PHARMACOLOGIC APPROACH TO ACHIEVE GLYCEMIC GOAL

SPED Convention and Diabetes Postgraduate Course

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Endocrinology

DISCLOSURES

Speaker for the following companies:

- Astra, Janssen ,Merck ,Sanofi

OBJECTIVES

- Appropriate goal setting

- ADA versus AACE clinical guidelines

- Comparative assessment of efficacy

- among antidiabetic drug

- regimens

- Second agent of choice

- Combination therapy with and without

- metformin

Type 2 diabetes care management

- Appropriate goal setting
- Dietary and exercise modification
- Medications
- Self monitoring of blood glucose
- Regular monitoring for complications
- Laboratory assessment

Landmark clinical trials assessing for macrovascular benefits of glycemic control in type 2 diabetes

LONGSTANDING POORLY CONTROLLED T2D, AGGRESSIVE A1C LOWERING

- ACCORD:increase in all cause death,no benefit/harm in CV outcomes

- ADVANCE : no benefit /harm in CV outcomes

- VADT: no benefit/harm during trial, after f/u reduction in CV, although not mortality

NEWLY DIAGNOSED PATIENTS WITH TYPE 2 DIABETES

- UKPDS 10y/:reduction in CV events and all cause death with metformin treatment

ADA and AACE recommendations for glycemic control targets[1,2]

Most nonpregnant adults with diabetes may be treated to meet the following glycemic goals:

Test	Glycemic control targets	
	ADA	AACE
A1C	<7%	≤6.5%[3]
FPG	80-130 mg/dL	<110 mg/dL[3]
PPG	<180 mg/dL (measured within 1 to 2 hours after the start of a meal)	<140 mg/dL[3] (2-hour value)

A1C target should be individualized based on numerous factors, including age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence[1,2]

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; FPG, fasting plasma glucose; PPG, postprandial glucose.

1. ADA. *Diabetes Care*. 2016;39(suppl 1):S1-S112. 2. Garber AJ et al. *Endocr Pract*. 2016;22(1):84-113. 3. Handelsman Y et al. *Endocr Pract*. 2015;21(suppl 1):1-87.
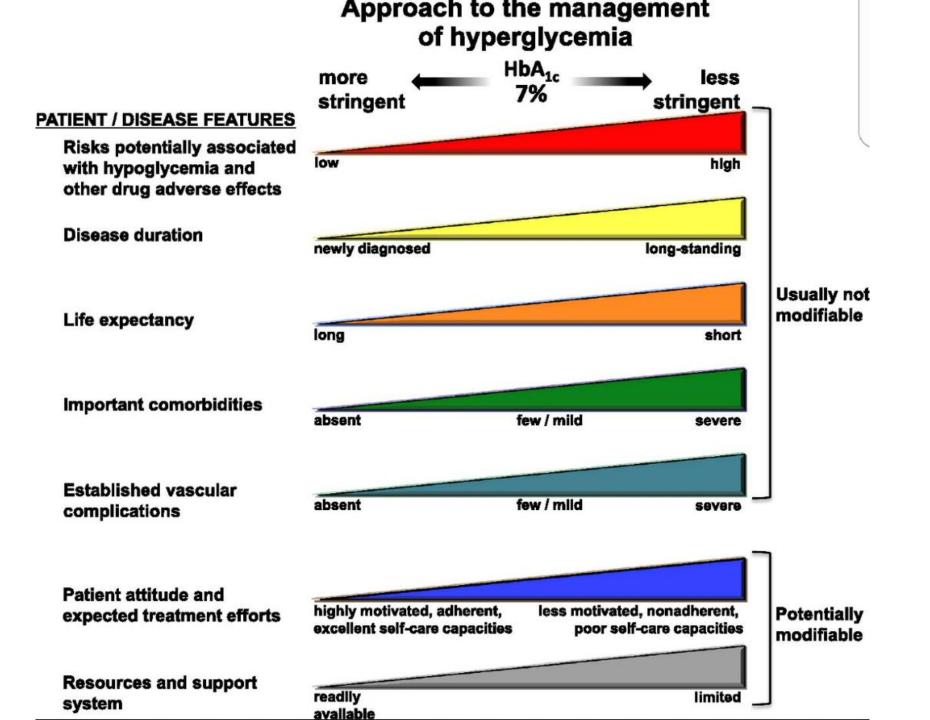
INDIVIDUALIZE GOALS

A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%
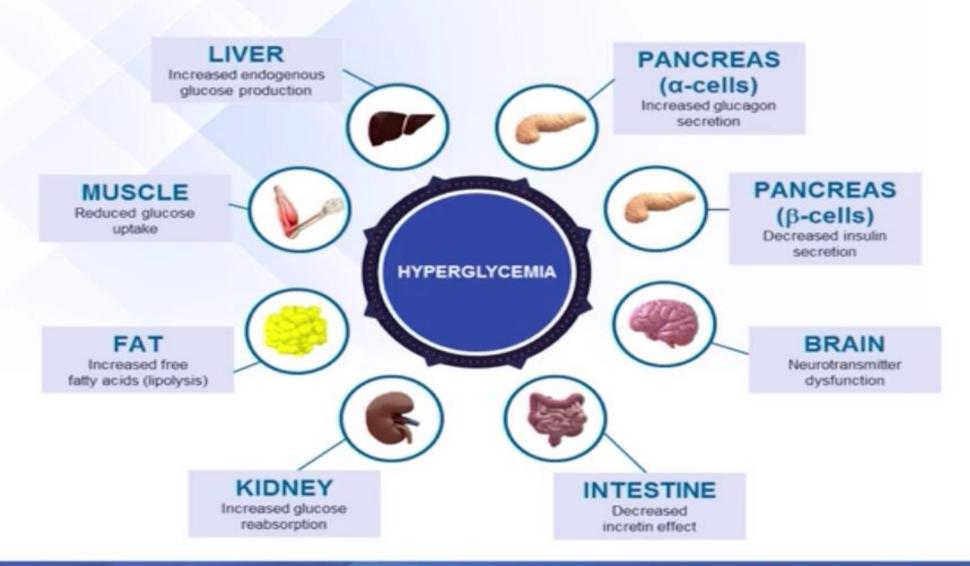
For patients with concurrent serious illness and at risk for hypoglycemia

Approach to the management of hyperglycemia
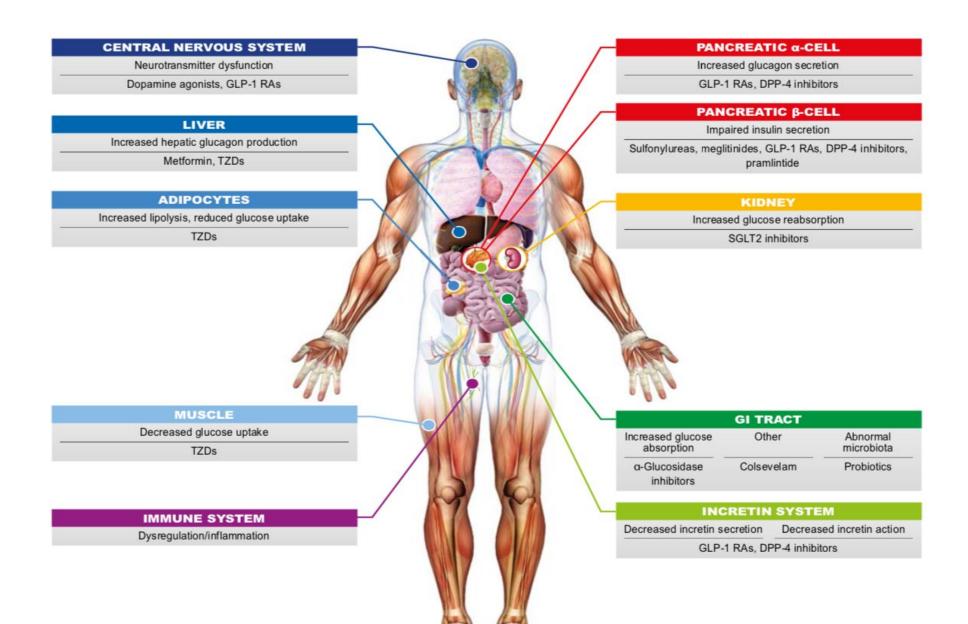
Type 2 diabetes: A multifactorial disease

LIVER
Increased endogenous glucose production

PANCREAS (α-cells)
Increased glucagon secretion

MUSCLE
Reduced glucose uptake

PANCREAS (β-cells)
Decreased insulin secretion

HYPERGLYCEMIA

FAT
Increased free fatty acids (lipolysis)

BRAIN
Neurotransmitter dysfunction

KIDNEY
Increased glucose reabsorption

INTESTINE
Decreased incretin effect

Beyond the ominous octec

CENTRAL NERVOUS SYSTEM
Neurotransmitter dysfunction
Dopamine agonists, GLP-1 RAs

LIVER
Increased hepatic glucagon production
Metformin, TZDs

ADIPOCYTES
Increased lipolysis, reduced glucose uptake
TZDs

MUSCLE
Decreased glucose uptake
TZDs

IMMUNE SYSTEM
Dysregulation/inflammation

PANCREATIC α-CELL
Increased glucagon secretion
GLP-1 RAs, DPP-4 inhibitors

PANCREATIC β-CELL
Impaired insulin secretion
Sulfonylureas, meglitinides, GLP-1 RAs, DPP-4 inhibitors, pramlintide

KIDNEY
Increased glucose reabsorption
SGLT2 inhibitors

GI TRACT

Increased glucose absorption	Other	Abnormal microbiota
α-Glucosidase inhibitors	Colsevelam	Probiotics

INCRETIN SYSTEM
Decreased incretin secretion   Decreased incretin action
GLP-1 RAs, DPP-4 inhibitors

Ideal agent for t2DM

- Delay or halt disease
- Excellent tolerability profile
- Few contraindications and interactions
- Clinically meaningful weight loss
- Positive impact on cardiovascular factors
- Cost effective
- Simple dosing

To address the complexity of T2DM, oral and injectable therapies that target different pathophysiologic abnormalities may be considered

Click buttons to turn each bar on and off

MET

INSULIN

GLP-1 RA

SGLT2i

DPP-4i

TZD

AGi

Liver

α-cells

Muscle

β-cells
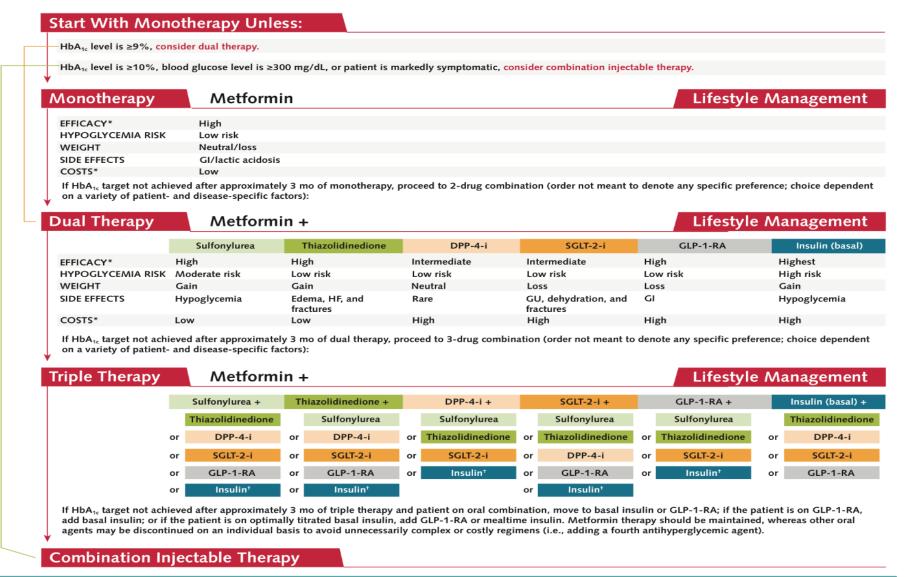
HYPERGLYCEMIA

Fat

Brain

Kidney

Intestine

AGi, α-glucosidase inhibitor;
DPP-4-i, dipeptidyl peptidase-4 inhibitor;
GLP-1-RA, glucagon-like peptide-1 receptor agonist;
MET, metformin; SGLT2-i, sodium-glucose co-transporter-2 inhibitor;
SU, sulfonylurea; TZD, thiazolidinedione

1. Ferrannini E et al. Eur Heart J. 2015;36(34):2288-2296.
2. ADA. Diabetes Care. 2017;40(suppl 1):S1-S135.

Therapeutic t2D Many opportunities ,too many factors

- Age
- Duration of diabetes
- Comorbidities
- Patient response to drugs

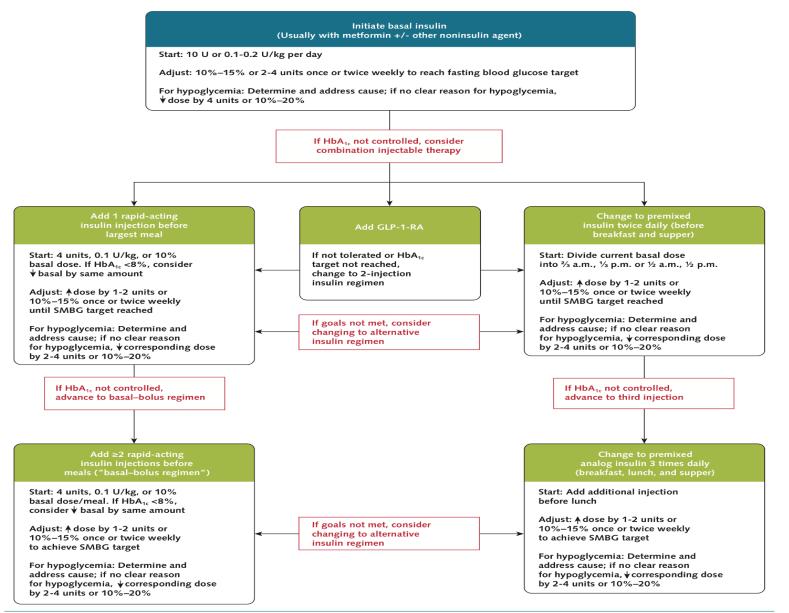**Figure 1.** Antihyperglycemic therapy for type 2 diabetes: general recommendations.

Start With Monotherapy Unless:

HbA$_{1c}$ level is ≥9%, **consider dual therapy.**

HbA$_{1c}$ level is ≥10%, blood glucose level is ≥300 mg/dL, or patient is markedly symptomatic, **consider combination injectable therapy.**

Monotherapy   Metformin   Lifestyle Management

EFFICACY*	High
HYPOGLYCEMIA RISK	Low risk
WEIGHT	Neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	Low

If HbA$_{1c}$ target not achieved after approximately 3 mo of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

Dual Therapy   Metformin +   Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4-i	SGLT-2-i	GLP-1-RA	Insulin (basal)
EFFICACY*	High	High	Intermediate	Intermediate	High	Highest
HYPOGLYCEMIA RISK	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
WEIGHT	Gain	Gain	Neutral	Loss	Loss	Gain
SIDE EFFECTS	Hypoglycemia	Edema, HF, and fractures	Rare	GU, dehydration, and fractures	GI	Hypoglycemia
COSTS*	Low	Low	High	High	High	High

If HbA$_{1c}$ target not achieved after approximately 3 mo of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference; choice dependent on a variety of patient- and disease-specific factors):

Triple Therapy   Metformin +   Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4-i +	SGLT-2-i +	GLP-1-RA +	Insulin (basal) +
Thiazolidinedione	Sulfonylurea	Sulfonylurea	Sulfonylurea	Sulfonylurea	Thiazolidinedione
or DPP-4-i	or DPP-4-i	or Thiazolidinedione	or Thiazolidinedione	or Thiazolidinedione	or DPP-4-i
or SGLT-2-i	or SGLT-2-i	or SGLT-2-i	or DPP-4-i	or SGLT-2-i	or SGLT-2-i
or GLP-1-RA	or GLP-1-RA	or Insulin†	or GLP-1-RA	or Insulin†	or GLP-1-RA
or Insulin†	or Insulin†		or Insulin†		

If HbA$_{1c}$ target not achieved after approximately 3 mo of triple therapy and patient on oral combination, move to basal insulin or GLP-1-RA; if the patient is on GLP-1-RA, add basal insulin; or if the patient is on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. Metformin therapy should be maintained, whereas other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy

The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote
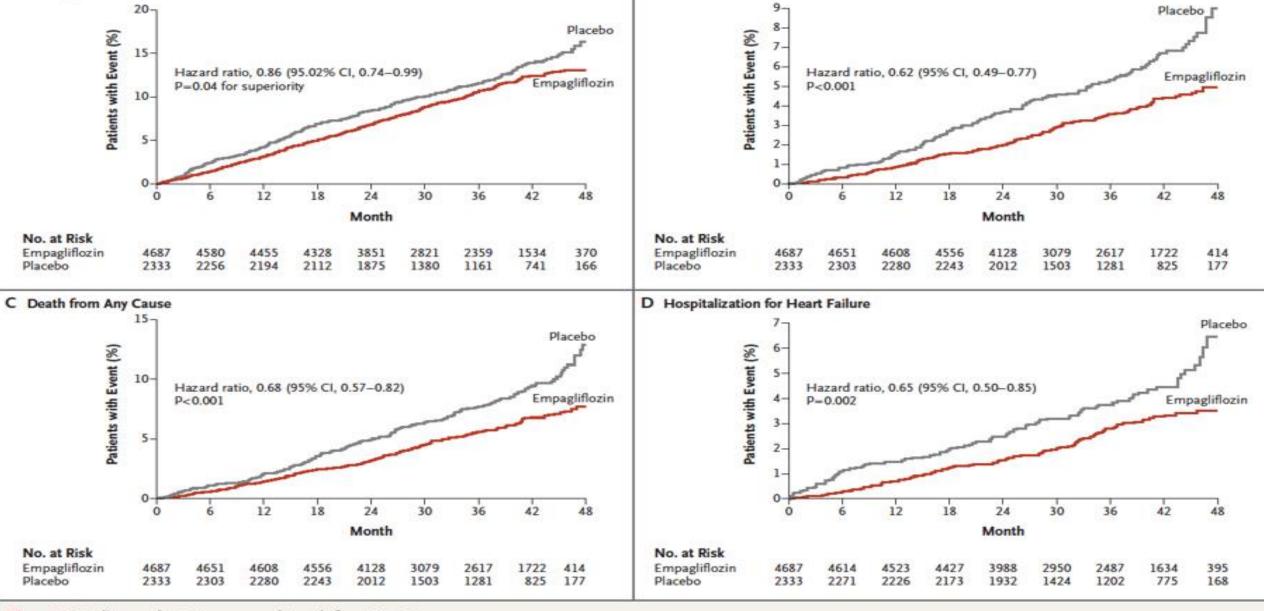
Figure 2. Combination injectable therapy for type 2 diabetes.

Initiate basal insulin
(Usually with metformin +/- other noninsulin agent)

Start: 10 U or 0.1-0.2 U/kg per day

Adjust: 10%–15% or 2-4 units once or twice weekly to reach fasting blood glucose target

For hypoglycemia: Determine and address cause; if no clear reason for hypoglycemia, ↓dose by 4 units or 10%–20%

If HbA₁c not controlled, consider combination injectable therapy

Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If HbA₁c <8%, consider ↓basal by same amount

Adjust: ↑dose by 1-2 units or 10%–15% once or twice weekly until SMBG target reached

For hypoglycemia: Determine and address cause; if no clear reason for hypoglycemia, ↓corresponding dose by 2-4 units or 10%–20%

Add GLP-1-RA

If not tolerated or HbA₁c target not reached, change to 2-injection insulin regimen

If goals not met, consider changing to alternative insulin regimen

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into ⅔ a.m., ⅓ p.m. or ½ a.m., ½ p.m.

Adjust: ↑dose by 1-2 units or 10%–15% once or twice weekly until SMBG target reached

For hypoglycemia: Determine and address cause; if no clear reason for hypoglycemia, ↓corresponding dose by 2-4 units or 10%–20%

If HbA₁c not controlled, advance to basal–bolus regimen

If HbA₁c not controlled, advance to third injection

Add ≥2 rapid-acting insulin injections before meals ("basal–bolus regimen")

Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If HbA₁c <8%, consider ↓basal by same amount

Adjust: ↑dose by 1-2 units or 10%–15% once or twice weekly to achieve SMBG target

For hypoglycemia: Determine and address cause; if no clear reason for hypoglycemia, ↓corresponding dose by 2-4 units or 10%–20%

If goals not met, consider changing to alternative insulin regimen

Change to premixed analog insulin 3 times daily (breakfast, lunch, and supper)

Start: Add additional injection before lunch

Adjust: ↑dose by 1-2 units or 10%–15% once or twice weekly to achieve SMBG target

For hypoglycemia: Determine and address cause; if no clear reason for hypoglycemia, ↓corresponding dose by 2-4 units or 10%–20%

Adapted with permission from Inzucchi and colleagues (7). GLP-1-RA = glucagon-like peptide-1–receptor agonist; HbA₁c = hemoglobin A₁c;

SUMMARY OF ADA 2017 STANDARDS OF CARE

- Metformin is the preferential agent. A rating .

- Insulin with or w/o orals in symptomatic in A1c 10% or more or glucose 300 or over . E rating.

- After failure of agent 1 at maximum tolerated dose in 3 month add second oral , GLP1-RA or basal insulin . A rating .

- For patients not at goal insulin therapy should be instituted w/o delay. B rating.

- A patient centered approach should be used to guide the choice of pharmacologic agents. E rating

Summary of ADA 2017 Standards of Care

- In longstanding sub-optimally controlled type 2 diabetes and ASHD empaglifozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all cause mortality when added to standard care.B.

A Primary Outcome

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority

No. at Risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

B Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001

No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001

No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

D Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002

No. at Risk

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

A Primary Outcome

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Placebo

Liraglutide

Patients with an Event (%)

Months since Randomization

No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007

Placebo

Liraglutide

Patients with an Event (%)

Months since Randomization

No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

AACE guidelines for the management of T2DM

Garber AJ et al. *Endocr Pract*. 2016;22(1):84-113.

5

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

*Glycemic Goal:

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2i
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain-dicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 / Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² / Genital Mycotic Infections / Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CARDIAC* — CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* — ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Legend:
- Green: Few adverse events or possible benefits
- Yellow: Use with caution
- Orange: Likelihood of adverse effects
- ? : Uncertain effect
- * FDA indication to prevent CVD death in diabetes plus prior CVD events

Oral medication summary Drug class	Approx A1c decrease (a)	Pros/cons CV	Safety In renal insufficiency	cost
metformin	1%	⬇ CV, weight, no hypoglycemia. Con: GI	Do not initiate with GFR below 45	low
SU	1%	provider comfort/ Cons : hypoglycemia weight gain	Caution risk of hypoglycemia	low
DPP4-i	0.5%	Safety data	Linagliptin best	high
TZD	1%	Cons: edema, increased risk CHF	No dose adjustment	low
SGLT2-i	0.5%	No hypos Potential reduction in CV /Cons :GMI	eGFR over 45 Dapa at 60mL/min	high

Table Summary medication	Of Dose	Currently A1c Lowering	available Weight Loss	GLP1-RA Rate of nausea	
Exenatide	5-10 mcg twice daily	0.7-0.9%	1.1-2.7Kg	8%-44%	
Exenatide QW	2mg weekly	1.3-1.6%		9.3%-27%	
Liraglutide	0.6-1.8mg daily	1.0-1.5%	1.0-2.8 Kg	7.5%-34%	
Albiglutide	30-50 mg weekly	0.6-0.9%	0.4-1.2Kg	11.1%	
Dulaglutide	0.75-1.5mg weekly	0.7-1.6%	+0.2-3.2 Kg	12.45-21.1%	

Second agent of choice other than metformin

- **ADA shared decision making and patient centered approach**
- In patients with A1c of 9% initiation of dual therapy
- No specific order of preference

- **AACE**
- Dual therapy in patients with A1c with 7.5% or more
- **GLP-1RA** as second agent of choice , followed by SGLT2-i and DPP4i in preferential order
- SU in the lowest scale

Triple therapy

- **ADA** shared decision making
  No specific preference in adding SU, TZD , DPP4i ,SGLT2i ,GLP1-RA, insulin

- **AACE**
- Again GLP1-RA over SGLT2i
- TZD and insulin over DPP4i
- SU the lowest in hierarchy

Combination inyectable therapy

- A comparative effectiveness meta-analysis (Bennet et al Ann Intern Med 2011;154:602-613), suggests that each new class of non insulin agents added to initial therapy lowers A1c approx. 0.9-1.1 %.

- The ongoing Glycemia Reduction Approaches in Diabetes, (GRADE) , will compare 4 drug classes , SU,DPP4-I, GLP1-RA and basal insulin when added to metformin therapy over 4 years

Comparative efficacy and safety of antidiabetic drug regimens added to stable and inadequate met and Tzd therapy in type 2 diabetes

efficacy

CANA	0.27 (0.03,0.51)	-0.15 (-0.4,0.1)	-0.12 (-0.36,0.12)	0.47 (0.23,0.71)	0.28 (0,0.56)	-0.13 (-0.52,0.26)	0.3 (0.01,0.59)	-0.7 (-0.88,-0.52)	0.07 (-0.17,0.3)	0.17 (-0.08,0.42)
-0.27 (-0.51,-0.03)	**DULA**	-0.42 (-0.66,-0.18)	-0.39 (-0.53,-0.26)	0.2 (-0.04,0.43)	0.01 (-0.26,0.28)	-0.4 (-0.79,-0.01)	0.03 (-0.26,0.31)	-0.97 (-1.13,-0.81)	-0.2 (-0.43,0.02)	-0.1 (-0.3,0.09)
0.15 (-0.1,0.4)	0.42 (0.18,0.66)	**EMPA**	0.03 (-0.21,0.27)	0.62 (0.38,0.86)	0.43 (0.15,0.71)	0.02 (-0.37,0.41)	0.45 (0.16,0.74)	-0.55 (-0.73,-0.37)	0.22 (-0.02,0.45)	0.32 (0.07,0.57)
0.12 (-0.12,0.36)	0.39 (0.26,0.53)	-0.03 (-0.27,0.21)	**EXEN**	0.59 (0.35,0.82)	0.4 (0.13,0.67)	-0.01 (-0.4,0.38)	0.42 (0.13,0.71)	-0.58 (-0.74,-0.41)	0.19 (-0.04,0.42)	0.29 (0.12,0.46)
-0.47 (-0.71,-0.23)	-0.2 (-0.43,0.04)	-0.62 (-0.86,-0.38)	-0.59 (-0.82,-0.35)	**GLIB**	-0.19 (-0.46,0.08)	-0.6 (-0.99,-0.21)	-0.17 (-0.46,0.12)	-1.17 (-1.33,-1)	-0.4 (-0.46,-0.34)	-0.3 (-0.54,-0.06)
-0.28 (-0.56,0)	-0.01 (-0.28,0.26)	-0.43 (-0.71,-0.15)	-0.4 (-0.67,-0.13)	0.19 (-0.08,0.46)	**GLIM**	-0.41 (-0.82,0)	0.02 (-0.3,0.34)	-0.98 (-1.2,-0.76)	-0.21 (-0.48,0.05)	-0.11 (-0.39,0.17)
0.13 (-0.26,0.52)	0.4 (0.01,0.79)	-0.02 (-0.41,0.37)	0.01 (-0.38,0.4)	0.6 (0.21,0.99)	0.41 (0,0.82)	**LINA**	0.43 (0.01,0.85)	-0.57 (-0.92,-0.22)	0.2 (-0.19,0.58)	0.3 (-0.09,0.69)
-0.3 (-0.59,-0.01)	-0.03 (-0.31,0.26)	-0.45 (-0.74,-0.16)	-0.42 (-0.71,-0.13)	0.17 (-0.12,0.46)	-0.02 (-0.34,0.3)	-0.43 (-0.85,-0.01)	**LIRA**	-1 (-1.24,-0.76)	-0.23 (-0.51,0.05)	-0.13 (-0.42,0.16)
0.7 (0.52,0.88)	0.97 (0.81,1.13)	0.55 (0.37,0.73)	0.58 (0.41,0.74)	1.17 (1,1.33)	0.98 (0.76,1.2)	0.57 (0.22,0.92)	1 (0.76,1.24)	**PLC**	0.77 (0.61,0.92)	0.87 (0.7,1.04)
-0.07 (-0.3,0.17)	0.2 (-0.02,0.43)	-0.22 (-0.45,0.02)	-0.19 (-0.42,0.04)	0.4 (0.34,0.46)	0.21 (-0.05,0.48)	-0.2 (-0.58,0.19)	0.23 (-0.05,0.51)	-0.77 (-0.92,-0.61)	**SITA**	0.1 (-0.13,0.33)
-0.17 (-0.42,0.08)	0.1 (-0.09,0.3)	-0.32 (-0.57,-0.07)	-0.29 (-0.46,-0.12)	0.3 (0.06,0.54)	0.11 (-0.17,0.39)	-0.3 (-0.69,0.09)	0.13 (-0.16,0.42)	-0.87 (-1.04,-0.7)	-0.1 (-0.33,0.13)	**TASPO**

weight

CANA	-1.23 (-2.57,0.11)	-0.87 (-2.09,0.35)	-0.75 (-2.06,0.57)	-10.24 (-11.44,-9.04)	-6.26 (-8.07,-4.45)	-2.78 (-4.2,-1.36)	-0.85 (-2.13,0.43)	-2.95 (-4.01,-1.89)	-3.24 (-4.42,-2.06)	-1.42 (-2.71,-0.14)
1.23 (-0.11,2.57)	**DULA**	0.36 (-0.66,1.39)	0.49 (-0.2,1.17)	-9.01 (-10.01,-8.01)	-5.03 (-6.71,-3.34)	-1.55 (-2.8,-0.3)	0.38 (-0.72,1.48)	-1.72 (-2.54,-0.89)	-2.01 (-2.98,-1.04)	-0.19 (-1.14,0.76)
0.87 (-0.35,2.09)	-0.36 (-1.39,0.66)	**EMPA**	0.12 (-0.86,1.11)	-9.37 (-10.2,-8.54)	-5.39 (-6.98,-3.8)	-1.91 (-3.03,-0.79)	0.02 (-0.93,0.97)	-2.08 (-2.69,-1.47)	-2.37 (-3.17,-1.57)	-0.55 (-1.5,0.39)
0.75 (-0.57,2.06)	-0.49 (-1.17,0.2)	-0.12 (-1.11,0.86)	**EXEN**	-9.5 (-10.46,-8.54)	-5.51 (-7.18,-3.85)	-2.03 (-3.25,-0.82)	-0.1 (-1.17,0.96)	-2.2 (-2.98,-1.43)	-2.5 (-3.43,-1.56)	-0.68 (-1.5,0.14)
10.24 (9.04,11.44)	9.01 (8.01,10.01)	9.37 (8.54,10.2)	9.5 (8.54,10.46)	**GLIB**	3.98 (2.41,5.56)	7.46 (6.36,8.56)	9.39 (8.47,10.31)	7.29 (6.72,7.86)	7 (6.76,7.24)	8.82 (7.9,9.74)
6.26 (4.45,8.07)	5.03 (3.34,6.71)	5.39 (3.8,6.98)	5.51 (3.85,7.18)	-3.98 (-5.56,-2.41)	**GLIM**	3.48 (1.73,5.23)	5.41 (3.77,7.05)	3.31 (1.84,4.78)	3.02 (1.46,4.58)	4.84 (3.2,6.47)
2.78 (1.36,4.2)	1.55 (0.3,2.8)	1.91 (0.79,3.03)	2.03 (0.82,3.25)	-7.46 (-8.56,-6.36)	-3.48 (-5.23,-1.73)	**LINA**	1.93 (0.74,3.12)	-0.17 (-1.11,0.77)	-0.46 (-1.53,0.61)	1.36 (0.17,2.54)
0.85 (-0.43,2.13)	-0.38 (-1.48,0.72)	-0.02 (-0.97,0.93)	0.1 (-0.96,1.17)	-9.39 (-10.31,-8.47)	-5.41 (-7.05,-3.77)	-1.93 (-3.12,-0.74)	**LIRA**	-2.1 (-2.83,-1.37)	-2.39 (-3.28,-1.5)	-0.57 (-1.6,0.45)
2.95 (1.89,4.01)	1.72 (0.89,2.54)	2.08 (1.47,2.69)	2.2 (1.43,2.98)	-7.29 (-7.86,-6.72)	-3.31 (-4.78,-1.84)	0.17 (-0.77,1.11)	2.1 (1.37,2.83)	**PLC**	-0.29 (-0.81,0.22)	1.53 (0.8,2.25)
3.24 (2.06,4.42)	2.01 (1.04,2.98)	2.37 (1.57,3.17)	2.5 (1.56,3.43)	-7 (-7.24,-6.76)	-3.02 (-4.58,-1.46)	0.46 (-0.61,1.53)	2.39 (1.5,3.28)	0.29 (-0.22,0.81)	**SITA**	1.82 (0.93,2.71)
1.42 (0.14,2.71)	0.19 (-0.76,1.14)	0.55 (-0.39,1.5)	0.68 (-0.14,1.5)	-8.82 (-9.74,-7.9)	-4.84 (-6.47,-3.2)	-1.36 (-2.54,-0.17)	0.57 (-0.45,1.6)	-1.53 (-2.25,-0.8)	-1.82 (-2.71,-0.93)	**TASPO**

Effect on SBP

CANA	−0.43 (−3.82, 2.96)	−0.72 (−4.11, 2.66)	1.29 (−2.39, 4.97)	−3.76 (−6.23, −1.29)	−1.37 (−4.83, 2.08)
0.43 (−2.96, 3.82)	DULA	−0.29 (−2.21, 1.62)	1.72 (−1.86, 5.3)	−3.33 (−5.65, −1.01)	−0.94 (−3.71, 1.83)
0.72 (−2.66, 4.11)	0.29 (−1.62, 2.21)	EXEN	2.01 (−1.56, 5.59)	−3.04 (−5.35, −0.72)	−0.65 (−3.06, 1.77)
−1.29 (−4.97, 2.39)	−1.72 (−5.3, 1.86)	−2.01 (−5.59, 1.56)	LIRA	−5.05 (−7.77, −2.33)	−2.66 (−6.3, 0.98)
3.76 (1.29, 6.23)	3.33 (1.01, 5.65)	3.04 (0.72, 5.35)	5.05 (2.33, 7.77)	PLC	2.39 (−0.03, 4.8)
1.37 (−2.08, 4.83)	0.94 (−1.83, 3.71)	0.65 (−1.77, 3.06)	2.66 (−0.98, 6.3)	−2.39 (−4.8, 0.03)	TASPO

Network meta-analysis conclusions

- All antidiabetic agents were associated with significant reductions in A1c 0.55-1.17% compared with placebo.

- Glimepiride was associated with statistically significant reductions in A1c compared with Empaglifozin and Exenatide.

- Dulaglutide and Liraglutide had A1c reductions greater than exenatide, linagliptin canaglifozin and empaglifozin

- The therapies that did not significantly reduced A1c in comparison with another active compound were sitagliptin,linagliptin,exenatide,canaglifozin and empaglifozin.

SGLT-2-inhibitors or GLP-1RA as second line

OUTCOME	GLP-1RA	SGLT2 INHIBITORS
A1c reduction	0.7-1,7	0.32-1.17
Target of BG lowering	Longer acting fasting and PPBG	Fasting and PPBG
Hypoglycemia risk	Low	Low
Weight loss Kg	2-5	1.5-3.0
SBP	2-5	3-5
Cardiovascular outcomes	Secondary prevention	Secondary prevention
Adverse effects	GI/pancreatitis/pancreatic cancer long-term safety not established	GMI, DKA,bone fractures , amputation, long-term safety not established

Liraglutide Versus SGLT-2 Inhibitors in People with Type 2 Diabetes: A Network Meta-Analysis

Authors   Authors and affiliations

Maria Lorenzi ✉, Uffe Jon Ploug, Jakob Langer, Rasmus Skovgaard, Michael Zoratti, Jeroen Jansen
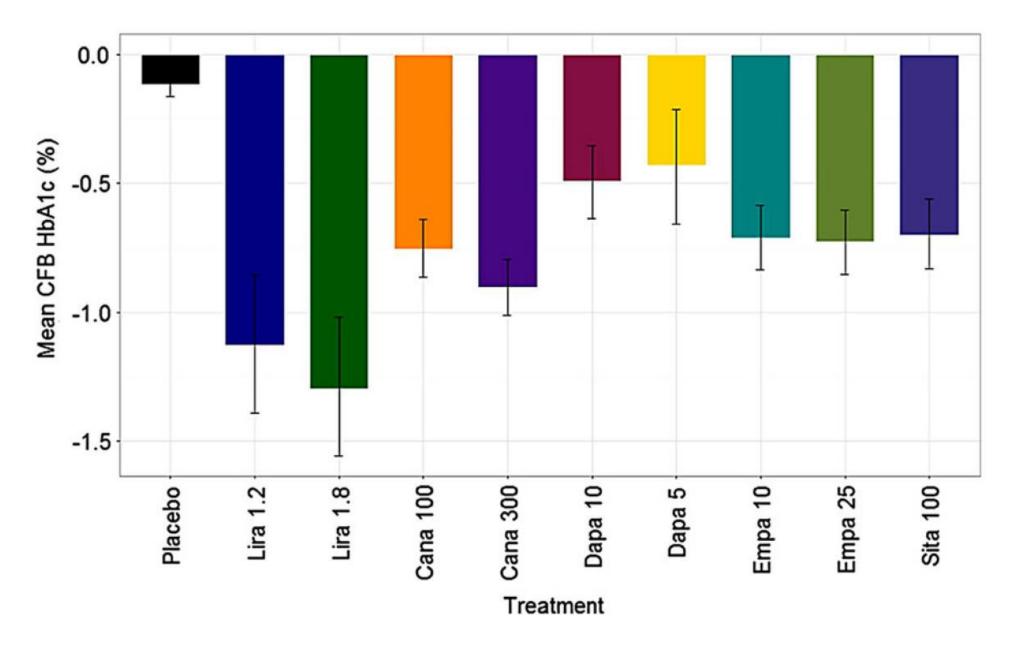
Fig. 3 Modelled outcomes in change from baseline in HbA1c (%) in metformin-experienced T2DM patients.

Table 5 Change from baseline in weight (kg) between treatments

Placebo	1.27 (0.61, 1.90)	1.59 (0.96, 2.24)	1.73 (1.25, 2.20)	2.27 (1.79, 2.71)	2.05 (1.44, 2.66)	2.12 (1.39, 2.86)	1.70 (1.26, 2.13)	2.00 (1.56, 2.44)	-0.49 (-0.96, 0.01)
-1.27 (-1.90, -0.61)	**Liraglutide 1.2 mg**	0.32 (-0.23, 0.86)	0.46 (-0.27, 1.19)	0.99 (0.31, 1.71)	0.79 (-0.11, 1.66)	0.86 (-0.14, 1.82)	0.44 (-0.36, 1.23)	0.74 (-0.05, 1.53)	-1.75 (-2.39, -1.09)
-1.59 (-2.24, -0.96)	-0.32 (-0.86, 0.23)	**Liraglutide 1.8 mg**	0.15 (-0.59, 0.83)	0.68 (-0.03, 1.35)	0.47 (-0.44, 1.35)	0.54 (-0.46, 1.50)	0.12 (-0.68, 0.88)	0.42 (-0.38, 1.19)	-2.07 (-2.73, -1.43)
-1.73 (-2.20, -1.25)	-0.46 (-1.19, 0.27)	-0.15 (-0.83, 0.59)	**Canagliflozin 100 mg**	0.53 (0.14, 0.94)	0.32 (-0.43, 1.11)	0.38 (-0.47, 1.27)	-0.03 (-0.67, 0.62)	0.27 (-0.37, 0.93)	-2.22 (-2.67, -1.73)
-2.27 (-2.71, -1.79)	-0.99 (-1.71, -0.31)	-0.68 (-1.35, 0.03)	-0.53 (-0.94, -0.14)	**Canagliflozin 300 mg**	-0.20 (-0.98, 0.55)	-0.14 (-1.02, 0.73)	-0.56 (-1.20, 0.07)	-0.26 (-0.89, 0.38)	-2.74 (-3.16, -2.32)
-2.05 (-2.66, -1.44)	-0.79 (-1.66, 0.11)	-0.47 (-1.35, 0.44)	-0.32 (-1.11, 0.43)	0.20 (-0.55, 0.98)	**Dapagliflozin 10 mg**	0.06 (-0.66, 0.80)	-0.35 (-1.11, 0.41)	-0.05 (-0.81, 0.69)	-2.54 (-3.31, -1.75)
-2.12 (-2.86, -1.39)	-0.86 (-1.82, 0.14)	-0.54 (-1.50, 0.46)	-0.38 (-1.27, 0.47)	0.14 (-0.73, 1.02)	-0.06 (-0.80, 0.66)	**Dapagliflozin 5 mg**	-0.42 (-1.29, 0.44)	-0.12 (-0.98, 0.72)	-2.61 (-3.48, -1.71)
-1.70 (-2.13, -1.26)	-0.44 (-1.23, 0.36)	-0.12 (-0.88, 0.68)	0.03 (-0.62, 0.67)	0.56 (-0.07, 1.20)	0.35 (-0.41, 1.11)	0.42 (-0.44, 1.29)	**Empagliflozin 10 mg**	0.30 (-0.14, 0.75)	-2.19 (-2.83, -1.51)
-2.00 (-2.44, -1.56)	-0.74 (-1.53, 0.05)	-0.42 (-1.19, 0.38)	-0.27 (-0.93, 0.37)	0.26 (-0.38, 0.89)	0.05 (-0.69, 0.81)	0.12 (-0.72, 0.98)	-0.30 (-0.75, 0.14)	**Empagliflozin 25 mg**	-2.49 (-3.14, -1.81)
0.49 (-0.01, 0.96)	1.75 (1.09, 2.39)	2.07 (1.43, 2.73)	2.22 (1.73, 2.67)	2.74 (2.32, 3.16)	2.54 (1.75, 3.31)	2.61 (1.71, 3.48)	2.19 (1.51, 2.83)	2.49 (1.81, 3.14)	**Sitagliptin 100 mg**

Table 3 Odds ratio for proportion of patients achieving HbA1c targets ($<7\%$ or $\leq 7\%$)

Placebo	0.15 (0.09, 0.27)	0.10 (0.06, 0.18)	0.44 (0.30, 0.65)	0.28 (0.19, 0.41)	0.42 (0.21, 0.79)	0.60 (0.30, 1.17)	0.26 (0.16, 0.40)	0.22 (0.14, 0.35)	0.40 (0.27, 0.60)
6.51 (3.67, 10.99)	**Liraglutide 1.2 mg**	0.66 (0.45, 0.97)	2.90 (1.56, 4.95)	1.84 (1.00, 3.07)	2.70 (1.11, 6.11)	3.90 (1.59, 9.01)	1.67 (0.80, 3.35)	1.43 (0.67, 2.84)	2.60 (1.56, 4.18)
9.80 (5.61, 16.65)	1.51 (1.03, 2.23)	**Liraglutide 1.8 mg**	4.38 (2.38, 7.49)	2.77 (1.55, 4.63)	4.07 (1.68, 9.26)	5.91 (2.39, 13.52)	2.51 (1.21, 5.14)	2.15 (1.03, 4.32)	3.91 (2.39, 6.30)
2.25 (1.54, 3.32)	0.34 (0.20, 0.64)	0.23 (0.13, 0.42)	**Canagliflozin 100 mg**	0.63 (0.47, 0.85)	0.93 (0.43, 1.99)	1.35 (0.62, 2.90)	0.58 (0.32, 1.06)	0.49 (0.27, 0.90)	0.90 (0.63, 1.34)
3.54 (2.47, 5.17)	0.54 (0.33, 1.00)	0.36 (0.22, 0.65)	1.58 (1.18, 2.13)	**Canagliflozin 300 mg**	1.47 (0.67, 3.10)	2.13 (0.98, 4.58)	0.91 (0.51, 1.66)	0.78 (0.43, 1.42)	1.41 (1.04, 2.02)
2.40 (1.26, 4.70)	0.37 (0.16, 0.90)	0.25 (0.11, 0.59)	1.07 (0.50, 2.32)	0.68 (0.32, 1.49)	**Dapagliflozin 10 mg**	1.45 (0.77, 2.74)	0.62 (0.28, 1.39)	0.52 (0.24, 1.18)	0.96 (0.45, 2.15)
1.67 (0.86, 3.29)	0.26 (0.11, 0.63)	0.17 (0.07, 0.42)	0.74 (0.34, 1.62)	0.47 (0.22, 1.02)	0.69 (0.37, 1.30)	**Dapagliflozin 5 mg**	0.43 (0.19, 0.96)	0.36 (0.16, 0.82)	0.67 (0.31, 1.50)
3.89 (2.47, 6.25)	0.60 (0.30, 1.26)	0.40 (0.19, 0.83)	1.73 (0.95, 3.16)	1.10 (0.60, 1.98)	1.62 (0.72, 3.57)	2.34 (1.04, 5.34)	**Empagliflozin 10 mg**	0.85 (0.56, 1.27)	1.55 (0.86, 2.93)
4.57 (2.88, 7.29)	0.70 (0.35, 1.48)	0.47 (0.23, 0.97)	2.04 (1.12, 3.73)	1.29 (0.71, 2.33)	1.91 (0.85, 4.20)	2.74 (1.22, 6.26)	1.18 (0.78, 1.78)	**Empagliflozin 25 mg**	1.83 (1.00, 3.44)
2.50 (1.66, 3.69)	0.38 (0.24, 0.64)	0.26 (0.16, 0.42)	1.12 (0.75, 1.59)	0.71 (0.49, 0.96)	1.04 (0.47, 2.21)	1.50 (0.66, 3.24)	0.64 (0.34, 1.17)	0.55 (0.29, 1.00)	**Sitagliptin 100 mg**

Liraglutide versus SGLT-2 inhibitors in people with type 2 diabetes: a network meta-analysis

In conclusion

Liraglutide appears to offer better glycemic control in terms of lowering A1c, FPG and achieve A1c targets in comparisons to SGLT2 inhibitors

No difference in hypoglycemia

Weight reduction is comparable except for Cana 300 which was statistically superior than liraglutide 1.2mg

Table 2. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs): summary of head-to-head clinical trials.

Study	Design	Baseline characteristics	Background therapy	Active comparators
DURATION-1 [Drucker *et al.* 2008]	R, OL, AC, NI N=295, 30 weeks	Mean age 55 years, A1C 8.3%, weight 102 kg, BMI 35 kg/m^2, duration of diabetes 6.7 years	Drug naïve or metformin, SU, TZD or a combination of two of those agents	Exenatide 10 µg BID Exenatide 2 mg QW
LEAD-6 [Buse *et al.* 2009]	R, OL, AC, NI N=464, 26 weeks	Mean age 57 years, A1C 8.1%, weight 93 kg, BMI 32.9 kg/m^2, duration of diabetes 8.2 years	metformin, SU, or both	Exenatide 10 µg BID Liraglutide 1.8 mg QD
DURATION-5 [Blevins *et al.* 2011]	R, OL, AC, NI N=252, 24 weeks	Mean age 56 years, A1C 8.4%, weight 96 kg, BMI 33.3 kg/m^2, duration of diabetes 7 years	Drug naïve or metformin, SU, TZD or any combination	Exenatide 10 µg BID Exenatide 2 mg QW
DURATION-6 [Buse *et al.* 2013]	R, OL, AC, NI N=911, 26 weeks	Mean age 57 years, A1C 8.5%, weight 91 kg, BMI 32.3 kg/m^2, duration of diabetes 8.5 years	Metformin, SU, both, or metformin + pioglitazone	Exenatide 2 mg QW Liraglutide 1.8 mg QD
GetGoal-X [Rosenstock *et al.* 2013]	R, OL, AC, NI N=634, 24 weeks	Mean age 57 years, A1C 8.0%, weight 95 kg, BMI 33.6 kg/m^2, duration of diabetes 6.8 years	Metformin	Lixisenatide 20 µg QD Exenatide 10 µg BID
HARMONY-7 [Pratley *et al.* 2014]	R, OL, AC, NI N=841, 32 weeks	Mean age 56 years, A1C 8.2%, weight 92 kg, BMI 32.8 kg/m^2, duration of diabetes 8.4 years	metformin, pioglitazone, SU, or any combination	Albiglutide 50 mg QW Liraglutide 1.8 mg QD
AWARD-1 [Wysham *et al.* 2014]	R, OL, PC, AC, S*, NI N=978, 26 weeks	Mean age 56 years, A1C 8.1%, weight 96 kg, BMI 33 kg/m^2, duration of diabetes 9 years	Metformin + pioglitazone	Dulaglutide 1.5 mg QW Dulaglutide 0.75 mg QW Exenatide 10 µg BID Placebo
AWARD-6 [Dungan *et al.* 2014]	R, OL, AC, NI N=599, 26 weeks	Mean age 57 years, A1C 8.1%, weight 94 kg, BMI 33.5 kg/m^2, duration of diabetes 7.2 years	Metformin	Dulaglutide 1.5 mg QW Liraglutide 1.8 mg QD

Abbreviations: R, randomized; OL, open label; AC, active comparator; PC, placebo controlled; S, superiority; NI, noninferiority; PC, placebo controlled; BID, twice daily; QD, once daily; QW, once weekly; SU, sulfonylurea; TZD, thiazolidinedione; BMI, body mass index.
Superiority testing *versus* placebo, noninferiority testing *versus* exenatide.
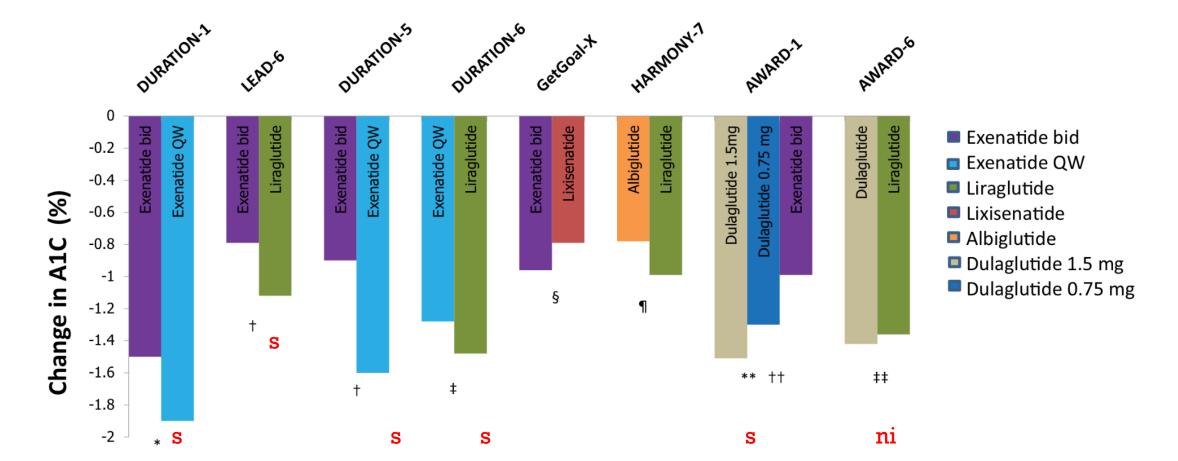
Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority unless otherwise noted as noninferiority; *$p<0.0025$, †$p<0.0001$, ‡$p=0.02$, §$p=$not significant, noninferiority *p*-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority *p*-value$=0.846$ (not meeting predefined noninferiority margin), **$p<0.001$ for both doses of dulaglutide *versus* exenatide bid, ††$p=$not significant, noninferiority *p*-value<0.0001 (meeting predefined noninferiority margin).

GLP1-RA how do we choose ?

- Neither Exe, EXE LAR, nor Dulaglutide have demonstrated increased efficacy over Liraglutide

- Liraglutide in LEADER t2D with high cardiovascular risk, only GLP1 with positive end point of fewer cardiovascular death, and death from any cause.

- MI , non fatal stroke and hospitalization for heart failure were non significant lower in Lira group
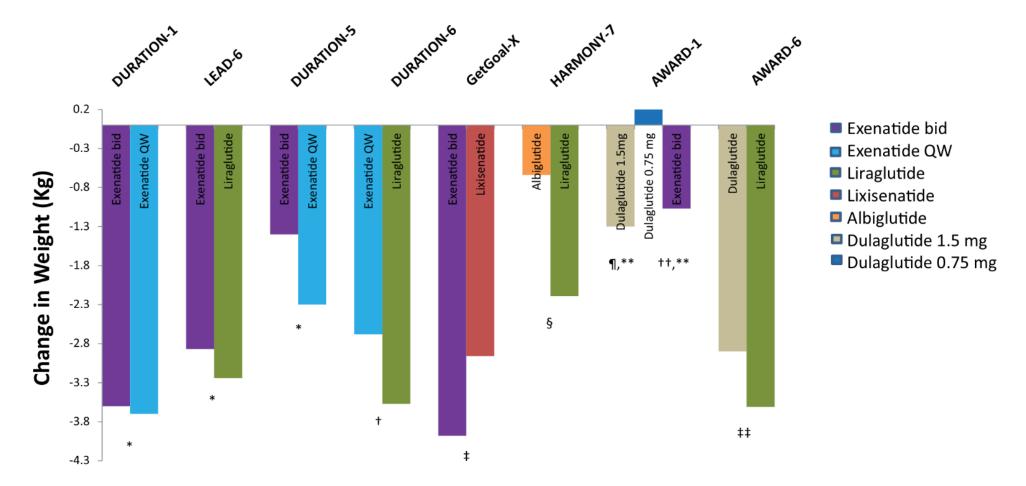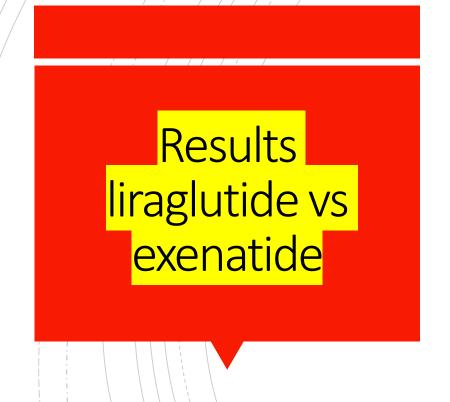
Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority (unless noted for noninferiority); *p = not significant, †p = 0.0005, ‡p-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §p < 0.0001, ¶ p < 0.001 *versus* dulaglutide 0.75 mg, **p = not significant between dulaglutide 1.5 mg *versus* exenatide bid, ‡‡p = 0.011.

Results liraglutide vs exenatide

- LEAD 6 .Lira vs Exe BID .Liraglutide – treated patients experienced greater reductions in A1c, 3% nausea vs 9% and less minor hypoglycemia.

- DURATION 6. EXE 2mg vs Lira. A1c reductions weight greater with Liraglutide.Less nausea 9%vs 21% w EXE 2mg. Similar hypoglycemia.

Liraglutide vs dulaglutide

- AWARD -6 No significant difference in A1c
- Similar safety and tolerability
- More weight loss with Lira

So what is the evidence for GLP1-RA versus DPP4i

Incretin based therapies for type 2 diabetes mellitus : a review of direct comparisons of efficacy and safety

GLP1-RA

Not recommended in moderate to severe renal disease

Liraglutide is not recommended in hepatic impairment

DPP4i

Saxa not recommended in ESRD

Linagliptin PK suggest no dose adjustment in hepatic insufficiency

Sitagliptin and Saxa adjusted per creat cl. No adjustment in Linagliptin

GLP 1 versus Sitagliptin

- Duration -2 .Significant reduction in A1c, weight and FBG in EXE 2mg vs sitagliptin 100 mg and further reduction in all parameters in those switched from Sita to EXE 2mg

- Liraglutide versus Sitagliptin. Mean Hgb A1c, FPG and weight reduction in Lira at 52 w

- LIRA-SWITCH. Greater reduction in A1c ETD -0.61%, weight ETD -1.67Kg at 26w

- AWARD-5. Dulaglutide versus sitagliptin superior A1c reduction and weight loss with Dulaglutide at 104 w

Efficacy and safety of SGLT-2 inhibitors in type 2 diabetes mellitus :a systematic review and network meta-analysis
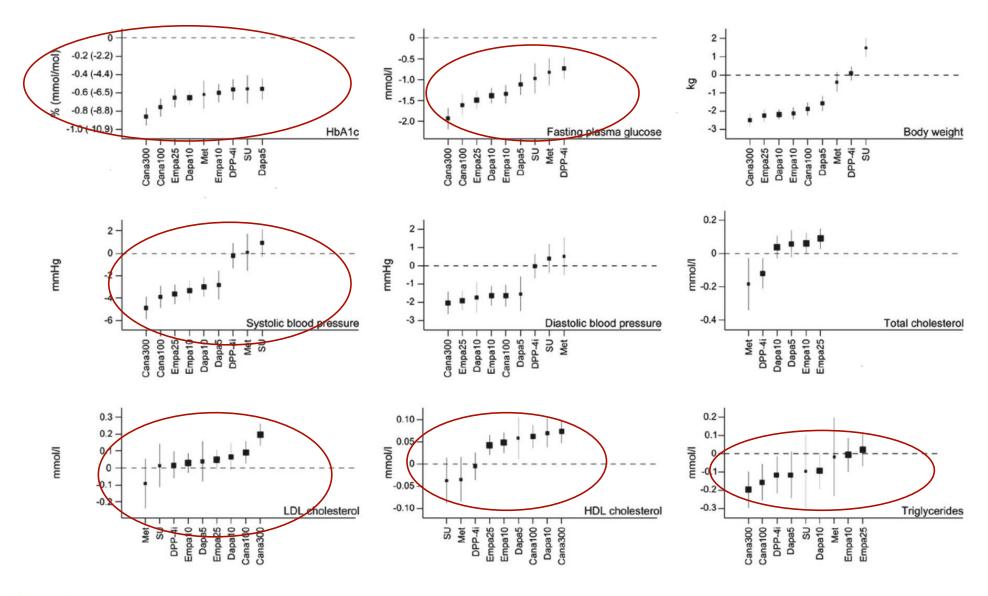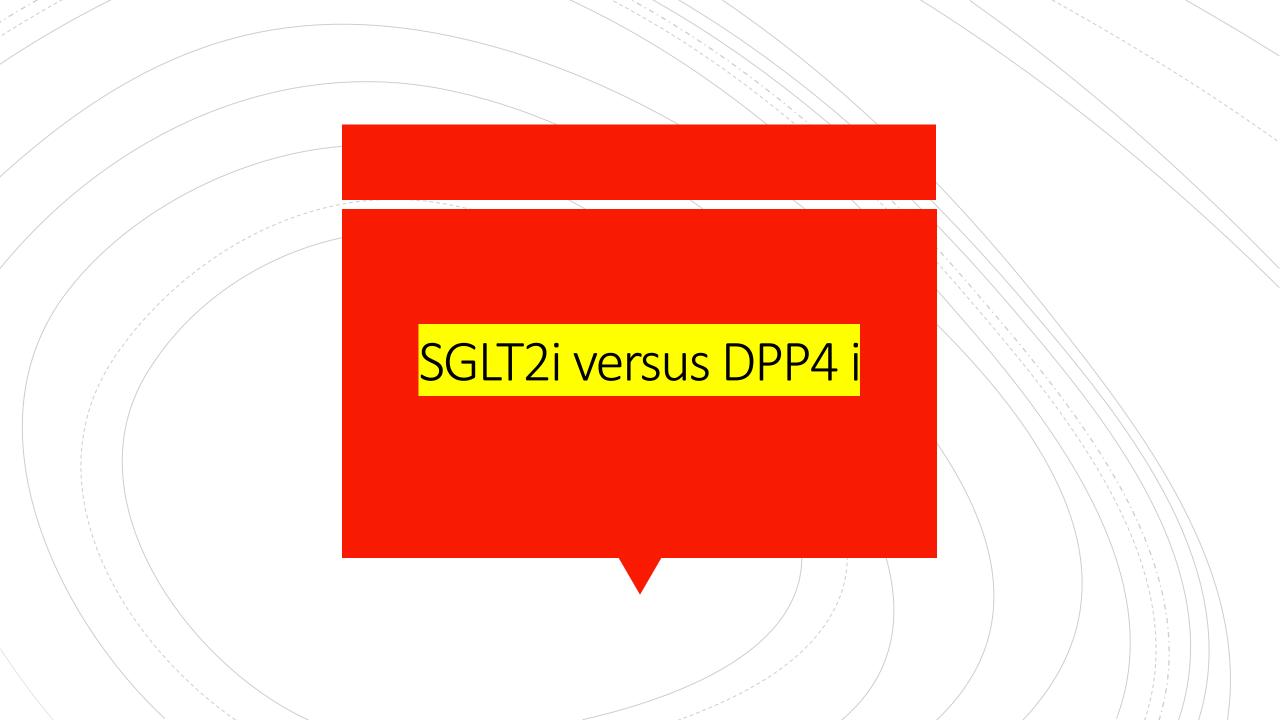
Figure 2. Differences vs placebo (dotted lines) in cardiometabolic outcomes for the drugs included in the network meta-analysis. Cana100, canagliflozin 100 mg; Cana300, canagliflozin 300 mg; Dapa5, dapagliflozin 5 mg; Dapa10, dapagliflozin 10 mg; Empa10, empagliflozin 10 mg; Empa25, empagliflozin 25 mg; DPP-4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; SU, sulphonylurea.
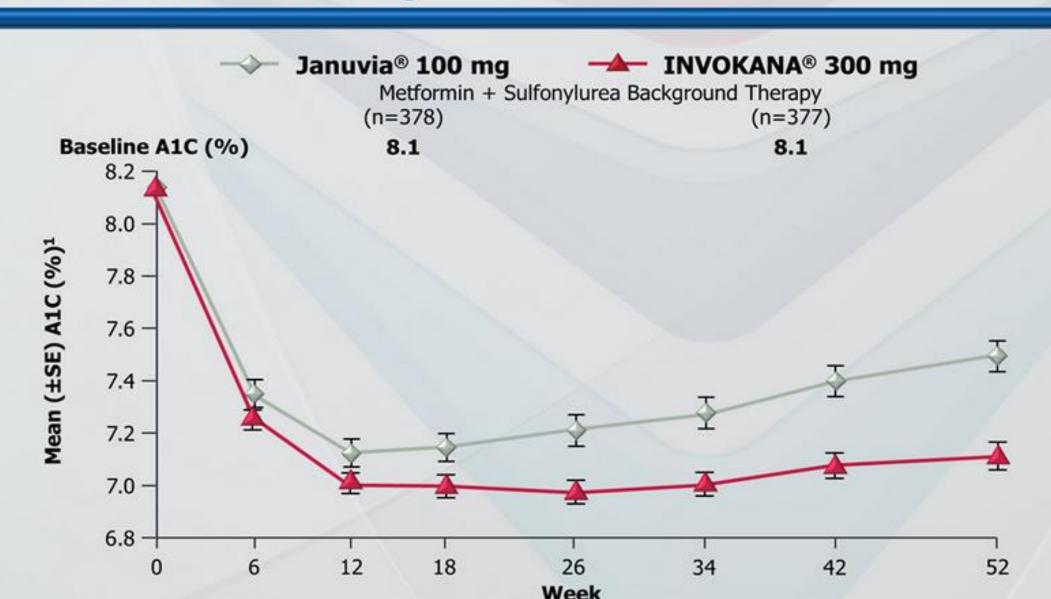
Results

38 RTC in NMA at least 24 w duration 2012-2015
baseline A1c 8.1% age 58
8 y duration of diabetes
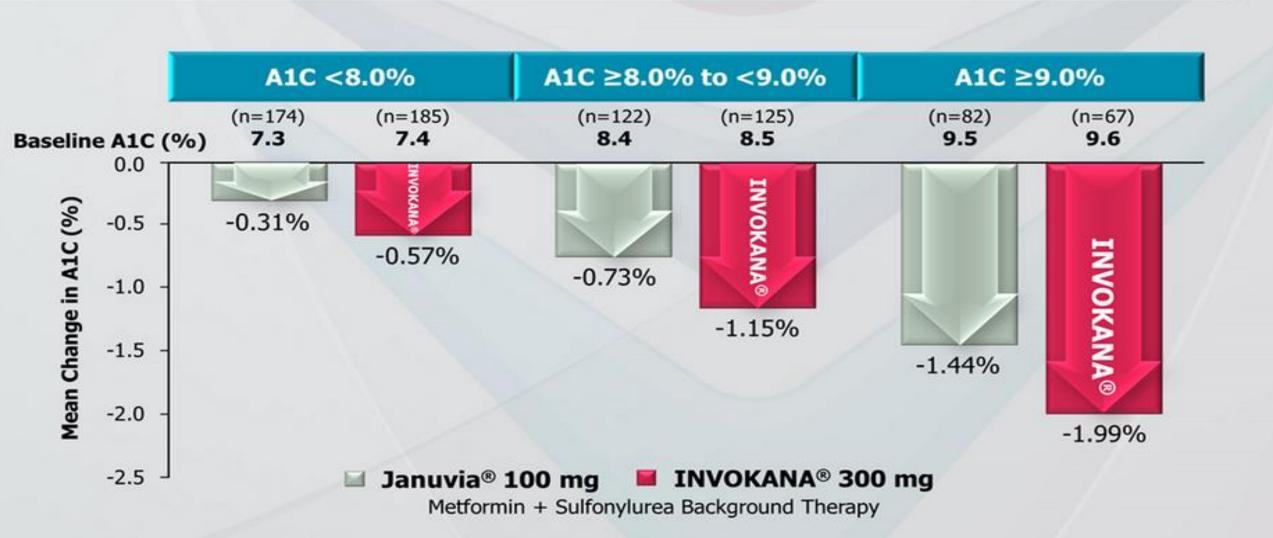
- Canaglifozin 300 reduced A1c, PPG and SBP and increased LDL to a greater extent compared with others

- The highest dose of inhibitors had similar effects on weight reduction

- All inhibitors similarly increased the risk of genital infections

SGLT2i versus DPP4 i
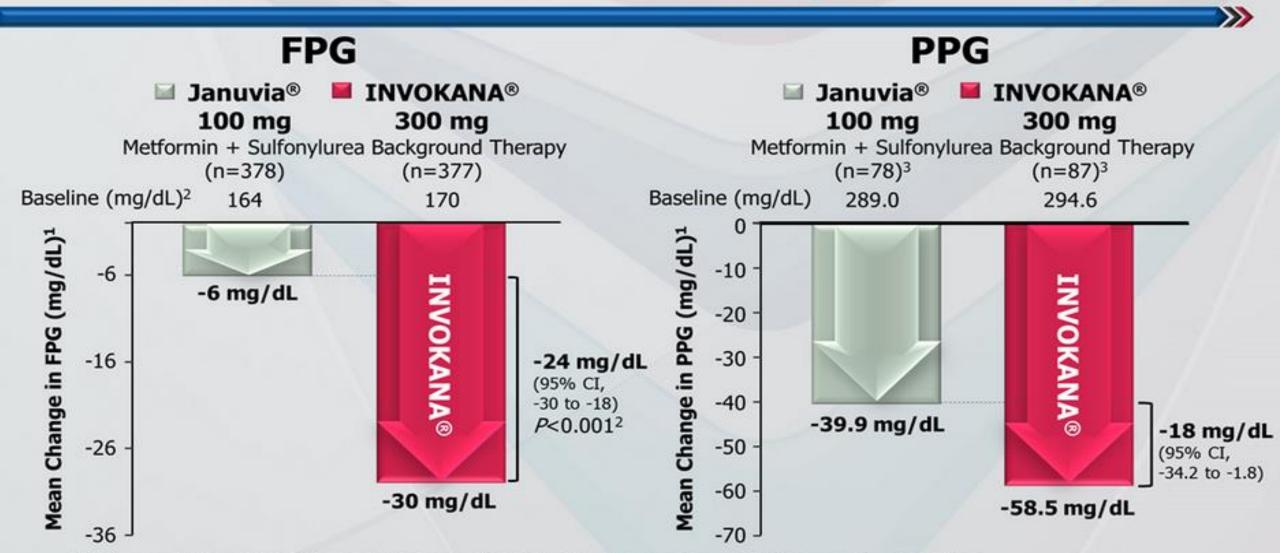
A1C Over 52 Weeks With INVOKANA® 300 mg vs Januvia® 100 mg

A1C Reductions at 52 Weeks by Baseline A1C Subgroups
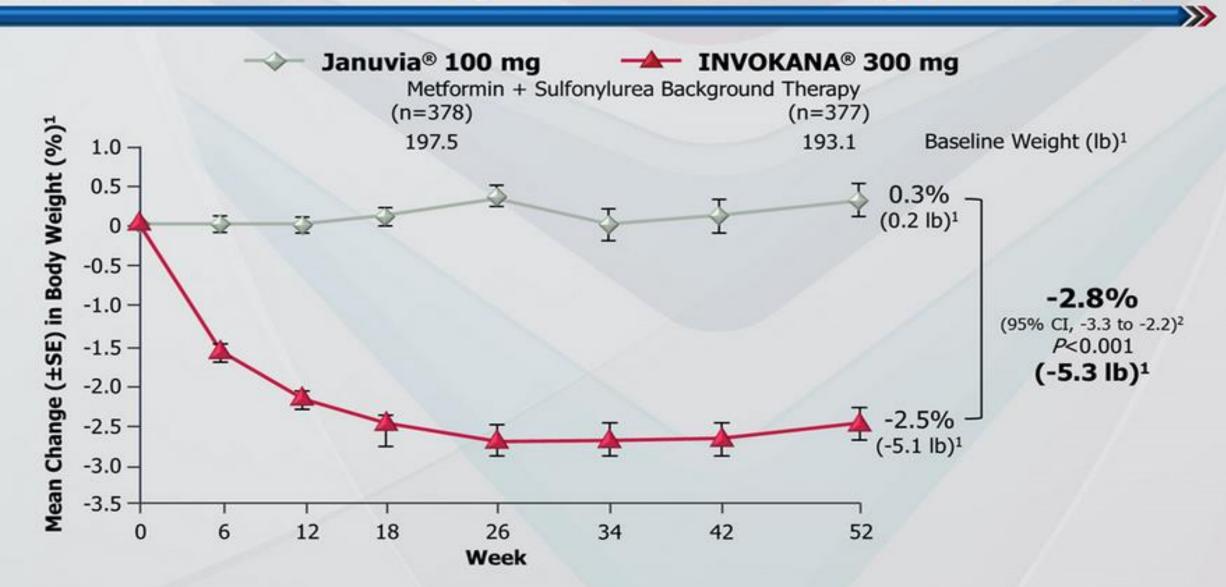
Greater Reductions in FPG* and 2-hour PPG† With INVOKANA® vs Januvia® (52 Weeks)

FPG

Januvia® 100 mg — INVOKANA® 300 mg
Metformin + Sulfonylurea Background Therapy
(n=378) (n=377)

Baseline (mg/dL)[2] 164 170

Mean Change in FPG (mg/dL)[1]

-6 mg/dL

-30 mg/dL

-24 mg/dL
(95% CI, -30 to -18)
$P<0.001$[2]

PPG

Januvia® 100 mg — INVOKANA® 300 mg
Metformin + Sulfonylurea Background Therapy
(n=78)[3] (n=87)[3]

Baseline (mg/dL) 289.0 294.6

Mean Change in PPG (mg/dL)[1]

-39.9 mg/dL

-58.5 mg/dL

-18 mg/dL
(95% CI, -34.2 to -1.8)

▶ PPG was determined in a subgroup of patients who underwent frequently sampled mixed-meal tolerance testing

Secondary Endpoint: Superior Body Weight Reductions With INVOKANA® 300 mg vs Januvia® 100 mg (52 Weeks)

Sglt-2 inhibitors versus DPP4-I plus insulin

- 14 double blinded RTC 6980 patients

- SGLT-2 I performed better

- change A1 -0.24 % difference
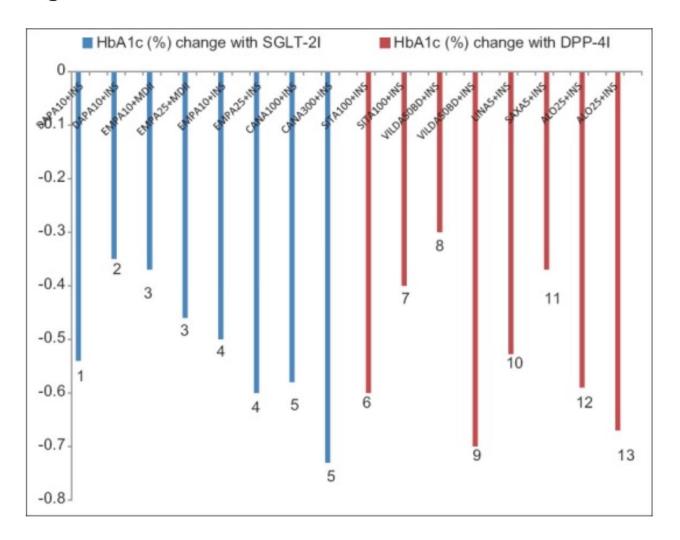
  FPG -18mg/dL

  body weight -2.38 Kg
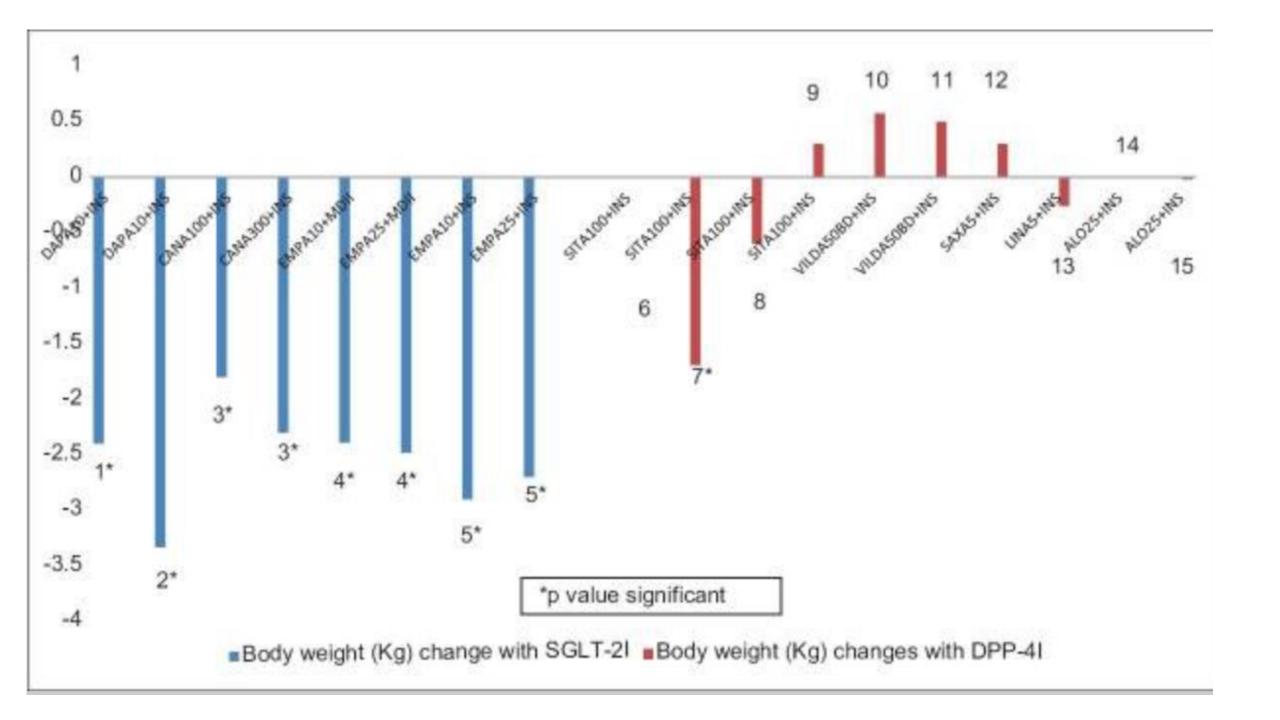
- No difference in hypoglycemia, reduction of insulin dose

Dipeptidyl peptidase-4 inhibitors or sodium glucose co-transporter -2 inhibitors as an add-0n to insulin therapy: A comparative review Awadeshesh Kumar Singh and Ritu Singh
Indian J Endocrinol Metab. 2-16- Jan- Feb 20(1) 32-42
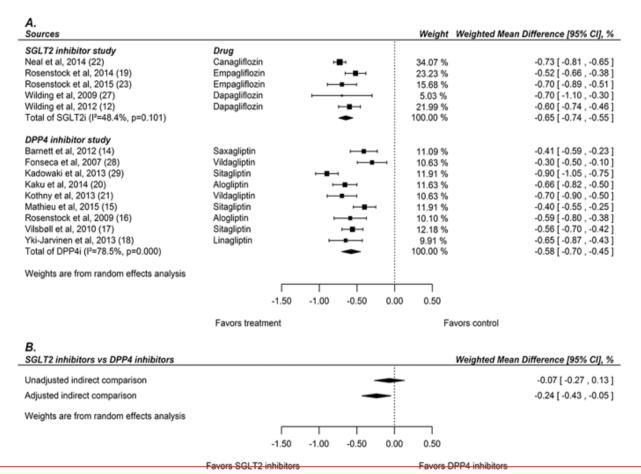
Figure 1

Placebo-subtracted glycated hemoglobin reduction with sodium-glucose co-transporter-2 inhibitors pl dipeptidyl peptidase-4 inhibitors plus insulin (red-panel), all *P* significant (1: Wilding *et al.*, 2012. 2: V Rosenstock *et al.*, 2014. 4: Rosenstock *et al.*, 2015. 5: Neal *et al.*, 2015. 6: Vilsboll *et al.*, 2010. 7: Ma *al.*, 2007. 9: Kothny *et al.*, 2013. 10: Jarvinen *et al.*, 2013. 11: Barnett *et al.*, 2013. 12: Rosenstock *et a*

*p value significant

Body weight (Kg) change with SGLT-2I   Body weight (Kg) changes with DPP-4I

Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: a systematic review with indirect comparison meta-analysis

A.

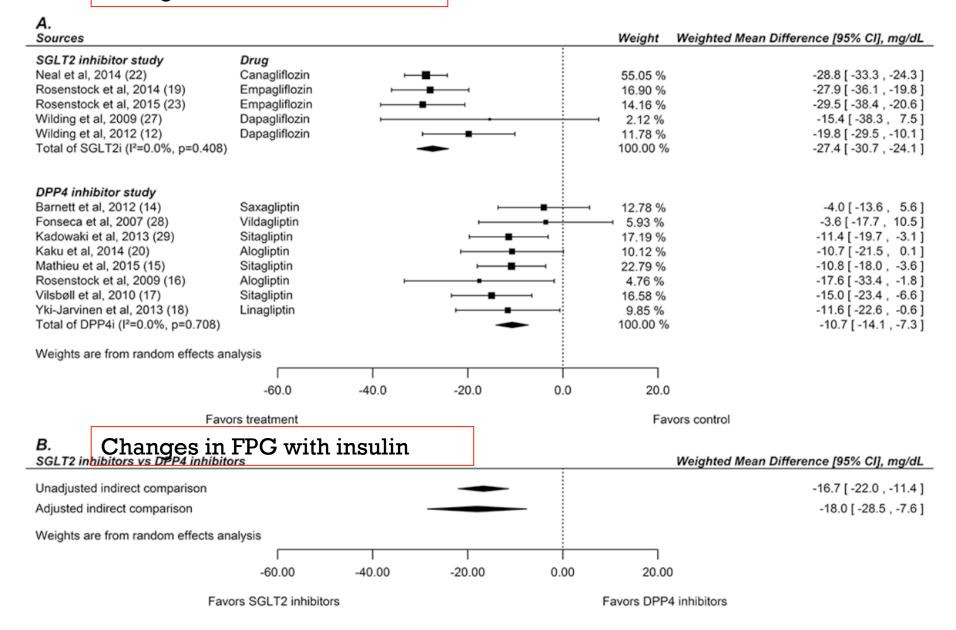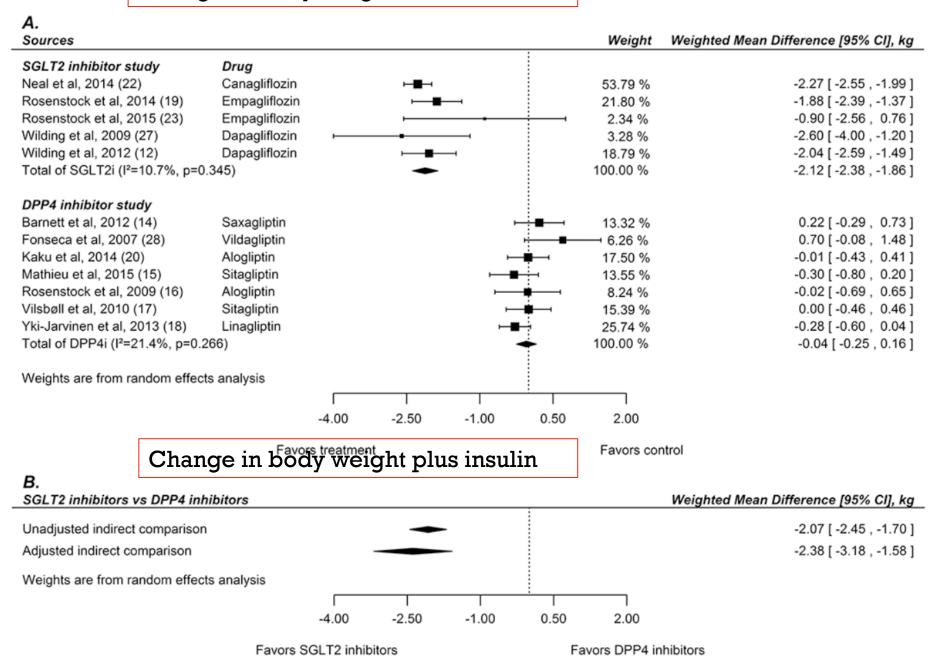| Sources	Drug		Weight	Weighted Mean Difference [95% CI], %
SGLT2 inhibitor study				
Neal et al, 2014 (22)	Canagliflozin		34.07 %	-0.73 [-0.81 , -0.65]
Rosenstock et al, 2014 (19)	Empagliflozin		23.23 %	-0.52 [-0.66 , -0.38]
Rosenstock et al, 2015 (23)	Empagliflozin		15.68 %	-0.70 [-0.89 , -0.51]
Wilding et al, 2009 (27)	Dapagliflozin		5.03 %	-0.70 [-1.10 , -0.30]
Wilding et al, 2012 (12)	Dapagliflozin		21.99 %	-0.60 [-0.74 , -0.46]
Total of SGLT2i (I²=48.4%, p=0.101)			100.00 %	-0.65 [-0.74 , -0.55]
DPP4 inhibitor study				
Barnett et al, 2012 (14)	Saxagliptin		11.09 %	-0.41 [-0.59 , -0.23]
Fonseca et al, 2007 (28)	Vildagliptin		10.63 %	-0.30 [-0.50 , -0.10]
Kadowaki et al, 2013 (29)	Sitagliptin		11.91 %	-0.90 [-1.05 , -0.75]
Kaku et al, 2014 (20)	Alogliptin		11.63 %	-0.66 [-0.82 , -0.50]
Kothny et al, 2013 (21)	Vildagliptin		10.63 %	-0.70 [-0.90 , -0.50]
Mathieu et al, 2015 (15)	Sitagliptin		11.91 %	-0.40 [-0.55 , -0.25]
Rosenstock et al, 2009 (16)	Alogliptin		10.10 %	-0.59 [-0.80 , -0.38]
Vilsbøll et al, 2010 (17)	Sitagliptin		12.18 %	-0.56 [-0.70 , -0.42]
Yki-Jarvinen et al, 2013 (18)	Linagliptin		9.91 %	-0.65 [-0.87 , -0.43]
Total of DPP4i (I²=78.5%, p=0.000)			100.00 %	-0.58 [-0.70 , -0.45]

Weights are from random effects analysis

-1.50   -1.00   -0.50   0.00   0.50

Favors treatment   Favors control

B.

SGLT2 inhibitors vs DPP4 inhibitors		Weighted Mean Difference [95% CI], %
Unadjusted indirect comparison		-0.07 [-0.27 , 0.13]
Adjusted indirect comparison		-0.24 [-0.43 , -0.05]

Weights are from random effects analysis

-1.50   -1.00   -0.50   0.00   0.50

Favors SGLT2 inhibitors   Favors DPP4 inhibitors

A. Changes in A1c from baseline
B. A1c difference in SGLT2 and DPP4 with insulin

Change in FPG from baseline

A.

Sources	Drug	Weight	Weighted Mean Difference [95% CI], mg/dL
SGLT2 inhibitor study	*Drug*		
Neal et al, 2014 (22)	Canagliflozin	55.05 %	-28.8 [-33.3 , -24.3]
Rosenstock et al, 2014 (19)	Empagliflozin	16.90 %	-27.9 [-36.1 , -19.8]
Rosenstock et al, 2015 (23)	Empagliflozin	14.16 %	-29.5 [-38.4 , -20.6]
Wilding et al, 2009 (27)	Dapagliflozin	2.12 %	-15.4 [-38.3 , 7.5]
Wilding et al, 2012 (12)	Dapagliflozin	11.78 %	-19.8 [-29.5 , -10.1]
Total of SGLT2i (I^2=0.0%, p=0.408)		100.00 %	-27.4 [-30.7 , -24.1]
DPP4 inhibitor study			
Barnett et al, 2012 (14)	Saxagliptin	12.78 %	-4.0 [-13.6 , 5.6]
Fonseca et al, 2007 (28)	Vildagliptin	5.93 %	-3.6 [-17.7 , 10.5]
Kadowaki et al, 2013 (29)	Sitagliptin	17.19 %	-11.4 [-19.7 , -3.1]
Kaku et al, 2014 (20)	Alogliptin	10.12 %	-10.7 [-21.5 , 0.1]
Mathieu et al, 2015 (15)	Sitagliptin	22.79 %	-10.8 [-18.0 , -3.6]
Rosenstock et al, 2009 (16)	Alogliptin	4.76 %	-17.6 [-33.4 , -1.8]
Vilsbøll et al, 2010 (17)	Sitagliptin	16.58 %	-15.0 [-23.4 , -6.6]
Yki-Jarvinen et al, 2013 (18)	Linagliptin	9.85 %	-11.6 [-22.6 , -0.6]
Total of DPP4i (I^2=0.0%, p=0.708)		100.00 %	-10.7 [-14.1 , -7.3]

Weights are from random effects analysis

-60.0   -40.0   -20.0   0.0   20.0

Favors treatment   Favors control

Changes in FPG with insulin

B.

SGLT2 inhibitors vs DPP4 inhibitors

	Weighted Mean Difference [95% CI], mg/dL
Unadjusted indirect comparison	-16.7 [-22.0 , -11.4]
Adjusted indirect comparison	-18.0 [-28.5 , -7.6]

Weights are from random effects analysis

-60.00   -40.00   -20.00   0.00   20.00

Favors SGLT2 inhibitors   Favors DPP4 inhibitors

Change in body weight from baseline

A.

Sources	Drug		Weight	Weighted Mean Difference [95% CI], kg
SGLT2 inhibitor study	*Drug*			
Neal et al, 2014 (22)	Canagliflozin		53.79 %	-2.27 [-2.55 , -1.99]
Rosenstock et al, 2014 (19)	Empagliflozin		21.80 %	-1.88 [-2.39 , -1.37]
Rosenstock et al, 2015 (23)	Empagliflozin		2.34 %	-0.90 [-2.56 , 0.76]
Wilding et al, 2009 (27)	Dapagliflozin		3.28 %	-2.60 [-4.00 , -1.20]
Wilding et al, 2012 (12)	Dapagliflozin		18.79 %	-2.04 [-2.59 , -1.49]
Total of SGLT2i (I^2=10.7%, p=0.345)			100.00 %	-2.12 [-2.38 , -1.86]
DPP4 inhibitor study				
Barnett et al, 2012 (14)	Saxagliptin		13.32 %	0.22 [-0.29 , 0.73]
Fonseca et al, 2007 (28)	Vildagliptin		6.26 %	0.70 [-0.08 , 1.48]
Kaku et al, 2014 (20)	Alogliptin		17.50 %	-0.01 [-0.43 , 0.41]
Mathieu et al, 2015 (15)	Sitagliptin		13.55 %	-0.30 [-0.80 , 0.20]
Rosenstock et al, 2009 (16)	Alogliptin		8.24 %	-0.02 [-0.69 , 0.65]
Vilsbøll et al, 2010 (17)	Sitagliptin		15.39 %	0.00 [-0.46 , 0.46]
Yki-Jarvinen et al, 2013 (18)	Linagliptin		25.74 %	-0.28 [-0.60 , 0.04]
Total of DPP4i (I^2=21.4%, p=0.266)			100.00 %	-0.04 [-0.25 , 0.16]

Weights are from random effects analysis

-4.00   -2.50   -1.00   0.50   2.00

Favors treatment   Favors control

Change in body weight plus insulin

B.

SGLT2 inhibitors vs DPP4 inhibitors   Weighted Mean Difference [95% CI], kg

	Weighted Mean Difference [95% CI], kg
Unadjusted indirect comparison	-2.07 [-2.45 , -1.70]
Adjusted indirect comparison	-2.38 [-3.18 , -1.58]

Weights are from random effects analysis

-4.00   -2.50   -1.00   0.50   2.00

Favors SGLT2 inhibitors   Favors DPP4 inhibitors

As an oral agent to preexisting insulin therapy SGLT2-I performed better than DPP-4I with a similar risk of hypoglycemia

What are the differences between DPP-4 Inhibitors and how do you choose ?

Evidence for DPP4 inhibitors

Table 1. Cardiovascular (CV) outcome studies with dipeptidyl peptidase-4 inhibitors [15–17,36].

Drug	Sitagliptin	Alogliptin	Saxagliptin	Linagliptin	Omarigliptin	Linagliptin
Study name	TECOS	EXAMINE	SAVOR-TIMI 53	CAROLINA	NCT01703208	CARMELINA
Comparator	Placebo	Placebo	Placebo	Glimepiride	Placebo	Placebo
Inclusion criteria (in addition to T2D)	Known CVD	Recent ACS	Known CVD or multiple risk factors	Known CVD or specified diabetes end-organ damage or age >70 years or more than two CV risk factors	Known CVD	Albuminuria and previous CV disease and/or impaired renal function with albuminuria
Patients (number)	14,671	5380	16,492	6115	4202	8300 (estimated, still recruiting)
Study start date	2008	2009	2010	2010	2012	2013
Study end date	2015	2013	2013	2019 (estimated)	May 2016	2018 (estimated)
Primary end point	CV death, nonfatal MI, nonfatal stroke, and hospitalization for UAP	CV death, nonfatal MI and nonfatal stroke	CV death, nonfatal MI and nonfatal stroke	CV death, nonfatal MI, nonfatal stroke, and hospitalization for UAP	CV death, nonfatal MI, nonfatal stroke, and hospitalization for UAP	CV death, nonfatal MI, nonfatal stroke, and hospitalization for UAP
Primary end point result	0.98 (0.88–1.09)	0.96 (upper boundary of 95% CI: <1.16)	1.00 (0.89–1.12)	Pending	Pending	Pending
Additional findings/ comments	Hospitalization for HF HR 1.27 (1.07–1.51)				Terminated early for business reasons	

T2D: type 2 diabetes; CI: confidence interval; HF: heart failure; CVD: Cardiovascular disease; ACS: Acute coronary syndrome; MI: myocardial infarction; UAP: unstable angina pectoris; HR: Hazard ratio.
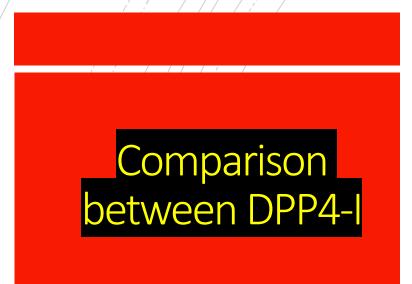
Diabetes type 2 management: what are the differences between DPP-4 inhibitors and how do you choose?

Kashif M. Munir & Elizabeth M. Lamos

Cardiovascular parameters, FDA safety warning of heart failure to Saxa and Alogliptin.

Update on Dpp4-I in The management of diabetes: use in unique populations

- Elderly frail population
- Moderate to severe renal insufficiency
- Potential benefit in albuminuria independent on A1c reduction
- No significant side effects or adverse events have been revealed in the large outcome studies including fractures, cancer or pancreatitis.

Comparison between DPP4-I
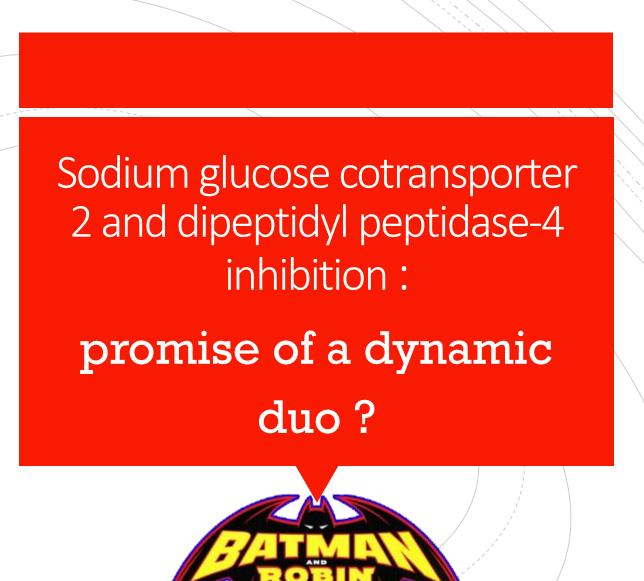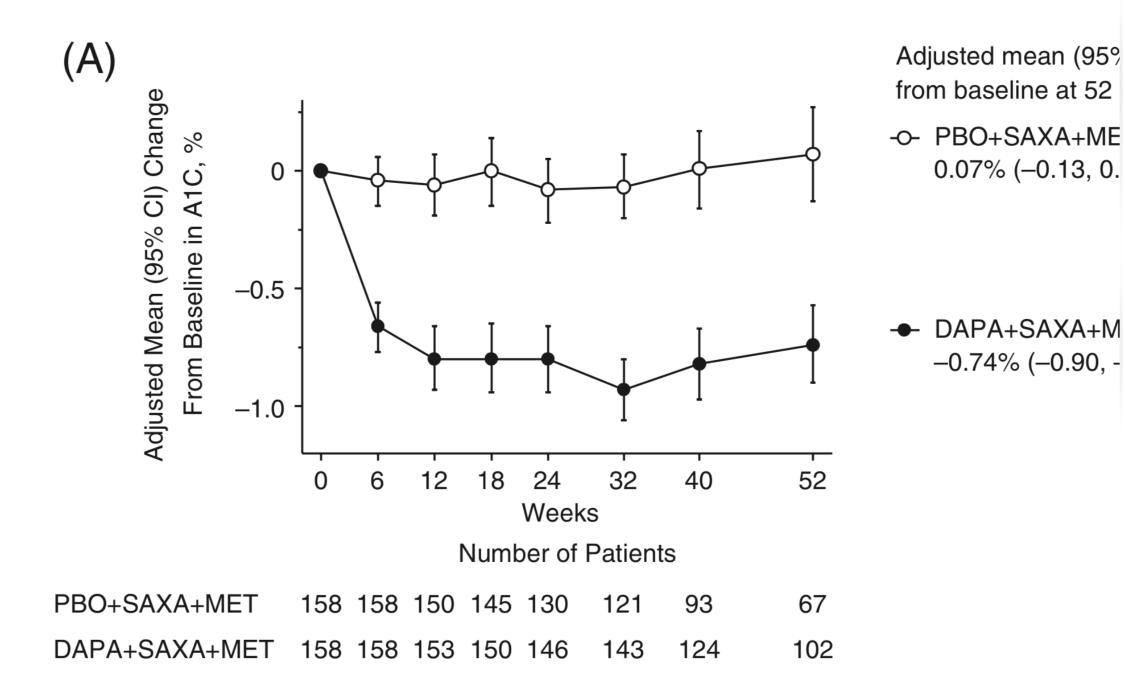
- Glycemic control. In general 0.5-1 % reduction in A1c.

- Indirect comparison Sita non inferior to SAXA in mean A1c change in metformin background. (Scheen et al) (Antonio Asti et al)(Chun- Jun- Li) Lina vs Sita and Vilda (Yun-Zhao)

Answering the question of which DPP4-I to utilize relies more on patient characteristics and side effects

Non metformin Dpp4-I based combination therapy
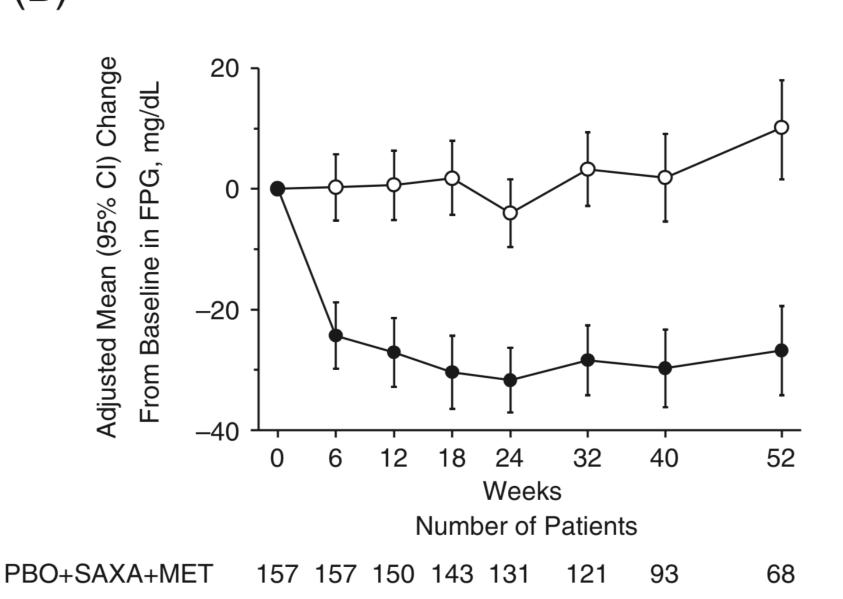
- Added to SU is preferred over increasing SU dose

- Useful combination with TZD in patients with high A1c who can not use metformin or are reluctant to injectables.

- Results from Savor-TIMI and TECOS showed neutral effect in MACE

(A)

Adjusted mean (95%
from baseline at 52

—○— PBO+SAXA+ME
0.07% (−0.13, 0.

—●— DAPA+SAXA+M
−0.74% (−0.90, -

Number of Patients

	0	6	12	18	24	32	40	52
PBO+SAXA+MET	158	158	150	145	130	121	93	67
DAPA+SAXA+MET	158	158	153	150	146	143	124	102

(B)

Adjusted mean (95% CI) change from baseline at 52 weeks

○─ PBO+SAXA+MET
10 mg/dL (1.6, 18.8)

●─ DAPA+SAXA+MET
−27 mg/dL (−34.2, −19...

Number of Patients

	0	6	12	18	24	32	40	52
PBO+SAXA+MET	157	157	150	143	131	121	93	68
DAPA+SAXA+MET	158	158	154	149	147	142	125	97

(C)

Number of Patients

	0	6	12	18	24	32	40	52
PBO+SAXA+MET	158	158	151	146	131	122	92	71
DAPA+SAXA+MET	158	157	154	150	147	142	126	104
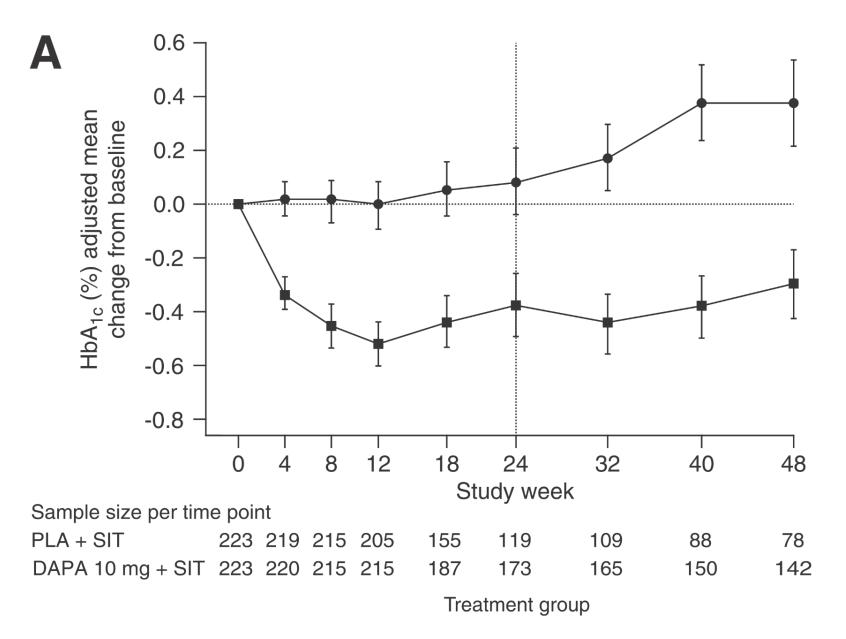
Adjusted mean (95% CI) c
from baseline at 52 weeks
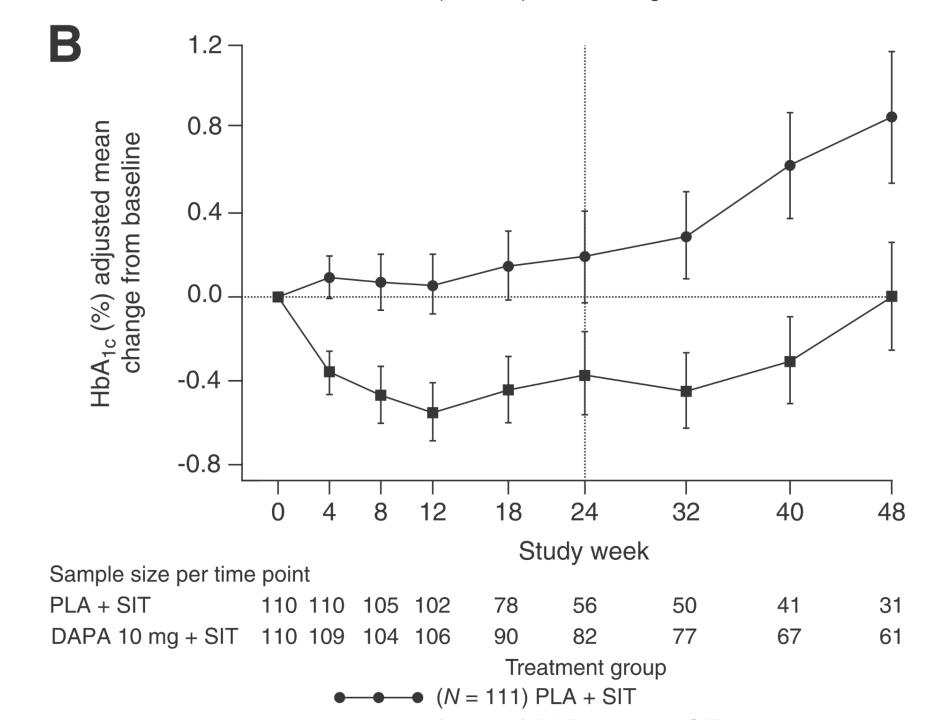
○— PBO+SAXA+MET
−0.4 kg (−1.01, 0.26)
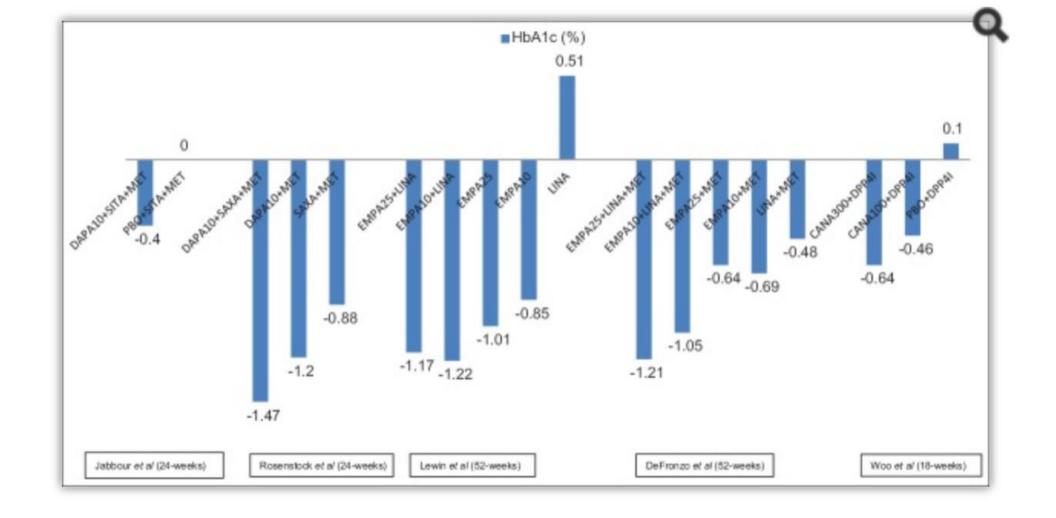
●— DAPA+SAXA+MET
−2.1 kg (−2.70, −1.56)

A

Sample size per time point

PLA + SIT	223	219	215	205	155	119	109	88	78
DAPA 10 mg + SIT	223	220	215	215	187	173	165	150	142

Treatment group

●——●——● ($N = 224$) PLA + SIT

■——■——■ ($N = 223$) DAPA 10 mg + SIT

B

Sample size per time point

PLA + SIT	110	110	105	102	78	56	50	41	31
DAPA 10 mg + SIT	110	109	104	106	90	82	77	67	61

Treatment group

●——●——● (N = 111) PLA + SIT

Change in hemoglobin A1c with dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors combination therapy

Sglt-2 inhibitors and Dpp4-I combination

Effect on A1c is less than additive

- Sitagliptin plus Dapa (Jabour et al)24 w placebo-controlled difference delta 0.4-0.6 % A1c plus delta -1.9Kg

- Saxagliptin plus Dapa, Rosenstock et al 24 w delta-0.6% A1c triple therapy w metformin -2.1 Kg reduction in body weight

- Linagliptin plus Empa no significant difference in A1c at 24w and 52w in 5/25 mg vs Empa 25 alone , delta weight -1.2-2 Kg

- However in a background with metformin (De Fronzo) lowered -0.5% delta A1c versus Empa 25 alone delta weight loss -2.3_ -1.9 Kg

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Where Does Combination Therapy With an SGLT2 Inhibitor Plus a DPP-4 Inhibitor Fit in the Management of Type 2 Diabetes?

Muhammad Abdul-Ghani⇑

+ Author Affiliations

Corresponding author: Muhammad Abdul-Ghani,

Number of patients with measurements[a]

SAXA+DAPA+MET	174	176	174	169	165	158
SAXA+MET	173	175	174	165	155	143
DAPA+MET	171	172	171	163	159	151

B

	SAXA+DAPA +MET	SAXA+MET	DAPA+MET
Baseline, %	8.93	9.03	8.87
n[b]	158	143	151

−0.59% (−0.81%, −0.37%)
$P < 0.0001$

−0.27% (−0.48%, −0.05%)
$P = 0.0166$
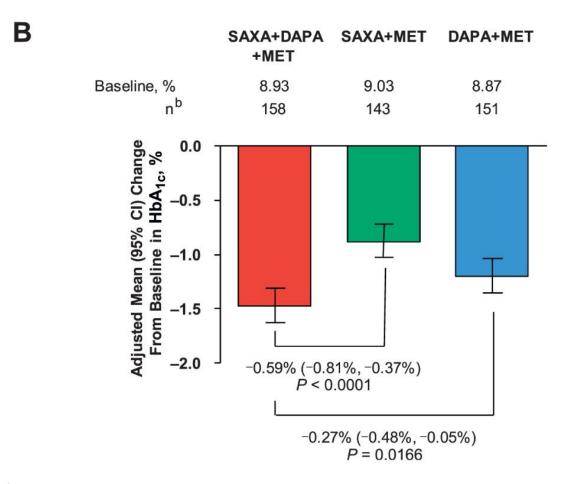
Figure 1—Mean (SE) HbA$_{1c}$ over time (*A*) and adjusted mean change from baseline in HbA$_{1c}$ at 24 weeks (*B*). [a]Observed values. [b]Number of randomized patients with nonmissing baseline values and week 24 values.

Rosenstock J. et al. Diabetes Care 2015;38:376-383

Diabetes C

American Diabetes As

SGlt2 inhibitor-based combination in non metformin candidates

SGLT_2i greater impact on A1c on high initial A1c ex 9%

- Dapaglifozin with glimepiride and Pioglitazone reduced A1c , mitigated weight gain w/o increase hypoglycemia'

- Dapa with sitagliptin reduced A1c , body weight, FPG, 2h PPBG in a 24 w study in patients not receiving metformin.

- Subgroup CANVAS showed Canaglifozin improved A1c and body weight in patients on DPP4-I or GLP1-RA.

- Of interest the combination of empaglifozin/linagliptin 25/5 resulted in similar reduction of A1c than empaglifozin 25 alone.

Combination therapy when metformin is not an option for type 2 diabetes: GLP1-RA based

- Recent meta-analysis of 15 studies showed that the combination of basal insulin and a GLP-1RA improved weight and A1c when compared with any other antidiabetic treatment with no increase in hypoglycemia.

- If metformin is not an option for renal concerns GLP1-RA might not be an option either . These agents should not be used in severe or ESRD.

ADA/EASD does not recommend GLP1-RA and SGLT2-I because no data is available at this time.
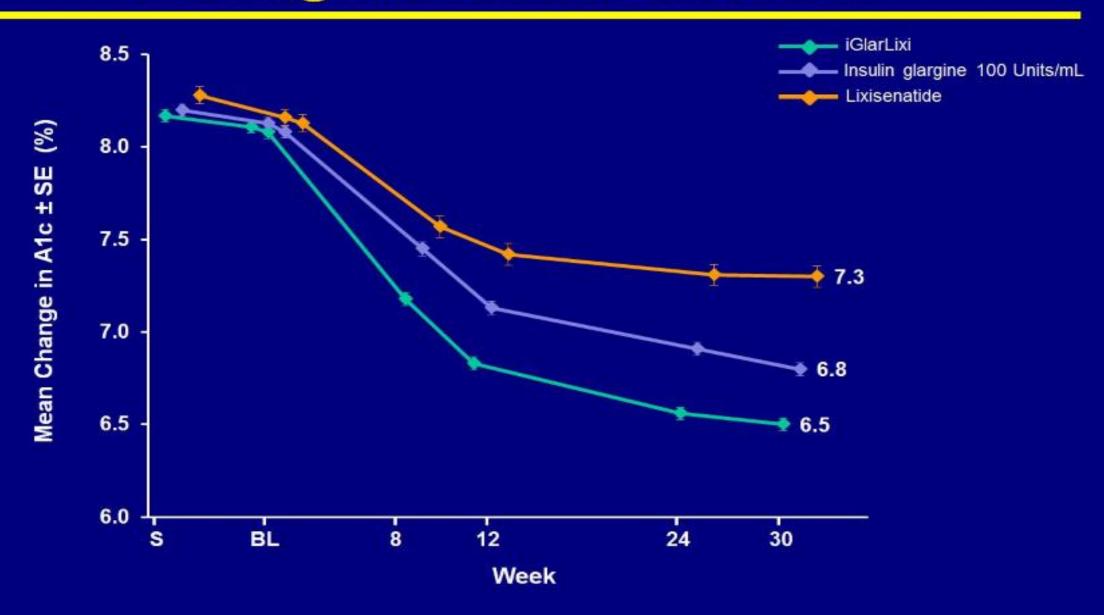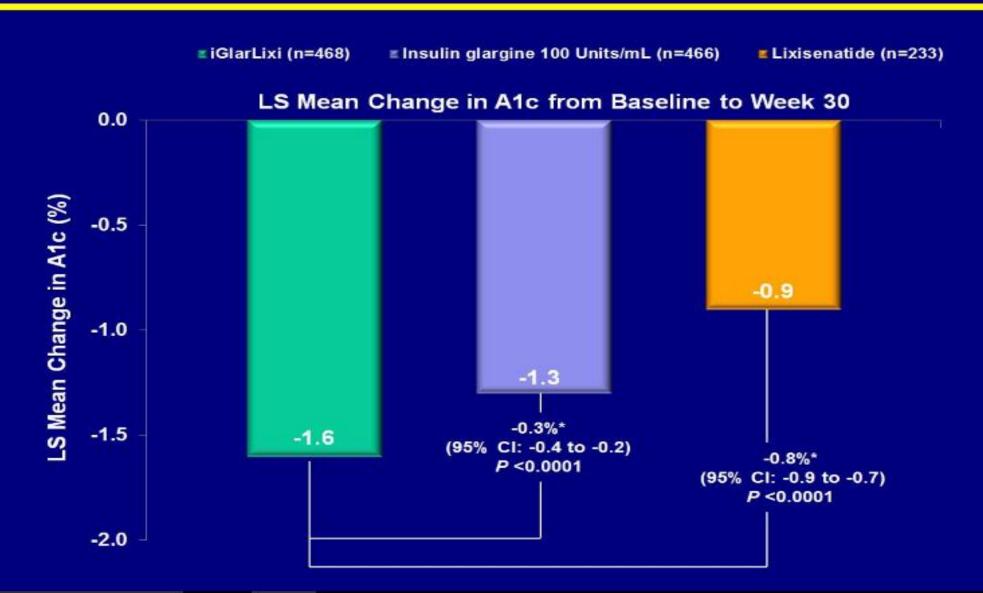
Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled With Oral Agents: The LixiLan-O Randomized Trial

Julio Rosenstock,[1] Ronnie Aronson,[2] George Grunberger,[3] Markolf Hanefeld,[4] PierMarco Piatti,[5] Pierre Serusclat,[6] Xi Cheng,[7] Tianyue Zhou,[8] Elisabeth Niemoeller,[9] Elisabeth Souhami,[10] and Melanie Davies,[11] on behalf of the LixiLan-O Trial Investigators*

Change in A1c Reduction
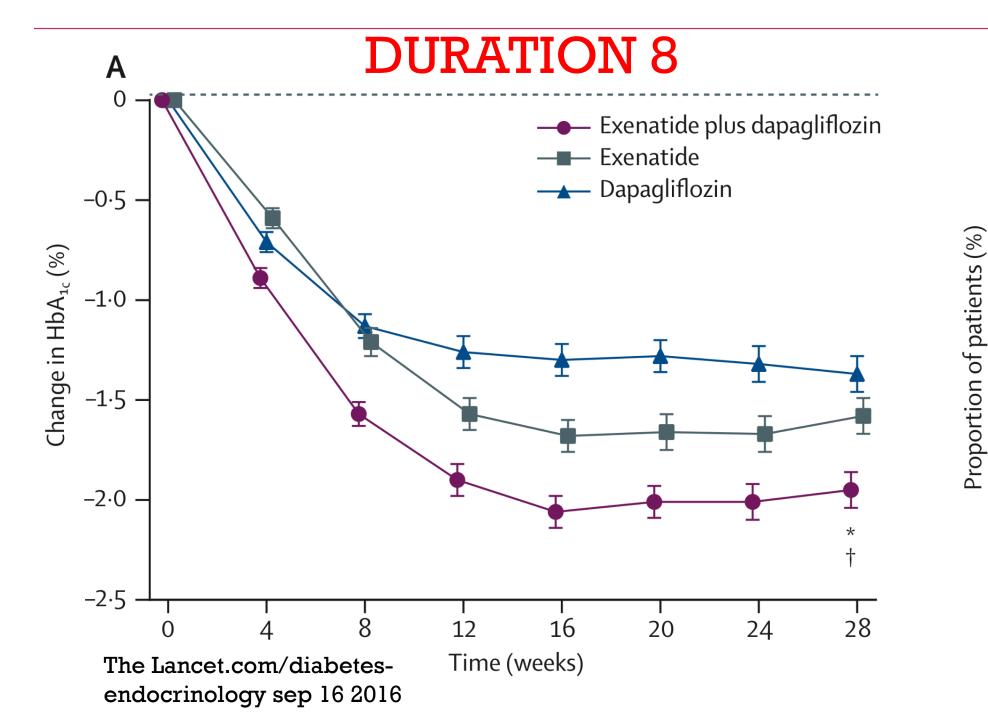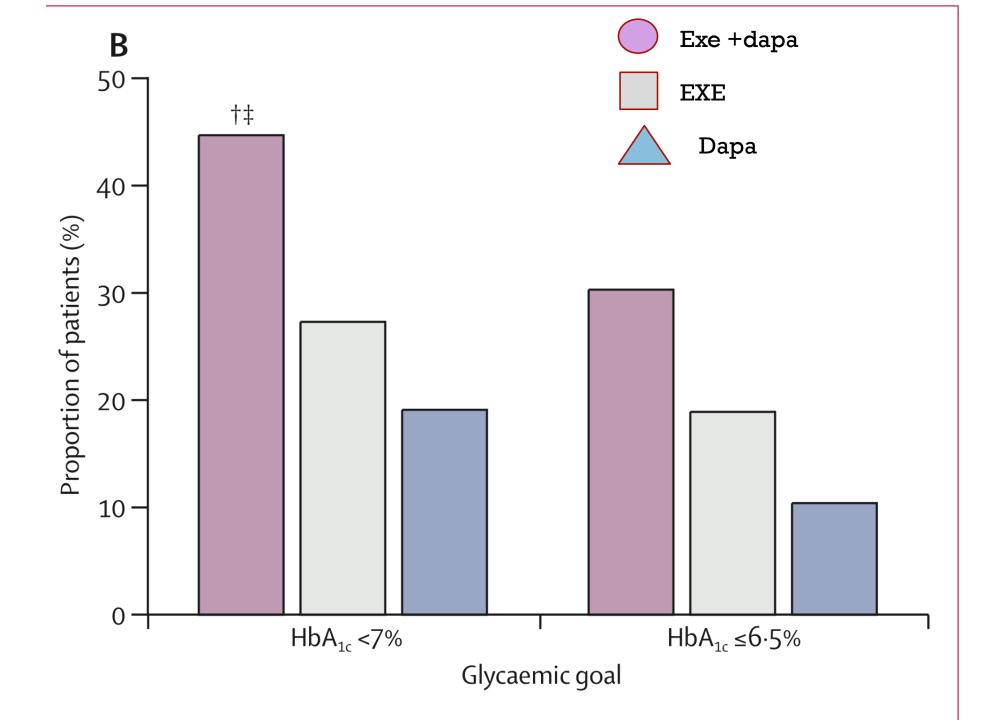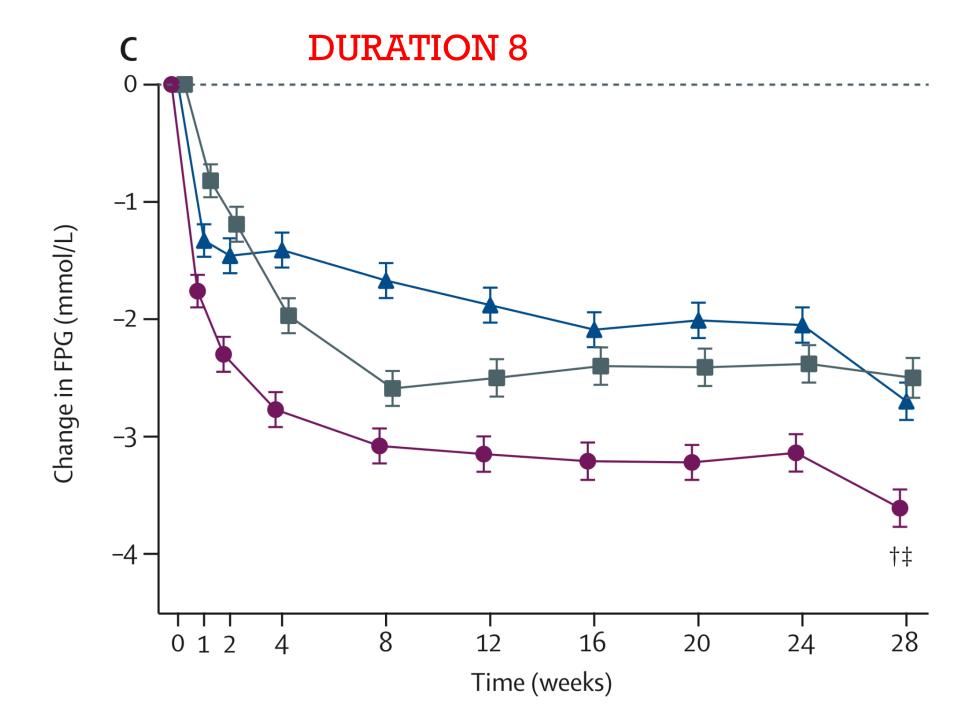
Rationale for the combo of sglt2 inhibitor and GLP-1RA
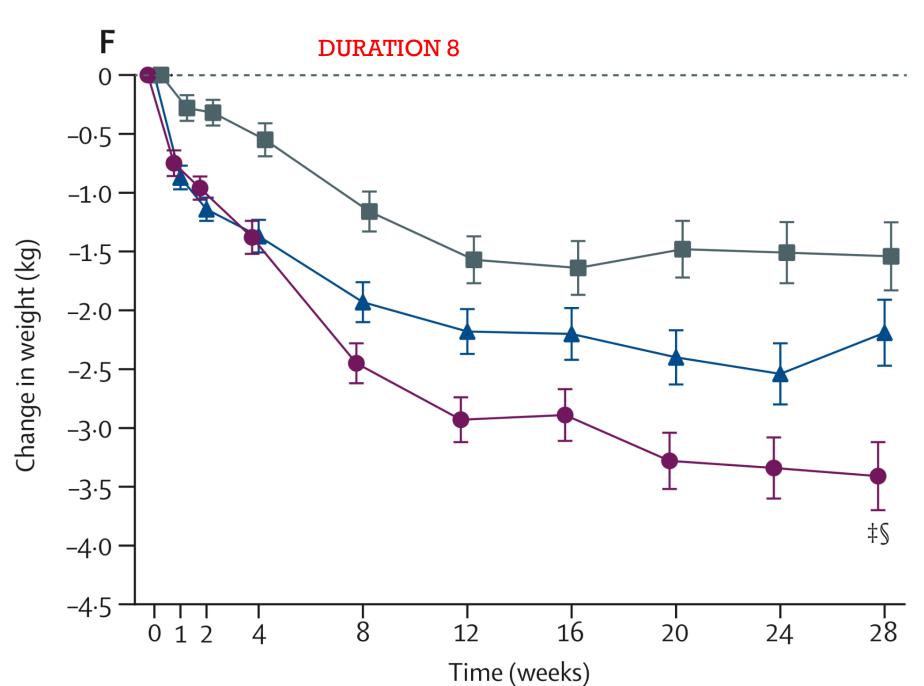
To address the complexity of T2DM, oral and injectable therapies that target different pathophysiologic abnormalities may be considered

DURATION 8

The Lancet.com/diabetes-endocrinology sep 16 2016

B

Proportion of patients (%)

†‡

Legend:
- Exe +dapa
- EXE
- Dapa

HbA$_{1c}$ <7%

HbA$_{1c}$ ≤6·5%

Glycaemic goal

C

DURATION 8

Week 28

F   DURATION 8

Triple Therapy

A

MD (95% CI)

	% NGSP	mmol/mol I
MET+SU+INS	-1.01 (-1.54, -0.47)	-11 (-16.8, -5.
MET+SU+GLP-1-RA	-0.96 (-1.49, -0.42)	-10.5 (-16.3, -
MET+SU+TZD	-0.9 (-1.39, -0.41)	-9.8 (-15.2, -4
MET+SU+SGLT2-i	-0.87 (-1.36, -0.38)	-9.5 (-14.9, -4
MET+SU+DPP-4-i	-0.69 (-1.02, -0.37)	-7.5 (-11.2, -4
MET+TZD+DPP-4-i	-0.5 (-1.3, 0.3)	-5.5 (-14.2, 3.

B

Kg (95% C

MET+SU+SGLT2-i	-1.76 (-2.74
MET+SU+GLP-1-RA	-1.55 (-2.35
MET+TZD+DPP-4-i	-0.61 (-2.09,
MET+SU+DPP-4-i	0.92 (0.33, 1
MET+SU+INS	2.39 (1.56, 3
MET+SU+TZD	3.11 (2.28, 3

C

OR (95% C

MET+SU+GLP-1-RA	1.61 (0.9, 2.
MET+SU+TZD	2.61 (1.39, 4
MET+SU+DPP-4-i	2.33 (1.29, 4
MET+SU+INS	3.67 (1.97, 6
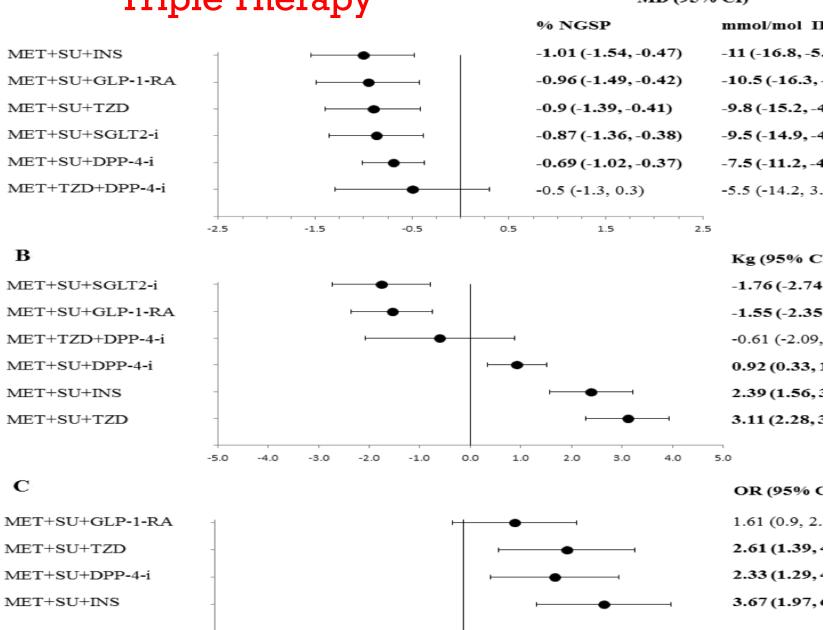
Better   Worse

My Conclusions

No one therapy fits every t2DM patient

- Set your goals

- Shoot your cannon

- Avoid clinical inertia

- Early combination therapy emphasizing complementary and synergistic

- Based on efficacy on A1c , weight, early adoption of GLP1-RA

- Although not recommended by ADA SGLT2 plus GLP1-RA present as a resourceful combination to achieve significant reductions in A1c, weight and SBP

conclusions

Think about combination therapy

- SGLT-2 DPP4-I combination seems to have a less than synergistic or additive effect

- For patients not achieving glycemic goals insulin therapy should not be delayed

- New GLP-1 insulin combinations represent a new area of interest

Remember

Guidelines are developed by experts in the field as a tool to help clinicians

How this gets translated into clinical practice is not always straight forward

Baseline HbA1c Levels

A1C LESS 7.5%

Treatment of PPG

Metformin

DPP-4i, GLP-1 RA
TZD,AGI,bromocriptine, colesevelam, SGLT2-i

A1C 7.5-9.0%

Treatment of FPG

Metformin

Consider low SU at dinner

SGlT2i on top metformin or SU

Basal insulin

Treatment of PPG as in less than 7.5 %GLP1-RA/SGLT2

A1C OVER 9%

FPG is the main driver

Basal insulin if symptomatic plus met

Treatment of PPG GLP-1/SGlt2i

Short acting insulin analogue

Amilyn mimetic**Treatment of PPG as in less 7.5%**
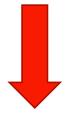
Baseline HbA1c Levels

A1C LESS 7.5%

Treatment of PPG

Metformin

DPP-4i, GLP-1 RA,

SGLT2i-

TZD,AGI,bromocriptine, colesevelam

A1C 7.5-9.0%

Treatment of FPG

Metformin

Consider low SU at dinner

SGlT2i on top metformin or SU

Basal insulin

Treatment of PPG as in less than 7.5 %GLP1-RA/SGLT2

A1C OVER 9%

FPG is the main driver

Basal insulin if symptomatic plus met

Treatment of PPG GLP-1/SGlt2i

Short acting insulin analogue

Amilyn mimetic**Treatment of PPG as in less 7.5%**

Glucose is not the only factor to be addressed in the treatment of diabetes

Age ,blood pressure, lipid levels , other risk factors and the side effects of glucose-lowering therapies must be incorporated into individualized treatment strategies to achieve maximal benefits in complication reduction and quality of life, while minimizing harm

: " *as to diseases, make a habit of two things-to help, or at least to do not harm.* "

So
do not
forget