Diabetes Management: Focus on Oral Antihyperglycemics

Henry Halapy, Pharm D, CDE
SATURDAY May 14, 2016
Contemporary Therapeutic Issues in CardiovascularDisease

Acknowledgements

- Some of the slides used in this presentation have been taken from or based upon slides in the "Spotlight on Diabetes – the Kidneys Role in Glucose Control in Type 2 Diabetes" – Richard Ward, Jean-Marie Ekoe, Christine Opstein, Brian Craig, Ronald Goldenberg, Jordan Weinstein, Johanne Desforges, Lawrence McClure, Vincent Woo.

Learning Objectives

1. Describe the use of SGLT-2i in patients with cardiorenal diseases.
2. Identify patients that would benefit from SGLT2 inhibitor therapy and assess need for adjustments to concurrent medications
3. Describe the use of DPP-4i and GLP-1 agonists in patients with cardiorenal diseases.

Disclosures

- I have served on advisory boards for Astra-Zeneca and have worked on medical/pharmacy education programs for Eli Lilly/ Boehringer IngelheimDiabetes Alliance

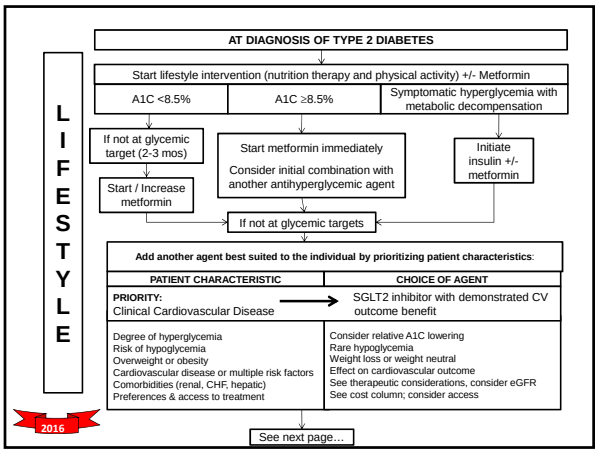
Canadian Diabetes Association Clinical Practice Guidelines

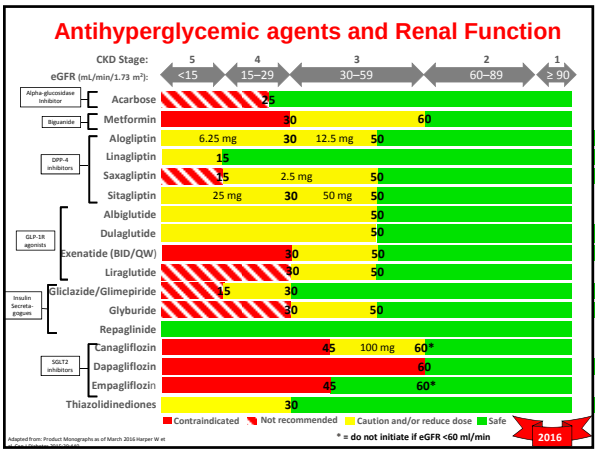
Pharmacologic Management of Type 2 Diabetes

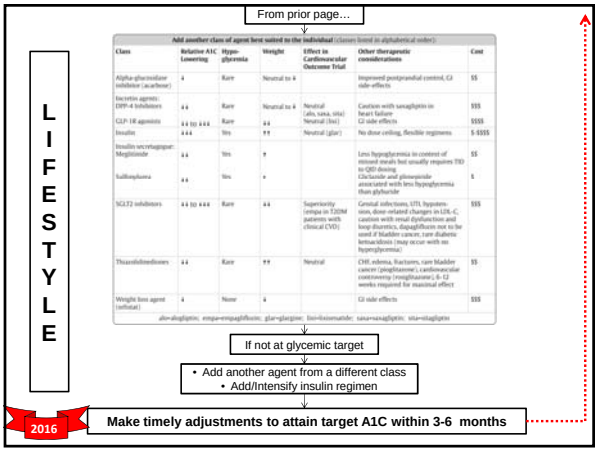
Chapter 13
(Updated March 2016)

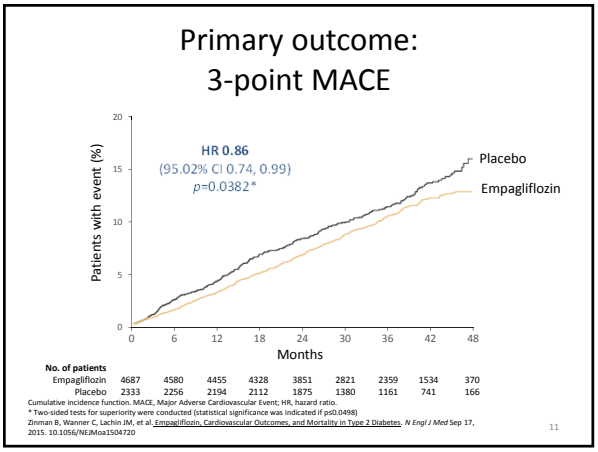
William Harper, Maureen Clement, Ronald Goldenberg, Amir Hanna, Andrea Main, Ravi Retnakaran, Diana Sherifali, Vincent Woo, Jean-François Yale

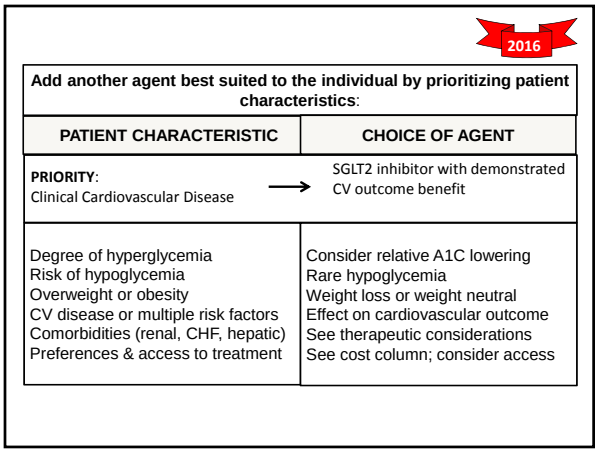
2016

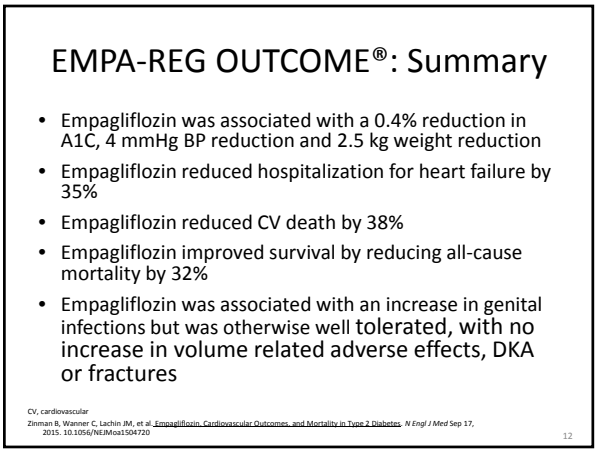

AT DIAGNOSIS OF TYPE 2 DIABETES
LIFESTYLE
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)
Start / Increase metformin
Start metformin immediately
Consider initial combination with another antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic targets
Add another agent best suited to the individual by prioritizing patient characteristics:
PATIENT CHARACTERISTIC
CHOICE OF AGENT
PRIORITY:
Clinical Cardiovascular Disease
SGLT2 inhibitor with demonstrated CV outcome benefit
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Cardiovascular disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment
Consider relative A1C lowering
Rare hypoglycemia
Weight loss or weight neutral
Effect on cardiovascular outcome
See therapeutic considerations, consider eGFR
See cost column; consider access
See next page…
2016


Antihyperglycemic agents and Renal Function
CKD Stage: 5 4 3 2 1
eGFR (mL/min/1.73 m²): <15 15–29 30–59 60–89 ≥ 90
Alpha-glucosidase inhibitor
Acarbose 25
Biguanide
Metformin 30 60
DPP-4 inhibitors
Alogliptin 6.25 mg 30 12.5 mg 50
Linagliptin 15
Saxagliptin 15 2.5 mg 50
Sitagliptin 25 mg 30 50 mg 50
GLP-1R agonists
Albiglutide 50
Dulaglutide 50
Exenatide (BID/QW) 30 50
Liraglutide 30 50
Insulin Secretagogues
Gliclazide/Glimepiride 15 30
Glyburide 30 50
Repaglinide
SGLT2 inhibitors
Canagliflozin 45 100 mg 60*
Dapagliflozin 60
Empagliflozin 45 60*
Thiazolidinediones 30
Contraindicated
Not recommended
Caution and/or reduce dose
Safe
* = do not initiate if eGFR <60 ml/min
2016


From prior page…
LIFESTYLE
If not at glycemic target
• Add another agent from a different class
• Add/Intensify insulin regimen
Make timely adjustments to attain target A1C within 3-6 months
2016


Primary outcome:
3-point MACE
HR 0.86
(95.02% CI 0.74, 0.99)
p=0.0382*
Placebo
Empagliflozin
Patients with event (%)
Months
No. of patients
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)
Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med Sep 17, 2015. 10.1056/NEJMoa1504720
11


2016
Add another agent best suited to the individual by prioritizing patient characteristics:
PATIENT CHARACTERISTIC
CHOICE OF AGENT
PRIORITY:
Clinical Cardiovascular Disease
SGLT2 inhibitor with demonstrated CV outcome benefit
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
CV disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment
Consider relative A1C lowering
Rare hypoglycemia
Weight loss or weight neutral
Effect on cardiovascular outcome
See therapeutic considerations
See cost column; consider access


EMPA-REG OUTCOME®: Summary
• Empagliflozin was associated with a 0.4% reduction in A1C, 4 mmHg BP reduction and 2.5 kg weight reduction
• Empagliflozin reduced hospitalization for heart failure by 35%
• Empagliflozin reduced CV death by 38%
• Empagliflozin improved survival by reducing all-cause mortality by 32%
• Empagliflozin was associated with an increase in genital infections but was otherwise well tolerated, with no increase in volume related adverse effects, DKA or fractures
CV, cardiovascular
Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med Sep 17, 2015. 10.1056/NEJMoa1504720
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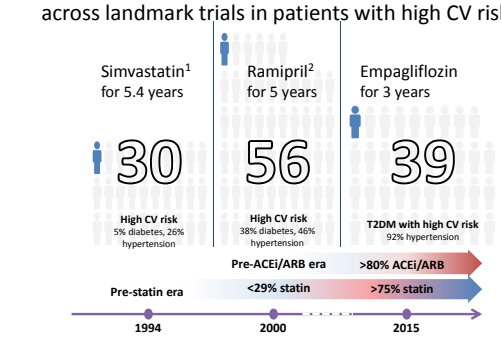
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm
3. Zinman B, Wanner C, Lachin JM, et al, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, *N Engl J Med* Sep 17, 2015. 10.1056/NEJMoa1504720

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Other Trials

- Sulphonylureas –
  - Controversial due to inconclusive data
  - Recent meta-analysis data suggest that sulphonylureas may elevate the risk of cardiovascular disease among patients with type 2 diabetes

Phung et al. Diabetic Medicine. 2013;30:1160-1171.

Other Trials

- SAVOR-TIMI 53 2013 – **saxagliptin** non-inferior to placebo for primary endpoint (CV death, myocardial infarction, ischemic stroke)
  - More patients in saxagliptin grp hospitalized for heart failure (3.5% vs 2.8%, p=0.007)
- ELIXA 2015 – **lixisenatide** (GLP-1 agonist) non-inferior for primary endpoint (CV death, MI, stroke, hospitalization for UA)

Ongoing Studies

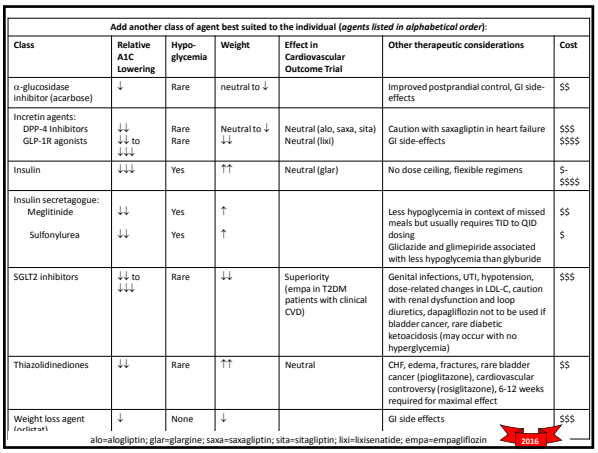
- LEADER 2015 – liraglutide non-inferiority trial – results have non-inferiority and superiority endpoints
- CANVAS/ CANVAS-R 2017 – will assess canagliflozin for major adverse cardiac events in type 2 diabetes
- DECLARE-TIMI 58 2019 – will assess dapagliflozin for MACE in type 2 diabetes

Other Trials

- EXAMINE 2013 - alogliptin non-inferior to placebo for primary endpoint (death from CV causes, nonfatal MI, nonfatal stroke)
- TECOS 2015 – sitagliptin non-inferior to placebo for primary endpoint (death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for UA). Rates of hospitalization for HF did not differ between the two groups

Ongoing Studies

- CAROLINA 2018 – assess effect of linagliptin on MACE in type 2 diabetes versus glimeperide
- CARMELINA 2018 – assess effect of linagliptin on MACE and renal outcomes in type 2 diabetes



Add another class of agent best suited to the individual (*agents listed in alphabetical order*):

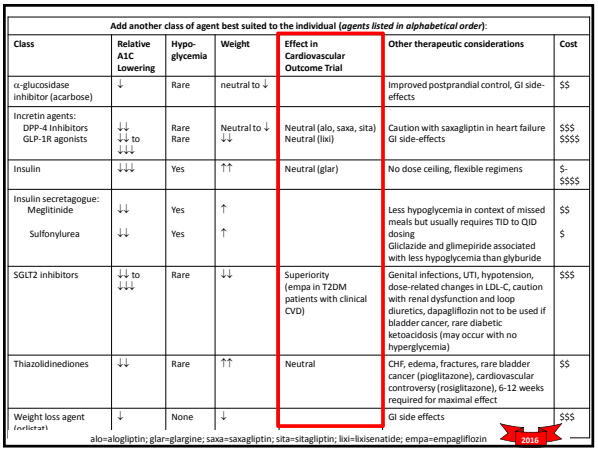
Class	Relative A1C Lowering	Hypo-glycemia	Weight	Effect in Cardiovascular Outcome Trial	Other therapeutic considerations	Cost
α-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓		Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors GLP-1R agonists	↓↓ ↓↓ to ↓↓↓	Rare Rare	Neutral to ↓ ↓↓	Neutral (alo, saxa, sita) Neutral (lixi)	Caution with saxagliptin in heart failure GI side-effects	$$$ $$$$
Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	↓↓ ↓↓	Yes Yes	↑ ↑		Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$$ $
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
Thiazolidinediones	↓↓	Rare	↑↑	Neutral	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓		GI side effects	$$$

alo=alogliptin; glar=glargine; saxa=saxagliptin; sita=sitagliptin; lixi=lixisenatide; empa=empagliflozin

2016

Case 1

- C.G. is a 56 year old male diagnosed with diabetes 2 years ago.
- Up until recently the metformin + lifestyle modifications have been working to control his A1C.
- In the 6 months, his A1C has increased from 7.0% to 7.8%. His lifestyle modifications have not changed.



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Insulin	↓↓↓	Yes	↑↑	Neutral (glar)	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	↓↓ ↓↓	Yes Yes	↑ ↑		Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	$$ $
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	Superiority (empa in T2DM patients with clinical CVD)	Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia)	$$$
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alo=alogliptin; glar=glargine; saxa=saxagliptin; sita=sitagliptin; lixi=lixisenatide; empa=empagliflozin

2016

Case 1

- Current meds:
  - metformin 1g bid, atorvastatin 20mg once daily, perindopril 8mg once daily
  - has medication insurance
- Labs:
  - eGFR>90mL/min, LDL=1.8 mmol/L, K+=4.0
- Assessment:
  - BMI=28 kg/m2, BP=125/80 mmHg, A1C 7.8%, no established CAD
- What do you recommend?

Case 1

- What do you recommend?
- Consider reasons for recent increase in A1C?

Case 1

- What medication would you consider next for C.G.? What are the considerations in general for adding oral medications?
- Would your suggestion be altered if C.G. has established CAD?

Case #2

- What considerations would you have regarding L.T.'s past medical history and current assessment?
- What considerations would you have regarding L.T.'s current medication use?

Case #2

- L.T. is a 65 yo man with type 2 diabetes x 10 years with worsening A1C levels, now 8.1%
- PmHx: hypertension x 15 yrs, gout x 6 yrs, mild heart failure x 3 years, post MI x 3 years, LUTS x 4 years, history of pancreatitis
- Meds: ramipril/HCT 10/25mg daily, furosemide 60mg daily, amlodipine 10mg daily, ECASA 325mg daily, atorvastatin 40mg daily, **metformin 1g bid, glyburide 10mg bid**, tamsulosin 0.4mg qhs, ibuprofen 200mg prn gout attacks

Patient Counseling

- What are some key counseling points for your choice of medication?

Case #2

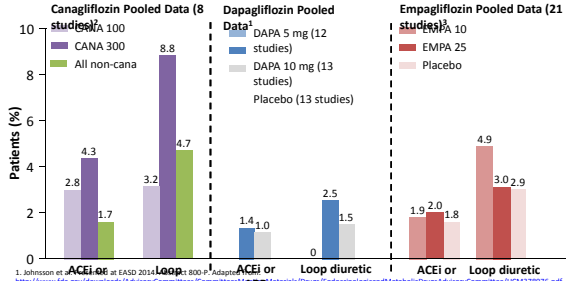
- Labs: eGFR=65mL/min, CrCl=62mL/min, K+=5.0, LDL=1.8 mmol/L
- Assessment: BMI=30kg/m2, weight=105kg, BP=112/78mmHg, A1C=8.1%
- SMBG – sporadic, ranges = 6-10 mmol/L, occasional hypoglycemia if forgets to eat
- What do you recommend for L.T.'s glycemic control?

Patient Counseling – SGLT-2i's

- Common SE's – mycotic infections, UTI's
- Hypoglycemia
- Hypotensive symptoms
- Hyperkalemia
- Sick day counseling – SADMANS
- Rare but serious - DKA

Volume-related Adverse Effects: Background ACEi or ARB; Loop Diuretics

Separate Studies & Not Direct Comparisons



1. Johnsson et al. Poster at EASD 2014; Poster 800-P. Adapted from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM378076.pdf
2. Adapted from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013.
3. Toto R et al. ASN kidney Week 2013; Poster SA-PO373.

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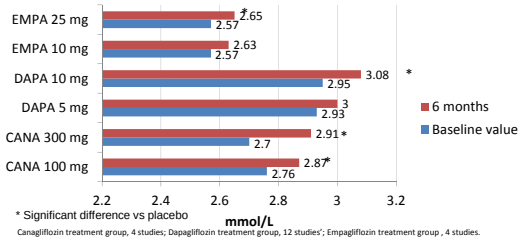
Summary of Trials on the impact of SGLT2 Inhibitors on LDL-C

Separate Studies & Not Direct Comparisons

Mean baseline and placebo-subtracted value at 6 months in pooled placebo-controlled trials



* Significant difference vs placebo

Canagliflozin treatment group, 4 studies; Dapagliflozin treatment group, 12 studies'; Empagliflozin treatment group , 4 studies.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013. Hardy P et al. ADA Annual Meeting 2013. Abstract 1188-P. Hach T et al. ADA Annual Meeting 2013. Abstract 69-LB.

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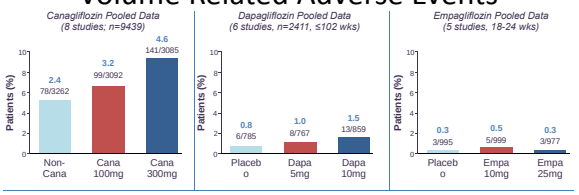
SGLT2 Inhibitors: Volume Related Adverse Events



Events include:
- Hypotension
- Postural hypotension
- Dehydration
- Syncope
- Reduced urine output

Events more common in:
- Pts on loop diuretics
- Pts with eGFR 30-60
- Elderly
- Pts on ACEi or ARBs

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs /EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM378076.pdf. Jardiance European Product Monograph 2014.

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Summary of Trials on the impact of SGLT2 Inhibitors on LDL-C

Separate Studies & Not Direct Comparisons

Mean baseline and placebo-subtracted value at 6 months in pooled placebo-controlled trials

What does this mean for your patient?
- 0.06-0.21 mmol/L increase in LDL-C
- 0.06-0.22 mmol/L decrease in triglycerides
- Non-significant in clinical practice, however, long term safety data is needed.

* Significant difference vs placebo

Canagliflozin treatment group, 4 studies; Dapagliflozin treatment group, 12 studies'; Empagliflozin treatment group , 4 studies.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf. Accessed January 23, 2013. Hardy P et al. ADA Annual Meeting 2013. Abstract 1188-P. Hach T et al. ADA Annual Meeting 2013. Abstract 69-LB.

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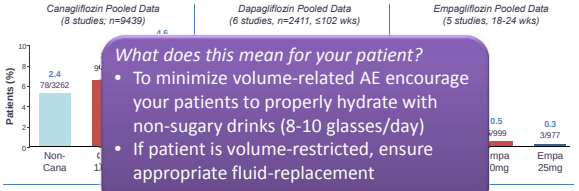
SGLT2 Inhibitors: Volume Related Adverse Events



What does this mean for your patient?
- To minimize volume-related AE encourage your patients to properly hydrate with non-sugary drinks (8-10 glasses/day)
- If patient is volume-restricted, ensure appropriate fluid-replacement

Events include:
- Hypotension
- Postural hypotension
- Dehydration
- Syncope
- Reduce urine output

Events more common in:
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SGLT2 Inhibitors and Ketoacidosis: FDA & HC Warning

- Atypical presentation: Patients with Type 1 & Type 2 were euglycemic
- Contributing factors: Major illness, reduced food and fluid intake, and reduced insulin dose
- Signs and symptoms: Nausea, vomiting, abdominal pain, unusual fatigue, confusion, and shortness of breath

What does this mean for your patient?
- "Sick day management" is likely warranted in the case of illness with prolonged fever, vomiting or diarrhea

Canagliflozin: Drug Information Lexicomp. Dapagliflozin: Drug Information Lexicomp Uptodate – Accessed May 28, 2015. Peters AL et al. Diab Care. Epub ahead of print July 2015. DOI: 10.2337/dc15-0843.

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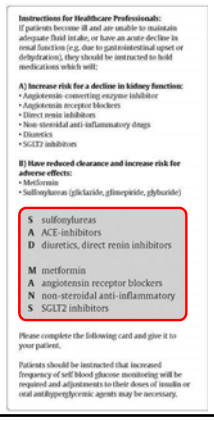
Counsel all Patients About

Sick Day Medication List

2015



Instructions for Healthcare Professionals:
If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE-inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N non-steroidal anti-inflammatory
S SGLT2 inhibitors

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

CDA CPG Expert Committee. Can J Diab 2015; 39:250-2

Case #3a

- Labs: eGFR=67mL/min, CrCl=62mL/min, K+=5.1, LDL=1.8 mmol/L
- Assessment: BMI= 28kg/m2, weight=85kg, BP=120/80mmHg, A1C=7.9%, ACR=30.2
- What do you recommend for C.P.'s glycemic control?

Case #3a

- C.P. is a 70 yo woman with a history of type 2 diabetes x 20 years
- PmHx: hypertension x 15 yrs, hypercholesterolemia x 12 years, CAD x 10 years, afib x 5 years, diabetic nephropathy x 10 years, history of mycotic infections
- Meds: ramipril/HCT 10/25mg daily, amlodipine 10mg daily, ECASA 81mg daily, warfarin daily per INR, rosuvastatin 40mg daily, metformin 1g bid, gliclazide MR 120mg daily, glargine 55 units qhs

Case #3a

- Adding oral medications to patients already on insulin:

  - SLGT-2i, GLP-1 agonists
  - reduce TDD of insulin by 10-20% to start
  - adjust insulin dose as needed
  - expected impact in 3-5 days

Case #3a

FBS	acL	acS	HS
4.3	7.8	9.2	9.8
4.7	6.1	8.7	10.1
5.4	8.2	10.1	11.1
4.9	5.4	8.6	8.8
4.1	7.2	7.8	8.4
5.1	8.9	9.8	8.5
4.2	6.9	7.9	10.1

Case #3a

- What if C.P. had postural hypotension?
  – BP 110/60mmHg

Case #3b

- What if C.P.'s renal function is more advanced?
  - eGFR = 32 mL/min; CrCl = 35mL/min

Case #4

- P.D. is 52 year old male, type 2 DM X 20 years, wt=113kg, BMI = 35 kg/m^2 recent A1C = 10.7%; otherwise generally healthy
- NovoMix 30 - 80 units before breakfast, lunch and dinner
- According to the patient:
  - he is taking all his insulin doses regularly at the correct doses (you verify with Rx refill histories). Has ODB & private coverage.
  - he states that he is compliant with his diet.
  - he is only able to walk a couple of blocks because of knee and hip pains.
  - he is unwilling to try other forms of exercise.

Patient Counseling

- What are some key counseling points for your choice of medication?

Case #4

FBS	acL	acS	HS
9.8	10.7	11.2	14.4
10.2	11.1	13.2	10.6
8.7	12.3	12.5	15.1
12.4	9.8	10.1	12.3
8.3	8.7	11.5	16.7
13.2	16.2	20.2	9.8
9.7	10.2	11.7	17.2

- What could be accounting for P.D.'s persistently elevated BG values?

Patient Counseling

- Hypotension
- Hypoglycemia, especially in am
- Hyperkalemia

- Sick Day Medications – SADMANS
- DKA

Case #4

- P.D.'s endocrinologist believes he has resistant diabetes.

- What treatment options could P.D.'s endocrinologist consider?

Case #4

- Adding oral medications to patients already on insulin:

  - SLGT-2i, GLP-1 agonists
  - reduce TDD of insulin by 10-20% to start
  - adjust insulin dose as needed
  - expected impact in 3-5 days

Combination Diabetes Medications

- Consider both SGLT-2i and GLP-1 agonist/ DPP-4 inhibitor

Summary

1. Remember key factors in helping to decide eligibility of patients for newer SGLT-2i, DPP-4, and GLP-1 agonist medications.

2. Consider if concurrent medications need to be adjusted when starting SLGT-2i, DPP-4, an GLP-1 agonist medications.