THE "NEW-ISH" DIABETES MEDICINES

Using GLP1s and SGLT2s

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January 31, 2019

FINANCIAL DISCLOSURES

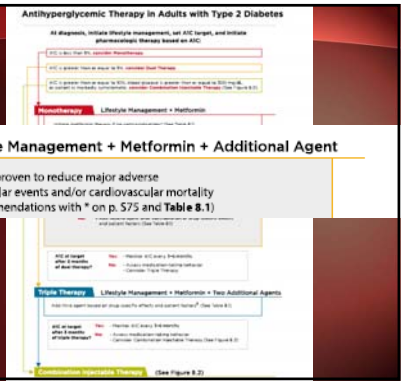
- None

OBJECTIVES

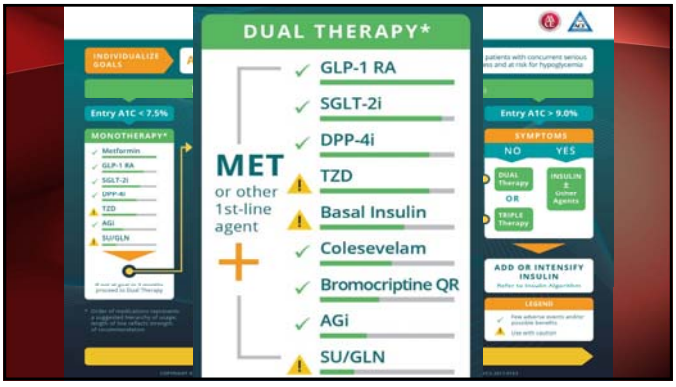
- Gain familiarity with GLP1 receptor agonists and SGLT2 inhibitors
- Learn when they might be a beneficial add-on to metformin
- Address potential side effects (and misconceptions)

SO WHAT NEXT AFTER METFORMIN?

ADA GUIDELINES



PREVIOUSLY: DEALER'S CHOICE



CAST OF CHARACTERS

GLP1 RECEPTOR AGONISTS

- Byetta (Exenatide short acting)
- Bydureon (Exenatide extended release)
- Victoza (Liraglutide)
- Trulicity (Dulaglutide)
- Ozempic (Semaglutide)
- Adlyxin (Lixisenatide)
- Tanzeum (Albiglutide)*

*Withdrew from market in 2018 for economic reasons

STARTING A GLP1

- Subcutaneous injections
- GFR > 30 for Exenatide
  - (others "use with caution")
- Stop DPP4 inhibitors
- Reduce or stop sulfonylureas
- Reduce or stop bolus insulin*

*Not FDA approved for use in conjunction with bolus insulins

SGLT2 INHIBITORS

- Invokana (Canagliflozin)
- Farxiga (Dapagliflozin)
- Jardiance (Empagliflozin)
- Steglatro (Ertugliflozin)

STARTING AN SGLT2

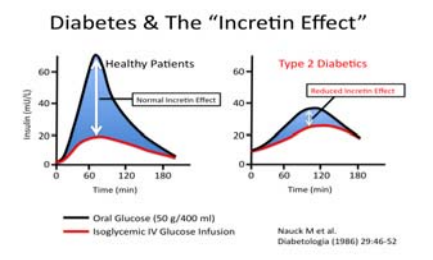
- Oral
- They all come in 2 doses
- They all come in combo with metformin
- Most come in combo with DPP4 inhibitors
- GFR > 45 (> 60 for dapagliflozin)

MECHANISMS OF ACTION

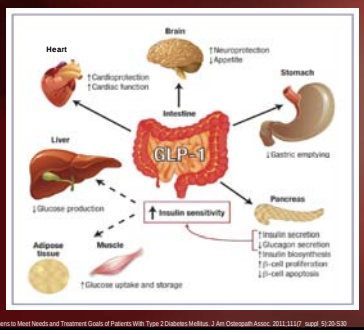
GLP1 MECHANISMS

- GLP1 (and GIP) are "incretins" – insulin promoting secretions
- Made by the L-cells of the small intestine
- Stimulated by oral ingestion of glucose
- Produced less in patients with DM2
- Native GLP1 is rapidly degraded in the body by DPP4

THE "INCRETIN EFFECT"



GLP1 MECHANISMS

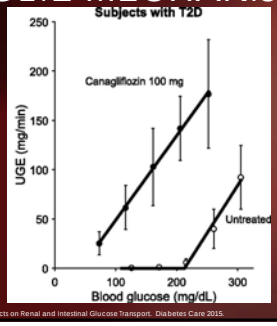


Garber. Novel Incretin-Based Agents and Practical Regimens to Meet Needs and Treatment Goals of Patients With Type 2 Diabetes Mellitus. J Am Osteopath Assoc. 2011;111(7 suppl 5):20-S30

SGLT2 MECHANISM

- SGLT2 reabsorbs 90% of glucose in the proximal tubule
- SGLT2 inhibitors block reabsorption thus increasing renal glucose excretion
- Glucose-dependent
- Insulin-independent

SGLT2 MECHANISM

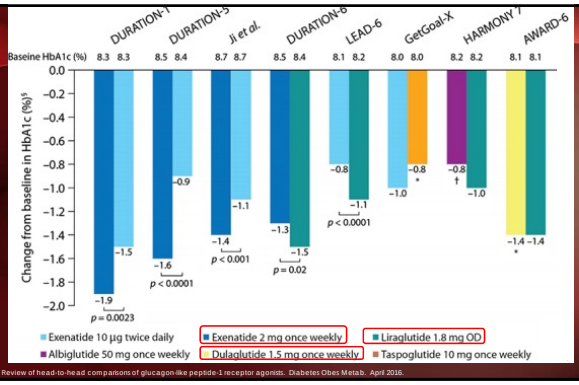


Mudaliar. Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport. Diabetes Care 2015.

A1C REDUCTION

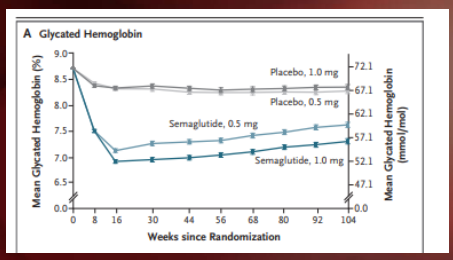
A1C REDUCTION

- Variable reports, but in general I think:
- GLP1
  - Low dose: 0.5-0.8%
  - High dose: 0.8-1.5%
- SGLT2
  - Low dose: ~0.5-0.6%
  - High dose: ~0.7-1.0%



Madsbad. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. April 2016.

SEMAGLUTIDE



Marso et al. Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes. NEJM Nov 2016.

GLP1 SUPERIOR TO DPP4

- 13 head to head RCT's
  - A1c 0.4% better
  - Weight loss > 2 kg more
- 5 trials switching from DPP4 to GLP1
  - A1c reduction of 0.7%
  - Weight loss of > 2 kg

Tran et al. Efficacy of glucagon-like peptide-1 receptor agonists compared to dipeptidyl peptidase-4 inhibitors for the management of type 2 diabetes: A meta-analysis of randomized clinical trials. Diabetes Obes Metab, 2018.

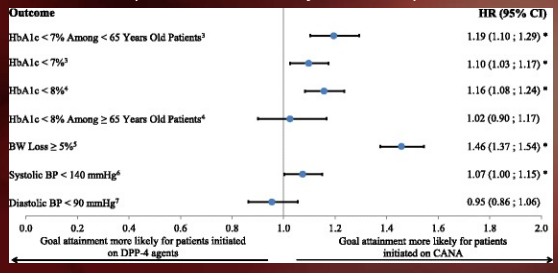
SGLT2 VS DPP4

- 25 RCT with 14,000 patients
- SGLT2
  - Lower A1c (0.13%)
  - Lower Fasting glucose (14 mg/dl)
  - No difference in hypoglycemia

Wang et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors vs dipeptidyl peptidase-4 inhibitors as monotherapy or add-on to metformin in patients with type 2 diabetes mellitus A systematic review and meta-analysis. Diabetes Obes Metab, 2018.

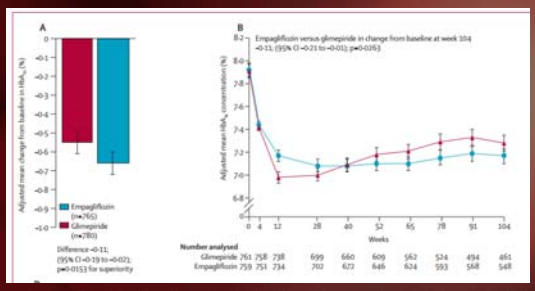
SGLT2 VS DPP4

Retrospective Case study of 28,000 patients



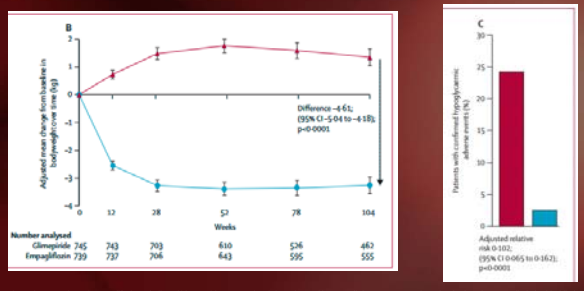
Wysham et al. Quality measure and weight loss assessment in patients with type 2 diabetes mellitus treated with canagliflozin or dipeptidyl peptidase-4 inhibitors. BMC Endo Disorders, June 2017.

SGLT2 VS SULFONYUREA



Ridderstrale et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endo. June 2014.

SGLT2 VS SULFONYUREA



Ridderstrale et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endo. June 2014.

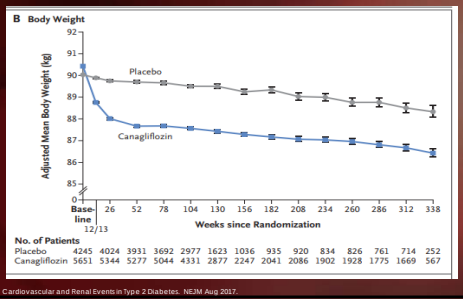
WEIGHT REDUCTION

WEIGHT REDUCTION

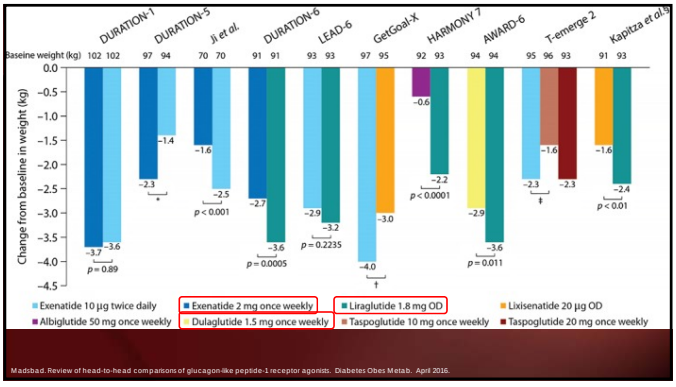
- Variable results based on drug and comparator group (insulin, metformin or SU)
- GLP 1: 2-5kg
- SGLT2: 2-3kg

Visboll et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomized controlled trials. BMJ 2012.
Liu et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2 years. J Diabetes Complications 2015.

CANAGLIFLOZIN

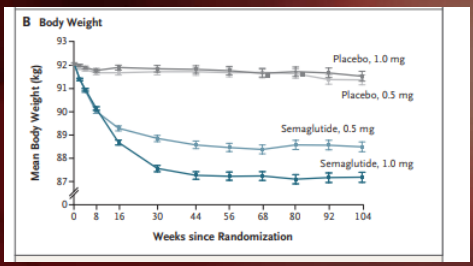


Neal et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. NEJM Aug 2017.



Madsbad. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab. April 2016.

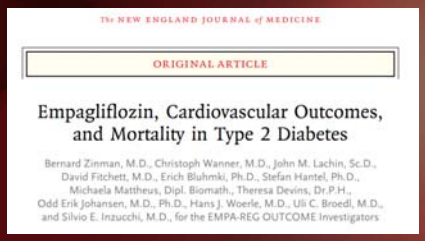
SEMAGLUTIDE



Marso et al. Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes. NEJM Nov 2016.

CARDIOVASCULAR BENEFITS

GAME CHANGER*


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

*Metformin actually showed CV benefit in the UKPDS extension trial

Zinman et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM Nov 2015.

SIDEBAR: FDA AND METFORMIN

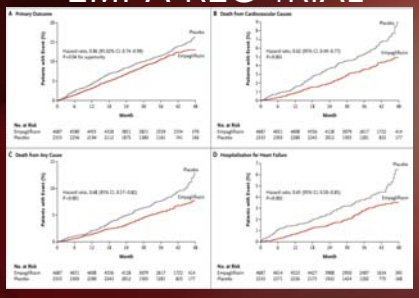
- No longer creatinine based
- Contraindicated with GFR < 30
- Not recommended to start with GFR 30-45
- If GFR falls below 45 on metformin, assess risks vs benefits

EMPA-REG TRIAL

- 7000 patients, 3.1 years
- Composite endpoint: CV death, MI, CVA
- 10.5% vs 12.1%
- RR reduction 13%
- Less CV death (3.7% vs 5.9% - 38% RRR)
- Fewer CHF admissions (2.7% vs 4.1% - 35% RRR)

Zinman et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM Nov 2015.

EMPA-REG TRIAL



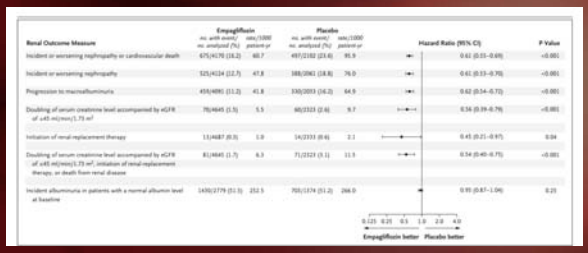
Zinman et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM Nov 2015.

EMPA-REG TRIAL

- Prespecified renal endpoint
- Microalbuminuria, Doubling of Cr, ESRD, or death from Kidney disease
- 12.7% vs 18.8% (32% RR reduction)

Wanner et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. NEJM July 2016.

EMPA-REG TRIAL



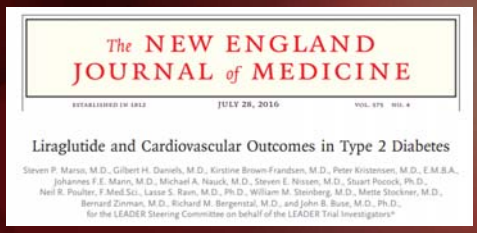
Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4176 (16.2)	40.7	497/2182 (23.6)	95.9	0.61 (0.53–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2003 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2331 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.9	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.23

0.125 0.25 0.5 1.0 2.0 4.0

Empagliflozin better | Placebo better

Wanner et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. NEJM July 2016.

LIRAGLUTIDE = CV BENEFIT



The NEW ENGLAND JOURNAL of MEDICINE

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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., F.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

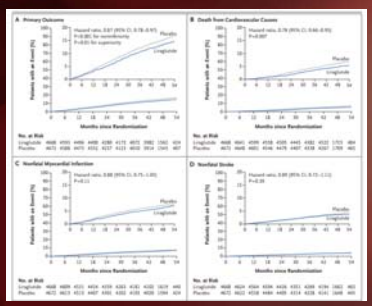
Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM July 2016.

LEADER TRIAL

- 9340 patients over 3.8 years
- Composite outcome: CV death, MI, CVA
- 13% vs 14.9%
- RR Reduction 13%

Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM July 2016.

LEADER TRIAL



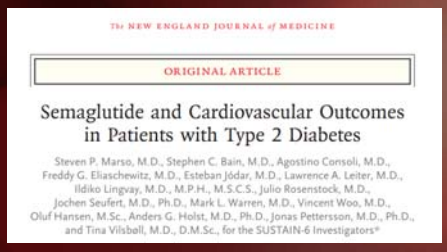
Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM July 2016.

LEADER TRIAL—RENAL OUTCOMES

- New microalbuminuria, Doubling of Cr, ESRD, or Death due to Kidney Disease
- 5.7% vs 7.2%

Mann et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. NEJM Aug 2017.

SEMAGLUTIDE = CV BENEFIT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ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

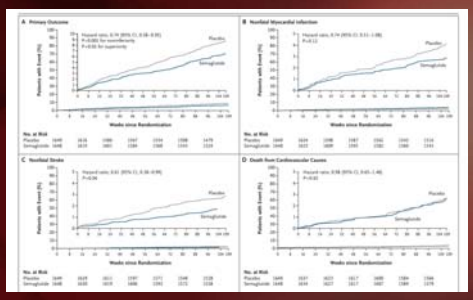
Marso et al. Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes. NEJM Nov 2016.

SUSTAIN-6 TRIAL

- 3300 patients, 83% with CV disease
- Composite outcome: CV death, MI, CVA
- 6.6% vs 8.9% at 2 years
- RR reduction 26%
- Less new or worsening nephropathy
- More retinopathy complications--3.0% vs 1.8%
- Drop out rate 13% vs 6.7% (mostly GI)

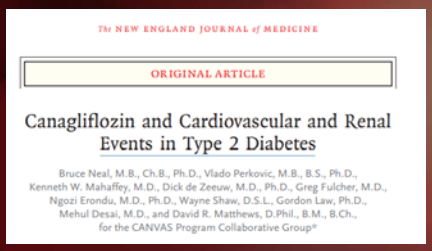
Marso et al. Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes. NEJM Nov 2016.

SUSTAIN-6 TRIAL



Marso et al. Semaglutide and Cardiovascular outcomes in patients with type 2 diabetes. NEJM Nov 2016.

CANAGLIFLOZIN = CV BENEFIT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ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

CANVAS TRIAL

- 10,000 patients, 3.6 years
- Canagliflozin vs placebo
- Outcome: CV death, MI, CVA
- 26.9 vs 31.5 events per 1000 patient yrs
- RR reduction 14.6%

Neal et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. NEJM Aug 2017.

SUMMARY OF CV BENEFIT TRIALS

Trial	EMPA-Reg	CANVAS	LEADER	SUSTAIN-6
Drug	Empagliflozin	Canagliflozin	Liraglutide	Semaglutide
Duration	3.1 years	3.6 years	3.8 years	2 years
Absolute RR	1.6%		1.9%	2.3%
Relative RR	13%	15%	13%	26%
FDA Label	CV Death	MI, CVA, CV death	CV events & death	Pending
Negative	Genital infections	Amputation		Retinopathy

RISKS AND RUMORS: GLP1-RA

RISKS AND RUMORS: GLP1-RA

- Nausea
- C-cell tumors of the thyroid
- Pancreatitis
- Pancreatic cancer

GLP1: NAUSEA

- Occurs in ~10-50% of patients
- Most pronounced in the short acting (exenatide and lixisenatide)
- Abates after a few doses
- Clinical trials showed 5% discontinuation
- Clinical practice shows about 5-10% discontinuation

MEDULLARY THYROID CANCER

- Black box warning
- Rodent studies showed C-cell hyperplasia
- Rodents get MTC at higher rates than humans
- Rodent thyroid have much higher expression of GLP1 receptors
- Functional studies in primates and humans did not show a GLP1 response on the thyroid

Boess et al. Effect of GLP1R agonists taspoglutide and liraglutide on primary thyroid C-cells from rodent and man. J Mol Endo. May 2013.

MEDULLARY THYROID CANCER

- At 36 months, no increase in calcitonin, C-cell hyperplasia, or MTC
- There have been no confirmed human cases of MTC due to GLP1 agents

Hegedus et al. No Evidence of Increase in Calcitonin Concentrations or Development of C-Cell Malignancy in Response to Liraglutide for Up to 5 Years in the LEADER Trial. Diabetes Care, Mar 2018
Prasad-Reddy. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs Context 2015.

THE PANCREATITIS ISSUE

- Some studies showed mildly increased lipase levels
- Post-marketing event reporting
- A case-control study from insurance database showed 2-fold risk of pancreatitis from sitagliptin or exenatide

Butler. Glucagon-Like Peptide 1 Drugs as Second-Line Therapy for Type 2 Diabetes. JAMA Intern Med, Nov 2016.

PANCREATITIS IS UNPROVEN

- The major CV outcome trials of GLP1 agonists showed no increased risk of pancreatitis
- Meta-analysis of 3 RCT with 20,000 patients showed no increased risk
- Overall risk is low– 16 cases among 15,000 patients

Storgaard et al. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. Diabetes Obes Metab. June 2017.
Monami et al. Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. Diabetes Res Clin Pract. Feb 2014.
Monami et al. Safety issues with glucagon-like peptide-1 receptor agonists: Data from randomized controlled trials. Diabetes Obes Metab. Sept 2017.

PANCREATIC CANCER?

- Autopsy study on 34 subjects, 8 of whom were on incretin therapy
- 3 out of 8 had glucagon-expressing microadenomas
- 1 had a neuroendocrine tumor
- Reported B-cell mass was 6x increased
- Many criticisms of control, matching, and generalizability of results

Butler et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. Diabetes July 2013.

PANCREATIC CANCER?

- 2,024,441 person years studied
- Hazard ratio of incretin treated vs sulfonylurea treated was 1.02 (not significant)
- FDA and European Medicines Agency determined insufficient evidence of risk
- Always the concern that there could be delayed effect

Azoulay et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. BMJ Feb 2016.
Monami et al. Safety issues with glucagon-like peptide-1 receptor agonists: Data from randomized controlled trials. Diabetes Obes Metab. Sept 2017.

BIGGEST SKEPTIC COMING AROUND

- "In patients with uncontrolled type 2 diabetes and obesity, the addition of GLP-1 mimetics to metformin and, if necessary, to insulin, is a logical choice given current evidence if there is no history of pancreatic or biliary disease or thyroid cancer. The possible increased risk of pancreatitis with the GLP-1 class of drugs, based on consistent findings in sufficiently powered RCTs, seems reassuringly low."

Butler. Glucagon-Like Peptide 1 Drugs as Second-Line Therapy for Type 2 Diabetes. JAMA Intern Med. Nov 2016.

RISKS AND RUMORS: GLP1-RA

- Nausea – yep, 10-15%, usually abates
- C-cell tumors of the thyroid – just rats
- Pancreatitis – probably not, rates low
- Pancreatic cancer – no increased rate, admittedly no 20 year follow up

RISKS AND RUMORS: SGLT2

RISKS AND RUMORS: SGLT2

- Polyuria
- GU infections
- Renal Failure
- Fractures
- DKA
- Amputations

GU INFECTIONS

- Myotic infections– yes
- UTI – no (only dapagliflozin 10mg)
- Mycotic genital infection risk increases about 3-5 fold
- In EMPA-REG trial, in women: 2.6% vs 10.0%

Li et al. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. March 2017.

Prepared exclusively for ENDOCRINE SOCIETY

Endocrine Daily Briefing

in affiliation with BulletinHealthcare

FDA Warns SGLT2 Inhibitors Can Cause Flesh-Eating Genital Infection.

GU INFECTIONS

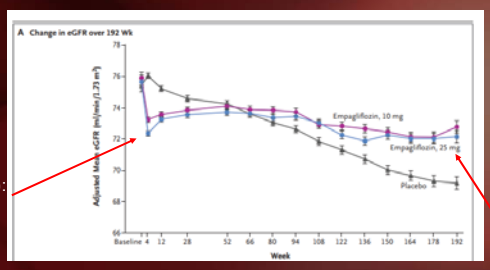
- 12 cases of Fournier's gangrene over a 5 year period reported to FDA
- Warning now added to prescribing label

ACUTE KIDNEY INJURY

- Only a few post marketing reports
- EMPA-REG, CANVAS and meta-analyses do not show increased rates of AKI, in fact they usually show protective effects

Nadkarni et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care. Nov 2017.

SGLT2'S DO NOT HARM KIDNEYS



Initial Drop: Diuresis?

Longterm protective

Wanner et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. NEJM July 2016.

FRACTURES

- Slight increase shown in CANVAS trial
- Over 3.6 years

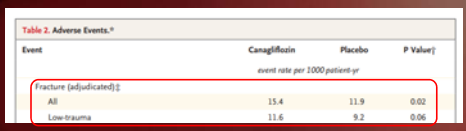


Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06

HOWEVER…

- Fractures as early as 12 weeks
  - Orthostasis? Urinary urgency?
- Meta-analysis of 24,000 patients did not show increased fracture
- BMD loss and bone turnover increase proportional to weight loss alone

Zaccardi et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab, Aug 2016.
Blezikian et al. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. J Clin Endo Metab, jan 2016.

DKA

- Possibility of euglycemic (glucose < 250) DKA
- Reduces sugar thus masking the usual first sign of insulinopenia
  - Applies mostly to type 1 or ketosis prone type 2
- Rate of DKA is twice that of DPP4

Fralick et al. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. NEJM June 2017.
Taylor et al. SGLT2 inhibitors may predispose to ketoacidosis. JCEM Aug 2015

AMPUTATION

- The CANVAS and CANVAS-R trials both showed a significant increase in rate of toe and mid-foot amputations
- Most patients had existing neuropathy, PAD, amputation

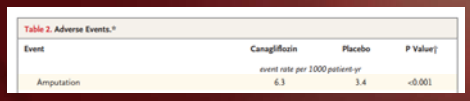


Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
Amputation	6.3	3.4	<0.001

AMPUTATION

- NO increased amputations have been shown in prospective RCTs of empagliflozin, dapagliflozin, ertugliflozin
- Black box warning is only on Canagliflozin

CLASS EFFECT OF AMPUTATION?

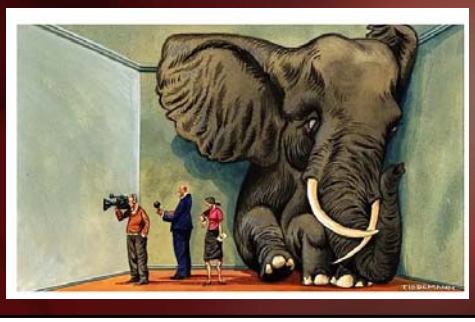
- Scandinavian database review of dapagliflozin and empagliflozin
- 34,000 patients, SGLT2 vs GLP1
- Incidence rate of 2.7 vs 1.1 per 1000 person years

Ueda et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ, Nov 2018.

RISKS AND RUMORS: SGLT2

- Polyuria – yep
- GU infx – yeast, not really UTI (Fournier's?)
- Renal Failure – no, actually protective
- Fractures – maybe, but seems commensurate to weight loss
- DKA – only in those at risk for DKA
- Amputation – rare, specific to Canagliflozin?

DID I FORGET ANYTHING?



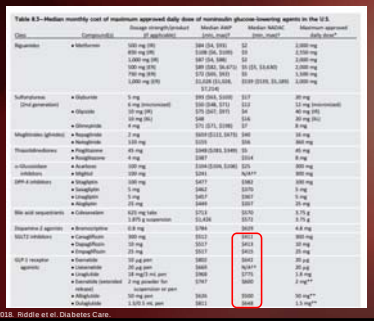
THE ELEPHANT IN THE ROOM-- $$$

- Sulfonylureas ~$15/month
- DPP4-i ~$370/month
- Insulin analog 30 units/day ~$300/month
- SGLT2-i ~$410/month
- GLP1-RA ~$650/month

*These are average acquisition prices, wholesale prices are ~$100 more

Standards of Medical Care in Diabetes – 2018. Riddle et el. Diabetes Care.

THE ELEPHANT IN THE ROOM-- $$$



Standards of Medical Care in Diabetes – 2018. Riddle et el. Diabetes Care.

HIDDEN COSTS OF SULFONYLUREAS

- Weight gain
- Hypoglycemia
  - Increased use of test strips
  - Increased ER visits
  - Possible risk of CV death

HIDDEN COSTS OF SULFONYLUREAS

- 2017 Italian analysis of SU vs DPP4
- Assigned costs to meds, strips, hypoglycemia, hospitalizations, CV events, rate of switch to insulin, productivity losses
- Showed that DPP4 would save hundreds of societal dollars over 3 years

Lorenzoni. Cost-consequence analysis of sitagliptin versus sulfonylureas as add-on therapy for the treatment of diabetic patients in Italy. Clinicoecon Outcomes Res. Nov 2017.

SU ASSOCIATED WITH MORE CV EVENTS

- 132,000 subjects
- Retrospective chart review
- Add-on's to metformin compared
- 36% higher risk of CV events with SU vs DPP4i
- ~20% lower risk with GLP1's

O'Brien et al. JAMA Network Open, 2018.

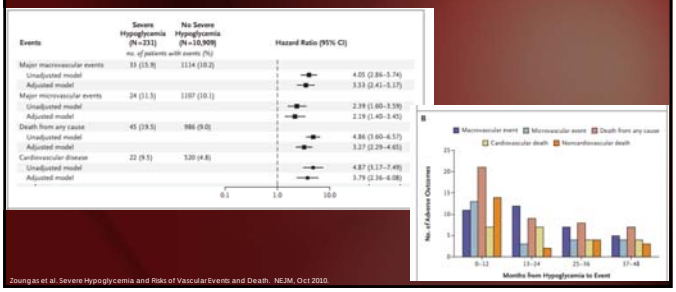
POSSIBLE INCREASED MORTALITY FROM SU

- FDA label -- "Potential Increased Risk of Cardiovascular Mortality with Sulfonylureas"
- Multiple observational studies have shown up to 60% mortality increase with SU vs metformin monotherapy

Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. *Diabetes, Obesity & Metabolism* 2014;16(10):957-62

Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. *Diabetes, Obesity & Metabolism* 2012;14(9):803-9

COSTS OF HYPOGLYCEMIA



Zoungas et al. Severe Hypoglycemia and Risks of Vascular Events and Death. NEJM, Oct 2010.

SUMMARY: GLP1 AGONISTS

- A1c reduction up to 1.5%
- Weight loss up to 5kg
- CV benefit Liraglutide (13%) and Semaglutide (26%)
- Nausea – usually abates
- Avoid with pancreatitis risk
- $$$$

SUMMARY: SGLT2 INHIBITORS

- Up to 1% A1c reduction
- Up to 2-3kg weight reduction
- CV benefit from Empagliflozin and Canagliflozin (especially in CHF)
- Polyuria, GU infections, amputation risk
- $$$

THANK YOU