 3b: High-intensity statin
• 3c: Measured LDL < 70
CVD Cohort Outcomes

- **1,700** additional patients with *tobacco-free status*
- **600** additional patients with *documented aspirin therapy (secondary prevention)*
- **1,000** additional patients with *documented aspirin therapy (primary prevention)*
- **775** additional patients with a *Rx for any statin*
- **1,900** additional patients with a *Rx for high-intensity statin*
- **1,640** additional patients with *LDL < 70 mg/dL*
Eye Care Cohort

10 groups
~4,000 FTE Physicians
160,000 T2D Patients
Eye Care Cohort Measure

• Patients with documented screening for diabetic retinal disease

✓ Increase the **number of screenings** conducted (*screening new patients that are at risk who have not been screened before*)

✓ Increase **documentation** of eye screenings (*could entail improving the capture of external or internal exams that previously weren’t recorded in the health record*)
Eye Care Cohort Outcomes

• **8,600** additional patients with documented screening
  – absolute improvement ranged from 2% to 21%
  – relative improvement ranged from 5% to 45%
Interactive Campaign Planks

**CAMPAIGN PLANKS**

**Empower Patients**
- Build an Accountable Diabetes Team
- Integrate Emotional & Behavioral Support
- Refer to Diabetes Self-Management Education and Support Programs

**Improve Care Delivery**
- Conducting Practice-Based Screening
- Adopt Treatment Algorithm
- Measure HbA1c Every 3-6 Months
- Assess and Address Risk of Cardiovascular Disease
- Contact Patients Not at Goal & with Therapy Change within 30 Days

**Leverage Information Technology**
- Use a Patient Registry
- Embed Point-of-Care Tools
- Publish Transparent Internal Reports
National Day of Action – Nov. 7, 2019

T2G Talk & Taste Events

• Watch a Plank Mentor video
• Discuss as a team
• Recognize exceptional staff
• Celebrate successes
• Enjoy a healthy meal!

Wrap Report coming soon!
New Partnerships

Know Diabetes by Heart

ENDOCRINE SOCIETY
1,082,000
336,000
T2G Patient Lives Improved
Baseline through Year 3
Nikita Stempniewicz, Cori Rattelman, Caitlin Shaw, John Cuddeback
September 2019
Tracking Achievement

Population Measures

- Proportion of patients in control (%)
  - A1c < 8.0
  - BP < 140/90
  - Statin Rx
  - Nephropathy
  - Bundle

- Cross-sectional
- Reported quarterly
- Ages 18 – 75

Patients Improved

- Number of patients with sustained improvement
  - New diagnosis of type 2 diabetes
  - Improve on at least one measure

- Longitudinal
- Reported annually
  - Year 3 concluded 2019 Q1
- Ages 18 – 89
- Number of patients with sustained control on bundle measure
HbA1c < 8.0 – 2016 Q1 (Baseline)

850,000 patients with type 2 diabetes, across 70 AMGA member organizations

T2G® 2016 Q1: Proportion of Patients with HbA1c in Control (< 8%)
HbA1c < 8.0 – 2019 Q1 (Year 3)

1,010,000 patients with type 2 diabetes, across 70 AMGA member organizations

T2G® 2019 Q1: Proportion of Patients with HbA1c in Control (< 8%)
T2G Bundle – 2016 Q1 (Baseline)

790,000 patients with type 2 diabetes, across 65 AMGA member organizations

T2G® 2016 Q1: Proportion of Patients Compliant with All Elements of the T2G Bundle
T2G Bundle – 2019 Q1 (Year 3)

930,000 patients with type 2 diabetes, across 65 AMGA member organizations

T2G® 2019 Q1: Proportion of Patients Compliant with All Elements of the T2G Bundle
Distribution of Measure Performance Rate

Number of Health Care Organizations (Reporting for 2018Q4)

- Bundle Control
- A1c Control
- BP Control
- Attn for Nephropathy
- Lipid Management

25th, 50th, 75th and 90th Percentiles
Measures – Population-level “Control” Rates: 2016 Q1 → 2019 Q1

- 70 organizations reporting measures for 3 years (65 Core Track + 5 Basic Track)
- Average performance rate (group weighted) from baseline (2016 Q1) to year 3 (2019 Q1)

<table>
<thead>
<tr>
<th>Measure</th>
<th>2016 Q1</th>
<th>2017 Q1</th>
<th>2018 Q1</th>
<th>2019 Q1</th>
<th>Δ 2016–2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM prevalence</td>
<td>13.8%</td>
<td>13.6%</td>
<td>13.8%</td>
<td>14.2%</td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt; 8.0</td>
<td>65.6%</td>
<td>66.4%</td>
<td>67.5%</td>
<td>67.3%</td>
<td>+1.6%</td>
</tr>
<tr>
<td>BP &lt; 140/90</td>
<td>72.9%</td>
<td>74.0%</td>
<td>75.3%</td>
<td>75.9%</td>
<td>+3.0%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>85.9%</td>
<td>87.0%</td>
<td>87.9%</td>
<td>88.5%</td>
<td>+2.6%</td>
</tr>
<tr>
<td>Lipid management</td>
<td>68.7%</td>
<td>69.5%</td>
<td>71.5%</td>
<td>73.3%</td>
<td>+4.5%</td>
</tr>
<tr>
<td>T2G Bundle</td>
<td>33.4%</td>
<td>34.9%</td>
<td>37.5%</td>
<td>38.5%</td>
<td>+5.1%</td>
</tr>
</tbody>
</table>
Opportunities for Improvement

• Patients with no prior diagnosis
  – New diagnosis for type 2 diabetes (on claim* or problem list)
    • Review clinical data for existing evidence that’s diagnostic or strongly suggestive of type 2 diabetes
    • Practice-based screening

• Patients with a diagnosis of type 2 diabetes
  – If A1c is not measured (during measurement period), measure A1c
  – If A1c ≥ 8.0, bring A1c into control
    – if BP is not measured, measure BP
  – If BP ≥ 140/90, bring BP into control
  – If no medical attention to nephropathy, screen/diagnose or refer to a nephrologist
  – If no statin prescribed and LDL ≥ 70 mg/dL, prescribe (or re-try) a statin

* We require Dx codes on claims to be associated with a face-to-face encounter with a provider, to ensure we don’t pick up a code for diabetes that’s used in a “rule-out” sense, on a claim for a lab test intended as screening for diabetes. This use of the code is technically not correct, but it’s a common error.
Have Dx: Opportunities for Improvement

Campaign baseline data (2016 Q1): Broader population, i.e., patients age 18 – 75 with ≥ 1 visit (instead of ≥ 2 visits required in T2G)

Opportunity to sustain bundle control
## Improvement Calculation

<table>
<thead>
<tr>
<th>Example</th>
<th>A1c (Baseline Year 3)</th>
<th>BP (Baseline Year 3)</th>
<th>Lipid (Baseline Year 3)</th>
<th>Nephropathy (Baseline Year 3)</th>
<th>Bundle (Baseline Year 3)</th>
<th>Improvement (Baseline Year 3)</th>
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<tbody>
<tr>
<td>Example A</td>
<td>✓ ✓</td>
<td>x ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>x ✓</td>
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<td>Example B</td>
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<td>x ✓</td>
<td>x ✓</td>
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<td>Example C</td>
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<td>x ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
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<tr>
<td>Example D</td>
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<td>x ✓</td>
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<td>✓ ✓</td>
<td>✓</td>
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<tr>
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<td>✓ ✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Example G</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Improvement is assessed for each patient, then summarized for all patients in the T2G denominator**

- Example A – Moving from out-of-control (✗) to in-control (✔) on any measure counts as improvement, provided it is not offset by movement from in-control to out-of-control on another measure (see Example D)
- Example B – Moving from out-of-control to in-control on multiple measures improves performance, but it counts the same as a single measure toward improvement
- Example C – Moving from out-of-control to in-control does not count as improvement if it is “offset” by regression (moving from in-control to out-of-control) on another measure
- Example D – Remaining out-of-control diminishes performance on the respective measure, but it does not offset improvement on another measure
- Examples E and F – Improvement on two measures is not offset by regression on one other measure, but it is offset by regression on two other measures
- Example G – Remaining in-control (✔) maintains performance on the respective measure, but it does not count as improvement for the campaign
Improvement Calculation

- Compare data from Year 3 (2019 Q1) to Baseline (2016 Q1)
- Look backward, to ensure that any improvements are sustained through end of measurement period
  - 47% of patients in T2G Cohort in 2019 Q1 were in T2G Cohort at Baseline (2016 Q1)
- Evaluate these patients for improvement in measures, from baseline to year 3

![Chart showing improvement calculation]
Improvement Calculation

• For remaining current T2G Cohort patients, evaluate cohorts quarterly—check how they entered the T2G Cohort
  – Patient new in T2G Cohort but Active in a prior quarter → established patient, newly diagnosed (diagnosis counts as improvement)
  – Patient new in T2G Cohort and in Active Population → new patient, already diagnosed (diagnosis does not count as improvement)
    • Evaluate these patients for improvement in measures, from cohort entry to current

• Consider patients who were active during the campaign, but not in the most recent quarter
  – Include improvements among patients who were active in ≥ 2 quarterly reporting periods but not the most recent quarter
    • Evaluate these patients for improvement in measures, from cohort entry to exit

• Lives improved includes only the AMGA members who are reporting data quarterly on the campaign measures

• For patients with bundle control at cohort entry or baseline, check to see if they sustained bundle control
  – These patients are not eligible for any improvements toward the campaign goal
Patients with Improved Care

- Among **1,780,000** patients with T2DM age 18 – 75, included in 2019 Q1 population
  - **735,000** patients with improved care, through the end of year 3 of the campaign (2019 Q1)
  - **223,000** patients with sustained bundle control for ≥ 1 year
    - These patients had all measures in control at baseline, i.e., they were not eligible for any improvements and have no overlap with the 735,000 patients above

- Among **3,100,000** patients with T2DM age 18 – 89, included in 2019 Q1 population or in ≥ 2 reporting periods during campaign
  - **1,082,000** patients with improved care, through the end of year 3 of the campaign (2019 Q1)
  - **336,000** patients with sustained bundle control for ≥ 1 year

- About 1/3 of improvements are people who have a new diagnosis of type 2 diabetes
- About 2/3 are patients who already had a diagnosis and achieved a net improvement in control, among the 4 measures that make up the T2G bundle
1,082,000

336,000
Update: Adoption of new therapies and guidelines in the management of patients with T2DM and CVD
Clinical Inertia can take place across all stages of chronic disease

- Screening and diagnoses
- Advancing therapy
- Adoption of new therapies and guidelines
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY) IF \( \text{HbA}_{1c} \) ABOVE TARGET PROCEED AS BELOW

**EITHER/ OR**

**Without Established ASCVD OR CKD**

**ASCVD PREDOMINATES**
- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit, if eGFR adequate

**HF OR CKD PREDOMINATES**
- PREFERABLY SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR if SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

**If \( \text{HbA}_{1c} \) above target**
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SU

**If further intensification is required or patient is now unable to tolerate GLP-1 RA or SGLT2i, choose agents demonstrating CV safety:**
- Consider adding the other class with proven CVD benefit
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin
- SU

**If \( \text{HbA}_{1c} \) above target**
- SGLT2i
- OR TZD

**Compelling Need to Minimize Hypoglycemia**
- Continue with addition of other agents as outlined above

**If \( \text{HbA}_{1c} \) above target**
- Consider the addition of SU OR basal insulin:
  - Choose later generation SU with lower risk of hypoglycemia
  - Consider basal insulin with lower risk of hypoglycemia

**Compelling Need to Minimize Weight Gain or Promote Weight Loss**
- DPP-4i
- GLP-1 RA
- SGLT2i

**If \( \text{HbA}_{1c} \) above target**
- GLP-1 RA with good efficacy for weight loss
- SGLT2i
- GLP-1 RA

**Cost is a Major Issue**
- SU
- TZD
- DPP-4i
- SU

Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i

- 4 cohorts of patients with type 2 DM across 22 AMGA member organizations

- Observed for existing or new Rx of novel antidiabetic agents: GLP-1 RA, SGLT2i, or DPP-4i during four 36-month periods ended
  - 2016 Q1 (n=361,496)
  - 2017 Q1 (n=375,246)
  - 2018 Q1 (n=399,137)
  - 2019 Q1 (n=443,224)

Data for AMGA members using an Optum population health analytics platform. Optum is AMGA’s Distinguished Data and Analytics Collaborator and is a Principal Corporate Collaborator for Together 2 Goal.
Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i

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  - 2019 Q1 (n=443,224)
Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i

- 4 cohorts of patients with type 2 DM across 22 AMGA member organizations

- Observed for existing or new Rx of novel antidiabetic agents: GLP-1 RA, SGLT2i, or DPP-4i during four 36-month periods ended
  - 2016 Q1 (n=361,496)
  - 2017 Q1 (n=375,246)
  - 2018 Q1 (n=399,137)
  - 2019 Q1 (n=443,224)
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  - 2018 Q1 (n=399,137)
  - 2019 Q1 (n=443,224)
Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i
By organization

- Each colored line represents the prescription rate at one of 22 AMGA member organizations.
Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i
By organization

- Each colored line represents the prescription rate at one of 22 AMGA member organizations
- Significant variation in rates but pattern of medication uptake is consistent across organizations
Prevalence of CVD among these type 2 DM patients ranges from 28% in 2016Q1 to 30% in 2019Q1

Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i by CVD status

- Ischemic vascular disease
- Myocardial infarction
- Coronary artery bypass graft
- Percutaneous coronary intervention
- Other revascularization procedure
Prevalence of CVD among these type 2 DM patients ranges from 28% in 2016Q1 to 30% in 2019Q1.

Patients with CVD are no more likely to be prescribed GLP-1 or SGLT2 than patients without.

Medication uptake: Patients with prescription for GLP-1 RA, SGLT2i, or DPP-4i by CVD status

CVD for T2G – HEDIS Value Sets (diagnoses, events, or procedures):
- Ischemic vascular disease
- Myocardial infarction
- Coronary artery bypass graft
- Percutaneous coronary intervention
- Other revascularization procedure
Adoption of guidelines: Among patients with A1c ≥ 8.0, proportion with **new Rx** for GLP-1 RA, SGLT2i, or DPP-4i, by CVD status

Patients with baseline DM medication regimen excluding: DPP-4, SGLT2i, GLP-1 and insulin
Adoption of guidelines: Among patients with A1c ≥ 8.0, proportion with new Rx for GLP-1 RA, SGLT2i, or DPP-4i, by CVD status

Patients with baseline DM medication regimen excluding: DPP-4, SGLT2i, GLP-1 and insulin

and A1c ≥ 8.0
Adoption of guidelines: Among patients with A1c ≥ 8.0, proportion with new Rx for GLP-1 RA, SGLT2i, or DPP-4i, by CVD status

Patients with baseline DM medication regimen excluding: DPP-4, SGLT2i, GLP-1 and insulin

and A1c ≥ 8.0

<table>
<thead>
<tr>
<th>2016Q1</th>
<th>2017Q1</th>
<th>2018Q1</th>
<th>2019Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVD</td>
<td>10,834</td>
<td>11,396</td>
<td>11,300</td>
</tr>
<tr>
<td>CVD</td>
<td>2,712</td>
<td>2,870</td>
<td>2,910</td>
</tr>
</tbody>
</table>
Adoption of guidelines: Among patients with A1c ≥ 8.0, proportion with new Rx for GLP-1 RA, SGLT2i, or DPP-4i, by CVD status

Patients with baseline DM medication regimen excluding: DPP-4, SGLT2i, GLP-1 and insulin

*and* A1c ≥ 8.0
T2DM patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

Each patient counted only once, based on the following order of interventions:

- Added GLP-1 and SGLT2
- Added GLP-1
- Added SGLT2
- Added DPP-4
- Added Sulfonylurea, TZD, or Metformin
- Added Insulin ONLY
- No change

N=12,371

- No CVD: 44.0%
- CVD: 39.3%

N=3,248

- No CVD: 7.9%
- CVD: 13.7%
T2DM patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

Each patient counted only once, based on the following order of interventions:

- added GLP-1 and SGLT2
- added GLP-1
- added SGLT2
- added DPP-4
- added Sulfonylurea, TZD, or Metformin
- added Insulin ONLY
- No change
T2DM patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

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- No change
T2DM patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

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T2DM patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

Each patient counted only once, based on the following order of interventions:

- added GLP-1 and SGLT2
- added GLP-1
- added SGLT2
- added DPP-4
- added Sulfonylurea, TZD, or Metformin
- added Insulin ONLY
- No change
2019Q1 measurement period: Potential clinical inertia among T2DM/CVD patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

Each patient counted only once, based on the following order of interventions:

- added GLP-1 and SGLT2
- added GLP-1
- added SGLT2
- added DPP-4
- added Sulfonylurea, TZD, or Metformin
- added Insulin ONLY
- No change

N=3,248
2019Q1 measurement period: Potential clinical inertia among T2DM/CVD patients with BL medication excluding DPP-4i, SGLT2i, GLP-1, and insulin and A1c ≥ 8.0

Each patient counted only once, based on the following order of interventions:

- **added GLP-1 and SGLT2**
- **added GLP-1**
- **added SGLT2**
- **added DPP-4**
- **added Sulfonylurea, TZD, or Metformin**
- **added Insulin ONLY**
- **No change**

![Graph showing the percentage of patients with different interventions.](image)
Adoption of guidelines: 2016Q1 to 2019Q1

Each patient counted only once, based on the following order of interventions:

- 49% added other 2nd line anti-diabetic agent and/or insulin
- 9% added GLP-1 and/or SGLT2
- 9% no new anti-diabetic agents added
- 20% 37% 40% 39% 39%
Adoption of guidelines: 2016Q1 to 2019Q1

N = 3,248

- Added GLP-1 and/or SGLT2
- Added other 2nd line anti-diabetic agent and/or insulin
- No new anti-diabetic agents added

Potential clinical inertia if ASCVD dominates for these patients: Fell from 87.7% to 80.0%
Summary

• Among patients with type 2 diabetes (T2DM), Rx for GLP-1 and SGLT2 continue to increase, but still only 13% in 2019 Q1 (vs. 18% for DPP-4)
  – Up ~ 5% since 2016Q for both GLP-1 and SGLT2
  – Flattening out for DPP-4
  – Same patterns observed at individual organizations but with significant variation in Rx rates (range for 2019Q1: 7 to 28% for GLP-1 Rx and 5 to 26% for SGLT2 Rx)

• Patients with T2DM and evidence of CVD are no more likely to be prescribed GLP-1 or SGLT2 than patients without
  – That is changing for those patients who are also not at goal (A1c > 8)

• Potential clinical inertia in adopting new Rx guidelines may be as high as 80%
  – But falling nearly 8% since 2016 Q1
Panel Discussion: Implementing Medication Care Paths for Type 2 Diabetes and Cardiovascular Disease and Congestive Heart Failure
T2D Management: Therapeutic Inertia, Newer Therapies, and Intensification Tools, Oh My!

Kevin M Pantalone, DO, ECNU, FACE
Director of Diabetes Initiatives
Department of Endocrinology
Endocrinology and Metabolism Institute
Cleveland Clinic
How Are We Doing?

Based on NHANES respondents
Weighted to represent US adults with diabetes

Cleveland Clinic

ACO 22 DM Patients with A1C < 8%

ACO 27 DM Patients with A1C ≥ 9%
The American Diabetes Association has launched a new initiative focused on Overcoming Therapeutic Inertia. Phase 1 of this multi-year activity kicked-off on November 28th, 2018 in Arlington, Virginia with a Summit.

This important meeting brought together over 120 members of the diabetes health care eco-system, including interprofessional primary care providers, diabetes specialists, health systems, payors, industry and patient advocacy groups. The objective was to identify and assess issues related to therapeutic inertia, address barriers, and develop solutions and next steps that will have a significant impact on long-term outcomes.

Summary of Proceedings

Newly-diagnosed T2D, Cleveland Clinic

• After at least 3 months of metformin monotherapy:

- Baseline A1C >7%
  • 38% did not undergo early intensification (≤ 6 months)

- Baseline A1C >7.5%
  • 31% did not undergo early intensification

- Baseline A1C >8%
  • 28% did not undergo early intensification

Figure 1—Rates of intensification and nonintensification of antihyperglycemic therapy observed among 7,389 patients with T2D during a 6-month period following an HbA1c ≥7% (≥53 mmol/mol). All patients had been using a stable regimen of two OADs for at least 6 months preceding the index HbA1c.
APPENDIX 1: CLEVELAND CLINIC TYPE 2 DIABETES CARE PATH OVERVIEW

Address Lifestyle Modifications
1. Diabetes education and nutrition counseling
2. Exercise recommendations
3. Smoking cessation plan
4. Psychosocial issues
5. Weight management - Diet/exercise - Medications - HbA1c ≤ 7.0%

Diabetes Type 2 Diagnosis
- 2-hr Glucose Tolerance Test ≥ 200 mg/dL
  - "Random glucose >200 mg/dL"
  - Fasting Blood Sugar >126
  - HbA1c ≥ 6.5%

Goals
- HbA1c ≥ 7.0%
- Treat BP to <140/90 mm Hg
- Monitor HbA1c at least every 6 months
- Foot exam 1 time a year
- HDL women > 50 mg/dL men > 40 mg/dL
- Monitor Serum Creatinine annually*
- Monitor Urine Albumin/Creatinine ratio annually
- LDL Cholesterol < 100 mg/dL and < 70 mg/dL if CVD present annually
- Flu Vaccine* and pneumococcal vaccine (1 x between ages 2-65 and 1 x after age 65)

Consider Referral
When HbA1c is > 9.0% after 6 months of treatment, consider referral to endocrinology.
Or for patients with:
- Hypoglycemia
- Insulin/injectable starts
- Needs consideration of insulin pump
- If inadequate diabetes knowledge is the main issue, the patient should be referred back to diabetes education.

Consider Referral
When HbA1c is stable < 8.0% consider referral back to PCP

Refer to Medication Benefits: Efficacy/Cost and Risks and Glycemic Control Algorithm

*Individualized based on age, hypoglycemic unawareness and complications (e.g., CAD, ESRD, proliferative nephropathy)

Bariatrics for bariatric surgery consult for BMI > 30 with major risk factors
Cardioloog for chest pain/pressure/vascular disease
Nephrology for renal insufficiency/proteinuria
Neurology for neuropathy
Ophthalmology for annual eye exam
Podiatry for calluses/depressed sensations/foot ulcers
Urology for unreponsive sexual dysfunction
# Ambulatory Pharmacist Referrals

<table>
<thead>
<tr>
<th>Expand/Collapse</th>
<th>2018</th>
<th>2019</th>
</tr>
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<tbody>
<tr>
<td>Main Campus Internal Medicine (G10)</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Stephanie Tubbs Jones Health Center</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Lorain FHC</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Solon FHC</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Independence FHC</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Wooster FHC</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Strongsville FHC</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Beachwood FHC</td>
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<td>14</td>
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<tr>
<td>Willoughby Hills FHC</td>
<td>36</td>
<td>71</td>
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<tr>
<td>Twinsburg FHC</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Richard E. Jacobs FHC</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chestnut Commons (Flyria FHC)</td>
<td>60</td>
<td>39</td>
</tr>
</tbody>
</table>

**Indications for Referrals**

- Diabetes follow-up
- Hypertension follow-up
- Medication Reconciliation
- Other
- Hyperlipidemia follow-up
- Chronic Obstructive Pulmonary...
- Asthma follow-up
- Smoking Cessation
- Medication Cost Reduction
- Medication Education
- Medication Reconciliation (po..)
- Polypharmacy Review by Phar..
T2D “Boot Camp” Order
Bundled EPIC Order

New Consult with Endocrinologist
T2D-related HM Updated/Addressed
Therapy/Management Plan Enacted

Follow-up Visit at 1 Month
NP or Ambulatory Pharmacist to Adjust Therapy/Regimen

Nutrition Consultation within 90 days of the New Consult
(Could be SMA)

CDE Consultation within 90 days of the New Consult
(Could be SMA)

Visit with NP/Ambulatory Pharmacist at 3 months

Visit with Endocrinologist at 6 months

Schedule with Nephrology, Podiatry, and Obesity Providers, etc., as indicated

Patient with A1C < 8% at 6 months Returned to PCP for Continued Management Moving Forward

Patients with A1C ≥ 8% at 6 months will remain with Endocrinology until A1C < 8%, New management Plan Enacted
Patients That Remain Poorly Controlled

• Leverage new approaches to engage
  - Virtual visits
  - SMAs (T2D)
  - E-consults
  - Remote monitoring (CDE)
  - CDE chronic care coordinators
  - Local care with access to services
GLP-1
Mechanisms of Action

Upon ingestion of food...

This in turn...
- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Improves insulin sensitivity
- Reduces food intake

GLP-1 is secreted from the L-cells in the jejunum and ileum

Long-term effects demonstrated in animals
- Increases β-cell mass and maintains β-cell function

GLP-1RAs

- **Benefits**
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved glycemic control
  - Reduction in systolic BP
  - CV risk reduction
  - ? In-vivo increase B-cell growth/replication
    - Durability
  - ? Kidney protection

- **Side Effects/Adverse Reactions/Warnings**
  - Nausea, vomiting, diarrhea, injection site reactions
  - Acute pancreatitis
  - Thyroid C-cell tumors, including medullary thyroid carcinoma (MTC)
Combo SGLT2 and DPP-4 Inhibitors: Complementary Mechanisms of Action
Authors: John Anderson, MD; Vivian Fonseca, MD, FRCP
https://www.medscape.org/viewarticle/837818_transcript
SGLT-2 Inhibitors

• Benefits
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved glycemic control
  - Reduction in systolic BP (~ 5 mmHg)
  - CV risk reduction
  - Reduction in risk of hospitalization for heart failure
  - Renal risk reduction/kidney protection (Canagliflozin, CREDENCE)
    • Also observed to varying degrees in studies with other SGLT-2i (CVOTs)

• Risks/Negatives
  - Slight increase in LDL cholesterol
  - Hypotension
    • Intravascular volume contraction
  - UTIs, genital mycotic infections
  - Fournier’s gangrene (???)
  - Bladder cancer (???)
  - Breast cancer (???)
  - Increase risk of DKA (largely in DM-1/insulin dependent DM-2)
  - Bone loss and increase in fracture risk (Canagliflozin)
  - Amputations (Canagliflozin, ? Ertugliflozin)
Table 2  Antidiabetic medication treatment patterns stratified by cardiovascular disease (CVD) status

<table>
<thead>
<tr>
<th>Medication*</th>
<th>No established CVD N = 54,659</th>
<th>Established CVD N = 40,910</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OAD</td>
<td>17,984 (32.9%)</td>
<td>17,137 (41.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OAD</td>
<td>36,675 (67.1%)</td>
<td>23,773 (58.1%)</td>
<td></td>
</tr>
<tr>
<td>1 OAD</td>
<td>23,166 (63.2%)</td>
<td>14,889 (62.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 OAD</td>
<td>9540 (26.0%)</td>
<td>6574 (27.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 3 OAD</td>
<td>3969 (10.8%)</td>
<td>2310 (9.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>6211 (11.4%)</td>
<td>7472 (18.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GLP-1RA</td>
<td>2978 (5.4%)</td>
<td>1685 (4.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1683 (3.1%)</td>
<td>916 (2.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGLT-2i</td>
<td>2265 (4.1%)</td>
<td>1042 (2.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>462 (0.8%)</td>
<td>209 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>1348 (2.5%)</td>
<td>691 (1.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other ADD</td>
<td>1101 (2%)</td>
<td>853 (2.1%)</td>
<td>0.444</td>
</tr>
</tbody>
</table>

OADs: biguanide (metformin), sulfonylurea, thiazolidinedione, dipeptidyl-peptidase-4 inhibitor, alpha-glucosidase inhibitor, sodium–glucose co-transporter-2 inhibitor

Other ADD—other antidiabetic drug: pramlintide, name brand bromocriptine (Cyloset®), coleselam, nateglinide or repaglinide

ADD antidiabetic drug. CVD cardiovascular disease, GLP-1RA glucagon-like peptide-1 receptor agonist, OAD oral antidiabetic drug

---

Table 2  Antidiabetic medication treatment patterns stratified by atherosclerotic cardiovascular disease (ASCVD) status

<table>
<thead>
<tr>
<th>Medication</th>
<th>Non-ASCVD N = 659,498</th>
<th>ASCVD N = 543,938</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAD only, n (%)</td>
<td>340,485 (77.0)</td>
<td>243,967 (73.6)</td>
</tr>
<tr>
<td>1 OAD</td>
<td>189,412 (55.6)</td>
<td>138,907 (56.9)</td>
</tr>
<tr>
<td>2 OAD</td>
<td>103,133 (30.3)</td>
<td>73,194 (30.0)</td>
</tr>
<tr>
<td>≥ 3 OAD</td>
<td>47,940 (14.1)</td>
<td>31,886 (13.1)</td>
</tr>
<tr>
<td>Insulin + OAD, n (%)</td>
<td>61,278 (13.9)</td>
<td>61,452 (18.5)</td>
</tr>
<tr>
<td>GLP-1RA ± OAD, n (%)</td>
<td>27,481 (6.2)</td>
<td>16,430 (5.0)</td>
</tr>
<tr>
<td>Insulin + GLP-1RA ± OAD, n (%)</td>
<td>13,095 (3.0)</td>
<td>9,805 (3.0)</td>
</tr>
<tr>
<td>Any GLP-1RA use, n (%)</td>
<td>40,576 (9.2)</td>
<td>26,235 (7.9)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>3202 (7.9)</td>
<td>2260 (8.6)</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>10,291 (25.4)</td>
<td>6358 (24.2)</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>2086 (5.1)</td>
<td>1240 (4.7)</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>5174 (12.8)</td>
<td>3129 (12.1)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>23,006 (56.7)</td>
<td>15,009 (57.2)</td>
</tr>
<tr>
<td>Any SGLT2i use, n (%)</td>
<td>51,997 (11.8)</td>
<td>29,103 (8.8)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>35,891 (69.0)</td>
<td>20,350 (69.9)</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>11,170 (21.5)</td>
<td>5836 (20.1)</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>6530 (12.6)</td>
<td>3791 (13.0)</td>
</tr>
</tbody>
</table>
Figure. Use of cardiovascular and glucose-lowering medications among patients with diabetes mellitus and atherosclerotic cardiovascular disease.

*Components of optimal medical therapy: high-intensity statin, antplatelet agent or anticoagulant (excluding triple therapy), ACE inhibitor or ARB (excluding glomerular filtration rate <30 mL/min·1.73 m²), and SGLT2 inhibitor or GLP1 receptor agonist (for type 2 diabetes mellitus; excluding glomerular filtration rate <30 mL/min·1.73 m²). ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP1, glucagon-like peptide 1; PCSK9, proprotein convertase subtilisin/kexin type 9; and SGLT2, sodium-glucose cotransporter-2.
Growth

GLP-1RA
24% YOY and 12% sequentially to $2.4 billion

SGLT-2i
25% YOY and 7% sequentially to $1.3 billion
Current Initiatives

• EHR-based T2D Intensification Tool
  - Leverage EHR in real-time
  - Facilitate care and improve outcomes

• Attempt to make T2D Care Path “Functional”
  - Follow progress with Care Path Dashboard

• Engage and collaborate with PCPs
1) Age ≥ 18 years
   AND
2) A1C Greater than or Equal to 8 in the last 6 months
   AND
3) No current T1D problem on the Problem List
   AND
4) Patient is not currently Pregnant
### Relevant Patient Data

**Weight (Today):** 304.0 lbs, 137.0 kg  
**Height (Today):** 5' 2"  
**BMI (Today):** 17.9 kg/m²  
**BMI (Goal):** 18.0 kg/m²  

### Medication Categories

- **Select Patient Goals:** Cardiovascular Risk Reduction  
- **Cardiovascular Risk Reduction:**  
- **Weight Los:**  
- **A1C Lowering:**  
- **Patient has Methimazole Allergy:**

### Applicable Medications

- Methimazole  
- SGLT-2 Receptor Agonists  
- SGLT-2 Transport Inhibitors  
- GLP-1  
- Alpha-glucosidase inhibitor

### Health Maintenance Checks

<table>
<thead>
<tr>
<th>Test</th>
<th>Status</th>
<th>Last Completion Date</th>
<th>Due Date</th>
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<tbody>
<tr>
<td>DILATED RETINAL EXAM</td>
<td>Overdue</td>
<td>1/6/1994</td>
<td></td>
</tr>
<tr>
<td>DIABETIC FOOT EXAM</td>
<td>Overdue</td>
<td>1/6/1994</td>
<td></td>
</tr>
<tr>
<td>PNEUMOCOCCUS PRIOR TO AGE 65</td>
<td>1/6/2000</td>
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<td></td>
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<tr>
<td>LDL CHOLESTEROL</td>
<td>Overdue</td>
<td>5/8/2002</td>
<td></td>
</tr>
<tr>
<td>INFLUENZA</td>
<td>Overdue</td>
<td>2/1/2018</td>
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</tr>
<tr>
<td>HBA1C</td>
<td>Not Due</td>
<td>1/2/2019</td>
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<tr>
<td>URINE ALBUMIN/CREATINIC RATIO</td>
<td>Information not on file</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional Notes:** Upon diagnosis of diabetes before age 45, Pneumovax 23 should be administered. At age 45, Pneumovax 13 pneumococcal vaccine should be administered and one year later, Pneumovax 23 should be administered only if the initial Pneumovax 23 shot was > 5 years ago. The second Pneumovax 23 injection should be administered at least 5 years after the first dose.

### Health Maintenance Orders

- **Use speed buttons to pre-populate SmartSet**

### Other Orders

- **Use speed buttons to pre-populate SmartSet**

### Diabetes Care Path Links

- **Insulin Initiation Algorithm**
- **Care Path Guide**
  - Medication Table (p. 12)
  - Type 2 Diabetes Goal Based Algorithm (p. 14)

---

[Smartform interface screenshot with data and notes]
**Insulin Initiation and Titration**

**Determine A1c goal**

**Candidate for starting insulin therapy?**

- Start with basal insulin if:
  - Inadequate control on 2 or 3 oral hypoglycemic agents.
  - 2 or 2 oral agents + GLP1 analog.
  - Inadequate control with 1-2 oral agents (w/wo GLP1 analog therapy) and contraindications to other therapies.
  - Inadequate control with 2 oral agents & inability to afford brand name medications.

- Start basal-bolus insulin regimen if:
  - Severe symptomatic hyperglycemia:
    - Polyuria, polydipsia and polyphagia.
    - Blood glucose $\geq 300$ mg/dl.
    - HgA1c $\geq 10\%$.

- Insulin analogs are available to qualified patients per patient's assistance programs.
- NPH and pre-mixed human insulin types are the cheapest, followed by pre-mixed insulin analogs (See candidates):
  - Greater weight gain.
  - Higher frequency of hypoglycemia.
  - Re-assess/relax A1c goal if those types of insulin were to be used.
  - See how and see pre-mixed insulin and human insulin types
Roll-out Plan
- E-Learning Module
- Walk-through Video
- Clinical Systems Support
- Physician Specialist Support

Retrospective Study
- Outcomes
**Outcome of BPA firing**

- **User use of tool**
  - % of base population with A1c <8%
  - % of base population with A1c >9%
  - PCP orders
    - Consult to one of the 4 specialties below
    - 2 results of A1C >9, minimum 3 months apart for 6 months or more CP orders
    - CONSULT TO ENDOCRINOLOGY or CONSULT TO DIABETES EDUCATION for A1C >9 FOR 6 MONTHS OR MORE
    - Endocrinology orders
      - REFER BACK TO PCP FOR DM TYPE 2 MAINT
      - HBA1C is stable < 8.0

- **T2D Smart form Usage**

- **Count of Diabetes Cases**

---

<table>
<thead>
<tr>
<th>Goal Category Name</th>
<th>Metric Name</th>
<th>Actual</th>
<th>N</th>
<th>Last Update</th>
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<td>% Intensified – Primary Care</td>
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<td>Count of Diabetes Cases</td>
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<td>Referral to Primary Care</td>
<td>36.44%</td>
<td>5,743</td>
<td>07/12/19</td>
</tr>
</tbody>
</table>
Cleveland Clinic

Every life deserves world class care.
SGLT2 Inhibitors
A Change In Paradigm And Call To Arms

Paula Pinell-Salles MD FACC

November 14, 2019
Outline

• Burden of disease

• ADA/AHA/ACC guideline updates

• SGLT2i pharmacology

• SGLT2i and cardiovascular protection
  • SGLT2i and renal protection

• Barriers to wide-spread implementation

• Expanding indications and ongoing Research
  • SGLT2i in HF reduced EF
Burden of disease

• Prevalence 30.3 million
• Incidence 1.4 million

• **ASCVD** leading cause of morbidity and mortality
• Cost $37.3 billion in cardiovascular-related spending per year

• Leading cause of **ESRD** (44%)
• Hemodialysis costs average $90,000 annually per patient, $28 billion overall and 69% higher among diabetics

• Overall **heart failure hospitalization** > 900,000 annually with 25% readmission within first month, cost $30 billion annually
• Incident heart failure hospitalization twofold higher in diabetic patients
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive SummarySept, 2019
ADA Guidelines for Diabetic Management 2018
SGLT2 Inhibitors

Pharmacology
SGLT2 Inhibitor Mechanism of Action

- Drops Hba1c 0.8
- Decrease SBP 4mm
- Decrease DBP 2mm
- Weight loss 2-4 kg

**CONTRAINDICATED:**
- Type I DM
- Type II DM prone to DKA

**CAUTION:**
- Diuretic use
- RAAS Inhibitor use
- eGFR < 60mL/min

- Hypoglycemia rare
- Osmotic diuresis

- Euglycemic DKA (delayed diagnosis)
- Hypovolemia and hypotension
- Yeast and genitourinary infections

Medscape: SGLT2 Inhibitors in the Modern Era: Why and Where?
SGLT2

Empagliflozin (®Jardiance) highest (~2,500 fold) selectivity SGLT2 over SGLT1

Ertugliflozin* (®Steglatro) ~2,000 fold)

Dapagliflozin (®Farxiga) ~1,200-fold)

Canagliflozin (®Invokana) ~250 fold)

SGLT1

*neutral in cardiovascular outcomes studies
SGLT2 Inhibitors
Cardiovascular outcomes
Empagliflozin reduced primary composite of CV death, nonfatal MI and CVA

7,020 patients
Median follow up 3.1 years
Mean age 63

Type 2 DM with A1C 7-10
Avg A1C 8.1
48% insulin
57% 10+ year diagnosis

Established CVD with high risk of CV events
ACS> 2mo prior
LM or 2vCAD
1vCAD with abnormal MPI or unstable angina w/in 12 mo
CVA (ischemic or hemorrhagic) > 2 mo prior
Occlusive PAD with ABI< 0.9, prior intervention or > 50%

EMPA-REG OUTCOMES TRIAL. NEJM 2015; 373:2117-2128
Empagliflozin reduced all-cause and CV death

All Cause Mortality HR 0.68
CV Death HR 0.62

NNT 39 for 3 years to prevent 1 death

EMPA-REG OUTCOMES TRIAL. NEJM 2015; 373:2117-2128
FDA NEWS RELEASE

FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes

For Immediate Release: December 02, 2016
Canagliflozin reduced primary composite of CV death, nonfatal MI and CVA

2 combined trials CANVAS and CANVAS-R
10,142 patients
Median follow up 2.4 years
Mean age 63

Type 2 DM with Hba1c 7.0-10.5
- 57% 10+ yr diagnosis
- Average A1C 8.2
- 50% on insulin

symptomatic ASCVD and >30 yo (66%)
OR
> 50 yo AND > 2 risk factors
DM ≥ 10 years duration
SBP ≥ 140mm Hg despite BP Rx
Active smoking
Micro- or macro- albuminuria
HDL < 38.7 mg/dL

CANVAS trial. NEJM 2017; 377:644-657
Reduced Primary Composite CV death, nonfatal MI or CVA

**Empagliflozin**

- **Event rate**: 26.93 vs 31.48/1000 patient years

**Canafliglozin**

- **Event rate**: 37.4 vs 43.4/1000 patient years

**EMPA-REG outcomes trial. NEJM 2015; 373:2117-2128**

**CANVAS trial. NEJM 2017; 377:644-657**

- **Hazard ratio**: HR 0.86 (95% CI: 0.74-0.99) *P* = 0.04 for superiority
Reduced Hospitalization for CHF

**Empagliflozin**

- **HR 0.65**

**Canagliflozin**

- **HR 0.67**

**EMPA-REG Outcomes Trial.** NEJM 2015; 373:2117-2128

**Canvas Trial.** NEJM 2017; 377:644-657
Dapagliflozin Reduced Hospitalization for CHF

17,160 patients
Median follow up 4.2 years
Mean age 64

- Type 2 DM with a1c > 6.5
  - Average A1C 8.3
  - 41% insulin

Established ASCVD
  - Prior Ml/revascularization with LM/2vCAD
  - Prior TIA/CVA or carotid revascularization
  - Prior LE revascularization, amputation or symptoms w ABI< 0.9
  - OR

2 risk factors in men > 55 or women > 60
  - LDL> 130 or on lipid lowering therapy
  - BP> 140/90 or on Rx
  - Current tobacco use > 5 cigarettes/d for > 1 year

Composite driven by decreased HF hospitalization HR 0.73

No subgroup difference related to
- History of HF (10%)
- Established ASCVD (40%)

DECLARE-TIMI 58. NEJM.org Nov 10 2018
SGLT2i and Cardiovascular Outcomes: Meta-analyses of RCTs parallel large propensity matched registries

- MACE reduction only in those with established ASCVD (HR 0.86)
  - MACE reduction limited to reduced cardiovascular death and nonfatal MI
  - No reduction in CVA risk

- Reduced composite of CV death or HF hospitalization in all (HR 0.77)
  - HF hospitalization reduction similar in all irrespective of prior HF or ASCVD
SGLT2 Inhibitors

Renal outcomes
Reduced Renal Composite outcome*

*ESRD (HD, kidney transplant or eGFR< 15mL/min/1.73m2), doubling of serum creatinine, or death from renal or cardiovascular outcomes

DECLARE-TIMI 58 NEJM.org Nov 11 2018

CANVAS-R NEJM 2017; 377:644-657
Canagliflozin reduced primary composite outcome in patients with CKD

4,395 patients
Median follow up 3.6 years
Age> 30 (Mean age 63)

Type 2 DM with AIC 6.5-12.0
- Average AIC 8.3
- Mean duration DM 16 yr
- 66% on insulin
- ASCVD 51%

ACE or ARB
eGFR 30-90mL/min/1.73m2
UACR 300-5000mg/g

CREDENCE. NEJM 2019; 380. 24;2295-2306
Canagliflozin reduced MACE and hospitalization for HF among diabetics with CKD

ADA updated recommendations on Diabetes and CKD June, 2019:
• Urinary albumin and eGFR should be assessed at least annually in DM type 2
• SGLT2i use preferred if eGFR > 30 especially if albuminuria > 300mg/d to lower renal and CV risk
SGLT2 Inhibitors

Barriers to Use
As little as $0 copay, max savings $250, 12 mo use, exp 12/31/2019
Canagliflozin (Invokana)
$497/mo
https://www.Invokana.com/patient-support/savings-card for commercially insured patients
As little as $0 copay, max savings $200 per mo, $3000 per year, 12 mo use, exp 12/31/2019
Dapagliflozin (Farxiga)
$495/mo
https://www.farxigasavingsrx.com/welcome.html online savings card
For commercially insured as little as $0 copay, max savings $378 per mo
For uninsured, save up to $150 per mo.

Barriers to SGLT2i Use
Euglycemic DKA

- Blood glucose < 200mg/dL, plasma bicarbonate < 15mEq/L
- Type I diabetics: intrinsic insulin deficiency

SGLT2i results in lower blood glucose, decrease circulating insulin, increase glucagon
Enhanced lipolysis, ketogenesis. Decreased ketone reabsorption and ketonemia
Increased insulin resistance due to stress or extended fasting can transform drug-induced ketogenic state to ketoacidosis
triggers: heavy alcohol consumption, decreased caloric intake, pregnancy

Hold during hospitalizations and when npo/ limited po intake
Maintain high index of suspicion and assess for DKA even if glc< 250 if symptoms present (e.g. nausea, abdominal pain)

Barriers to SGLT2i Use
Barriers to SGLT2i Use

Adverse effects
- Hypovolemia, dehydration
- Hypotension
- Hypoglycemia (rare)
- UTI
- Yeast infections
- Perineal infections (Fournier's gangrene, extremely rare)
- Amputation risk*
- Fracture risk*

* CANVAS only. Not in other SGLT2i even in PVD subgroups, not in meta-analyses or further canagliflozin studies
Clinical education and research
Get with the guidelines (GWG) initiatives targeting system wide coordination (PCP, urgent cares and ER, subspecialists especially endocrinologist, cardiologist, nephrologist)
Lessons re initiation of medication at discharge (e.g. BB, ACE/ARB, ARNI in HF)
Optimizing EMR for guideline implementation and data collection (akin to EPIC with GWTG)
Patient education

Drug cost and Insurance coverage
Continued FDA fast-tracking of expanding indications
Ongoing safety monitoring and reporting through EMR and registries
SGLT2 Inhibitors

Expanding clinical indications
Dapagliflozin *in* HF *reduced* EF patients *reduced* HF hospitalization

4,744 patients  
NYHA class II-IV  
EF of 40% or less  
Median follow up 18.2 mos

Mean EF 31%  
NYHA class II 67%, class III 32%  
Diabetes *NOT* inclusion criteria

41.8% diabetic  
27% insulin  
92% ACE/ARB/ARNI  
93% diuretic  
40% eGFR<60

**HR 0.7**

NNT 27 for 18 mos

DAPA-HF. NEJM Sept 19, 2019
Dapagliflozin *in HF reduced EF patients*

Reduced CV death **HR 0.82**

Reduced all cause death **HR 0.83**

NNT 52 for 18 mo  

NNT 43

DAPA-HF. NEJM Sept 19, 2019
# Guideline directed medical therapy for HF

## Reduced EF
- ACE inhibitor/ ARB
- Beta blockers
- Mineralocorticoid Receptor Agonists
- Sacubitril/neprilisyn
- Cardiac Resynchronization therapy

## Preserved EF
- ACE inhibitor/ ARB
- Beta blockers
- Mineralocorticoid Receptor Agonists
- Sacubitril/neprilisyn
- Cardiac Resynchronization therapy
Continuum of disease progression

Heart failure stages

- **Stage A**: At high risk for HF but without structural heart disease or symptoms of HF
- **Stage B**: Structural heart disease but without signs or symptoms of HF
- **Stage C**: Structural heart disease with daily or current symptoms
- **Stage D**: Advanced HF

DAPA HF: greatest benefit in class II HFrEF

Progression of CKD

- **Stage 1**: Below normal to mild loss of kidney function
- **Stage 2**: Mild to moderate loss of kidney function
- **Stage 3**: Moderate to severe loss of kidney function

CREDENCE: greatest benefit in eGFR 45-60

 VIRGINIA HEART
 Excellence in Cardiovascular Care
Future Research:
FDA Fast Track Designation

- **Farxiga** to reduce the risk of CV death, or the worsening of heart failure in adults with heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) based on the Phase III DAPA-HF and DELIVER trials.

- **Farxiga** to delay the progression of renal failure and prevent CV and renal death in patients with chronic kidney disease (CKD) based on the Phase III DAPA-CKD trial.
Discussion
Breakout Groups

- Group 1 – Curie Room
- Group 2 – Edison G
- Group 3 – Edison EF (*Stay here*)
Insight Showcase
AMGA Foundation

Morning Sessions
“You put 16 people on this drug (canaglifozin), you’ll prevent one patient from going on dialysis. This is the newest thing that can really prevent renal disease. That’s huge.”

“It’s the people, it’s the right drugs, it’s communication and it’s data.”

“Much more variance at the site of care level than at the organizational level. At AMGA we try and find commonalities across organizations for top performers and share with them so they can achieve those better rates at all their sites of care.”
Insight Showcase

**Affordability, Implementation and Ownership**

“We have to go from “the diabetes” to “my diabetes.”

“Industry needs to be a part of the solution but they need to fit the workflow of the primary care provider.”

“Top three challenges are education, education and education.”
Afternoon Sessions
Insight Showcase

*T2G, Therapeutic Inertia, Type 2 Diabetes and CVD*

1,082,000 patients with improved care!

“90% of patients with diabetes are managed by their primary care provider who are overwhelmed. Patients trust their pharmacists more than their physicians.”

“We need license to prescribe this class of drugs more broadly. As a cardiologist, I am shy of prescribing these for fear of hypoglycemia. As we get expanded clinical indications and more comfort as cardiologists prescribing this in even non diabetic populations, maybe I’ll feel more comfortable.”
Insight Showcase

Implementing Medication Care Paths

“More education on patient portals is needed for example, what a specific lab measurement means.”

“Are we in the value based world or are we still doing widgets?”
Thank You for a Great Day!