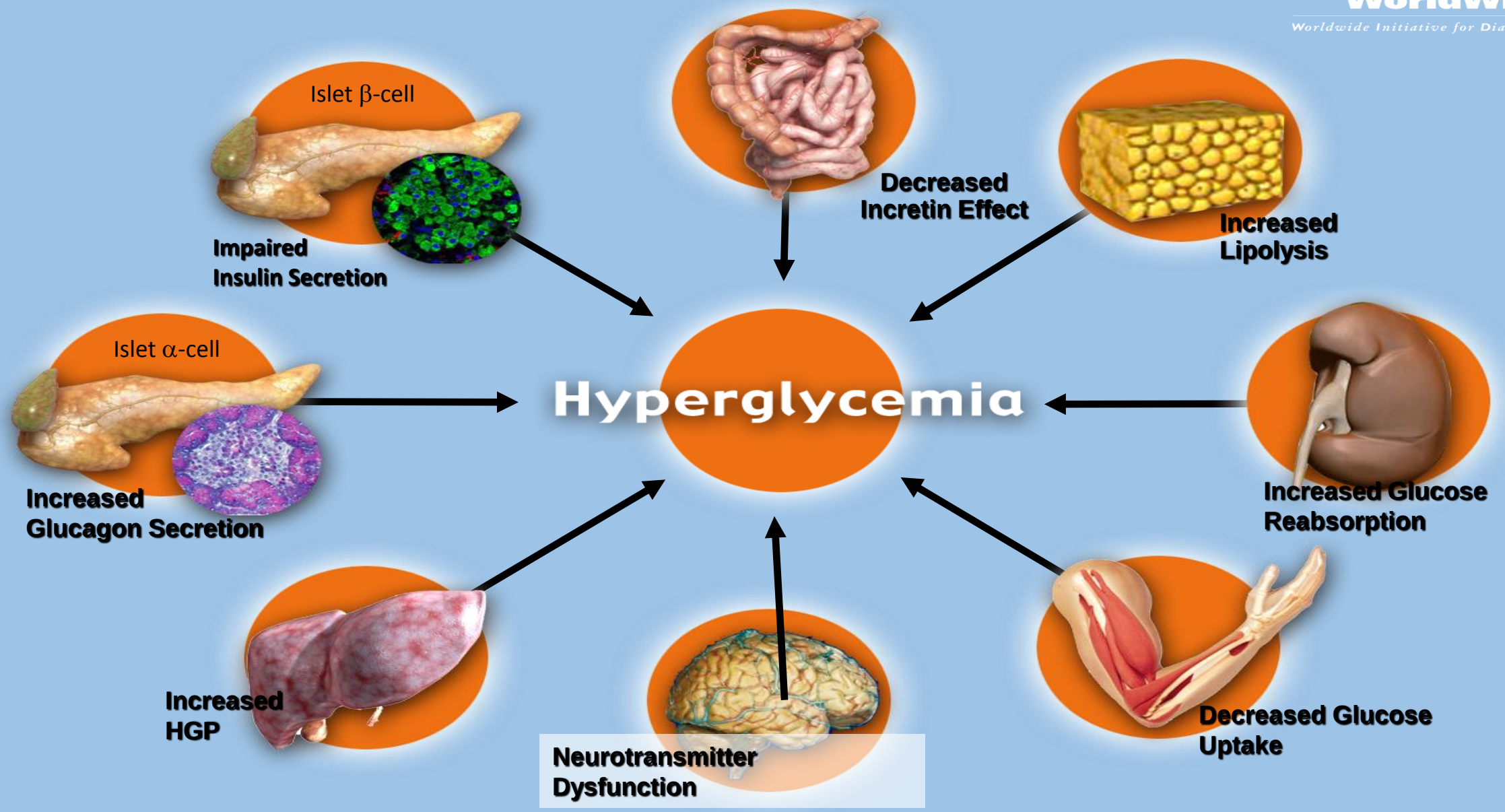
DIABETES MELLITUS
TYPE 2

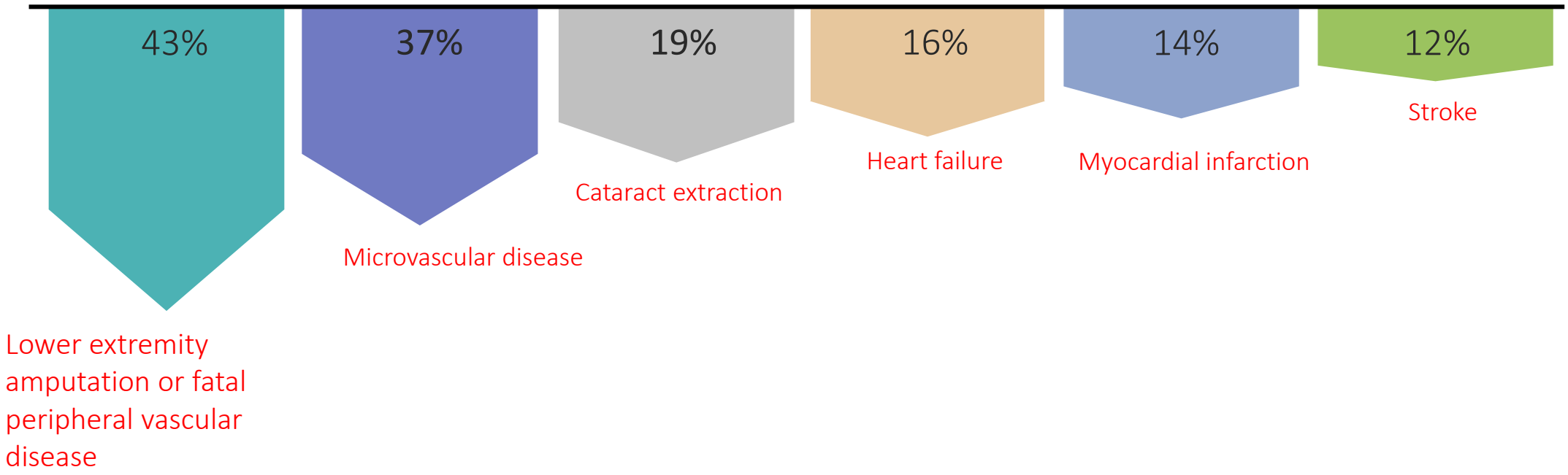
DR.K.SHAHEBRAHIMI
INTERNIST
ENDOCRINOLOGIST

The Ominous Octet-Type 2



Improving control reduces risks of long-term complications

- **Every 1% drop in HbA_{1c} can reduce long-term diabetes complications**



UKPDS 35: Stratton et al. BMJ 2000;321:405–12.

Pharmacologic Therapy for Type 2 Diabetes

A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include:

- **Comorbidities** (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease)
- **Hypoglycemia risk**
- **impact on weight**
- **cost**
- **risk for side effects**
- **patient preferences**.

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019;42(Suppl. 1):S90-S102

What are the glycemic goals?

- HBA1C < 7%.
- Fasting/Preprandial/Bedtime capillary blood glucose (CBG) 70 - 130 mg/dl.
- Postprandial CBG 1 - 2 hours after starting a meal < 180 mg/dl
- .
- Goal is to achieve glycemic target without causing hypoglycemia.

- Reaching goal glycemia has been clearly shown to prevent ***microvascular*** complications; its effect on the prevention of ***macrovascular*** complications is less clear, but seems to be most important when attained early in the course of DM.

- Control of BP & lipids, use of ASA, and smoking cessation are essential in preventing CVD.

ADA.*Diabetes Care*, 2014;37 (Suppl 1):S5-S80.

Does tight glycemic control prevent macrovascular disease?

- Based upon the findings of the UKPDS, ACCORD, ADVANCE and VADT trials, the ADA, AHA, and ACC issued a joint statement supporting the **individualization** of treatment goals, and stressing the importance of aggressive treatment and control ***early*** in the course of the disease.

- Patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular and macrovascular complications, extensive comorbidities, or longstanding difficult to control DM, may reasonably have a HBA1C goal that is > 7%.

- Patients with a shorter duration of DM, a long life expectancy, and no significant complications, may reasonably have a HBA1C goal that is lower, < 6.5% or even < 6.0%.

Skyler etal.*Diabetes Care*.2009;32:187-192.

How do you choose medication for glycemic control?

- Choose based upon potency, safety, side effects, ease of use, effect on other risk factors, and **cost**.
-
- New guidelines are more patient-centered.

Medications for DM:

- **Biguanides - Metformin (Glucophage) - decrease hepatic glucose output - weight neutral or mild loss, no hypoglycemia, cheap - GI side effects, contraindicated in CRI and unstable CHF because of risk of lactic acidosis, B12 deficiency.**

- **Sulfonylureas - Glipizide (Glucotrol), glimeperide (Amaryl) - enhance insulin secretion - cheap - weight gain, hypoglycemia.**

  Glyburide and chlorpropamide are not recommended because of long half lives and risk of severe hypoglycemia.

- **Insulins - Lispro (Humalog), aspart (Novolog), glulisine (Apidra); Regular; NPH; glargine (Lantus), detemir (Levemir); and fixed combinations - no dose limit, NPH and Regular are cheap, improve lipids - injections, weight gain, hypoglycemia, analogs are expensive.**

  Inhaled insulin (Exubera) was taken off of the market because of poor sales.

- **Thiazolidinediones (TZD's or Glitazones)** - Pioglitazone (Actos) - increase sensitivity to insulin - improve lipids, potential decrease in MI, no hypoglycemia - fluid retention, weight gain, CHF, fractures, ?bladder cancer (taken off of market in France and Germany).

  ** Rosiglitazone (Avandia) is not recommended*

- **DPP-4 Inhibitors** - Sitagliptin (Januvia), saxagliptan (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina) - increase glucose-mediated insulin secretion, suppress glucagon secretion - weight neutral, no hypoglycemia - expensive, /pancreatitis/pancreatic cancer, long term effects not known.

- **GLP-1 Agonists (Incretin Mimetics)** - Exenatide (Byetta, Bydureon), liraglutide (Victoza) - potentiate glucose-stimulated insulin secretion, suppress glucagon secretion, slow gastric motility - weight loss, ?delay/prevention of beta cell failure, no hypoglycemia - injections, expensive, GI side effects, ?pancreatitis/pancreatic cancer, ?medullary CA of the thyroid, long term effects not known.

α-Glucosidase Inhibitors - Acarbose (Precose), miglitol (Glyset) - reduce the rate of digestion of polysaccharides - weight neutral, no hypoglycemia - severe GI side effects,, three times daily.

- Glinides - Nateglinide (Starlix), repaglinide (Prandin) - stimulate insulin secretion - weight gain, three times daily, hypoglycemia.

- Amylin Agonists - Pramlintide (Symlin) - slow gastric emptying, decrease glucagon secretion - weight loss, no hypoglycemia - injections, expensive, GI side effects, long term effects not known.

- Bile Acid Resins - Colesevelam (WelChol) - mechanism of action unknown.

- Dopamine Receptor Agonists - Bromocriptine (Cycloset) - mechanism of action unknown, but probably normalizes aberrant hypothalamic neurotransmitter activities.

- Sodium-glucose Transporter-2 Inhibitors (SGLT2s) – empagliflozin, Canagliflozin (Invokana) - block reabsorption of glucose in the kidneys.

How potent are these medications?

If initial HBA1C is ≥ 9%, **use 2 medications. If initial glucose is ≥ 300-350mg/dl, or HBA1C is ≥ 10-12%, **use insulin**.*

• **Medication**	• **Expected decrease in HBA1C**
Biguanides	1.0 - 2.0
Sulfonylureas	1.0 - 2.0
Insulin	No limit
TZD's	0.5 - 1.4
DPP - 4 Inhibitors	0.5 - 0.8
GLP - 1 Agonists	0.5 - 1.0
α - Glucosidase Inhibitors	0.5 - 0.8
Glinides	0.5 - 1.5
Amylin Agonists	0.5 - 1.0
Colesevelam	0.5 - 1.0
Bromocriptine	0.5 - 1.0
Canagliflozin	0.5 - 1.0

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (***agents listed in alphabetical order by CV outcome data***):

Class	Effect on CVD Outcomes	Hypo-glycemia	Weight	Relative A1C Lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1R agonists	lira: Superiority in T2DM with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease Contraindicated with personal / family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	Cana & empa: Superiority in T2DM patients with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin. Reduced progression of nephropathy & CHF hospitalizations with empagliflozin and canagliflozin in those with clinical CVD	$$$
DPP-4 Inhibitors	alo, saxa, sita: Neutral	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$- $$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks for maximal effect	$$
α-glucosidase inhibitor (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretagogue: **Meglitinide**		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing.	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide. Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

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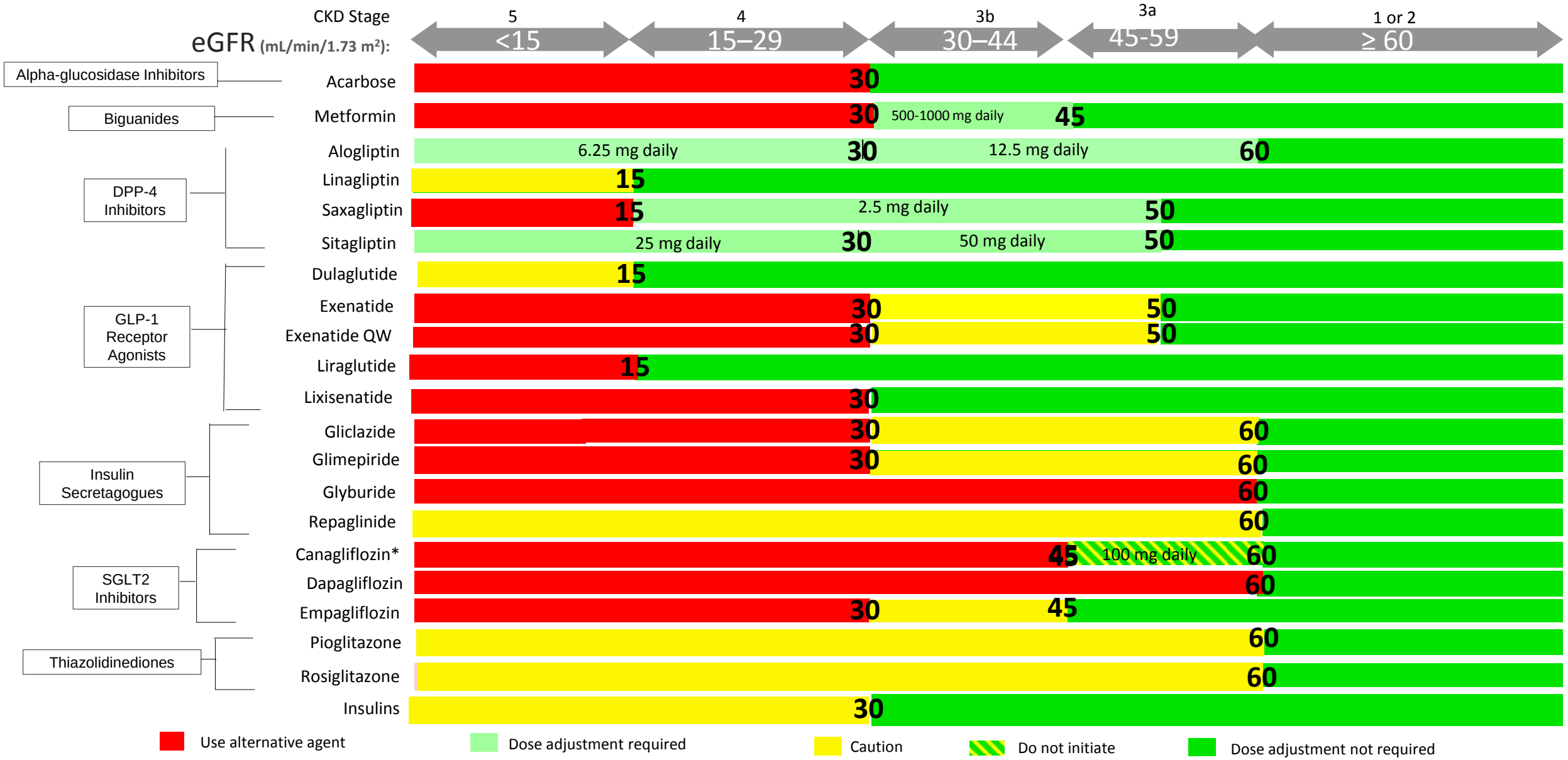
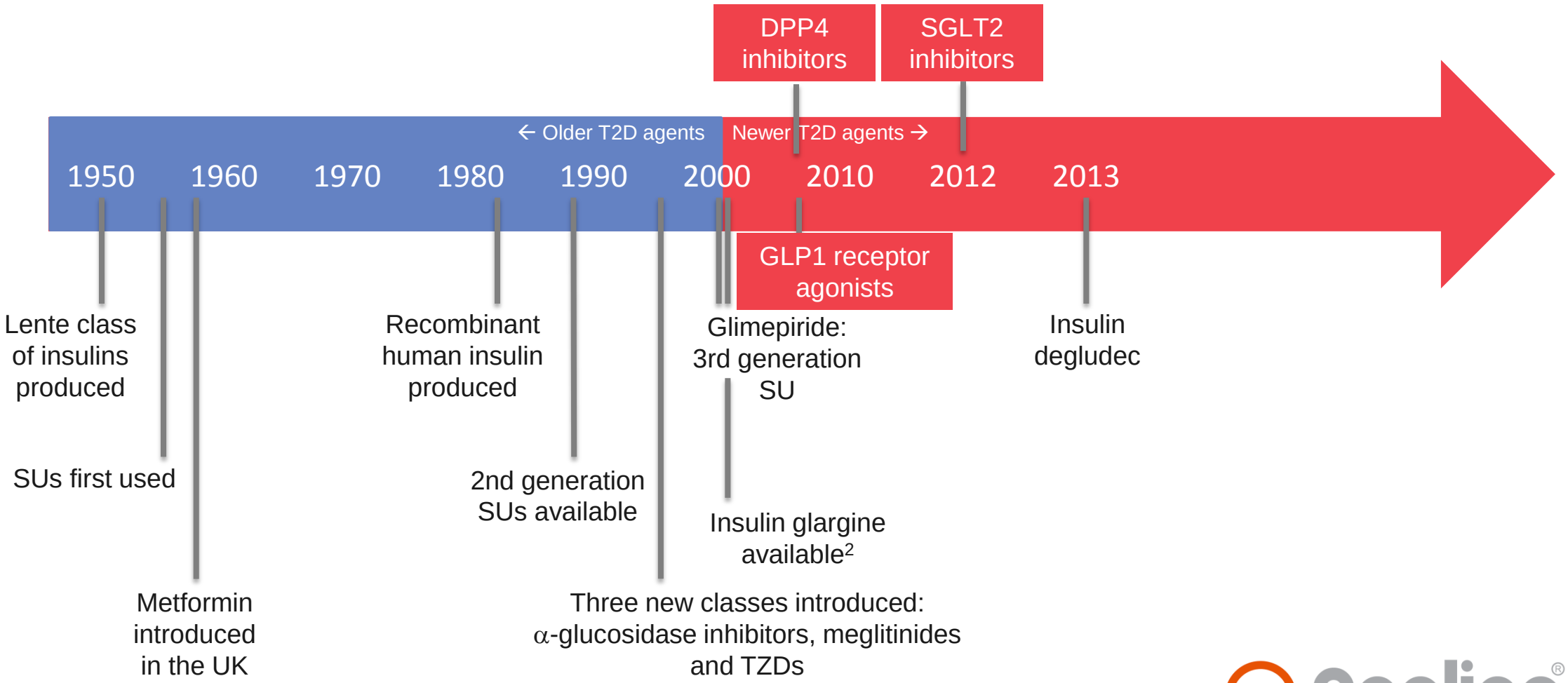
Antihyperglycemic Agents and Renal Function



** May be used for cardiorenal benefits in those with clinical CVD, A1C above target and eGFR >30 mL/min/1.73m²*

Timeline of Antidiabetic drugs



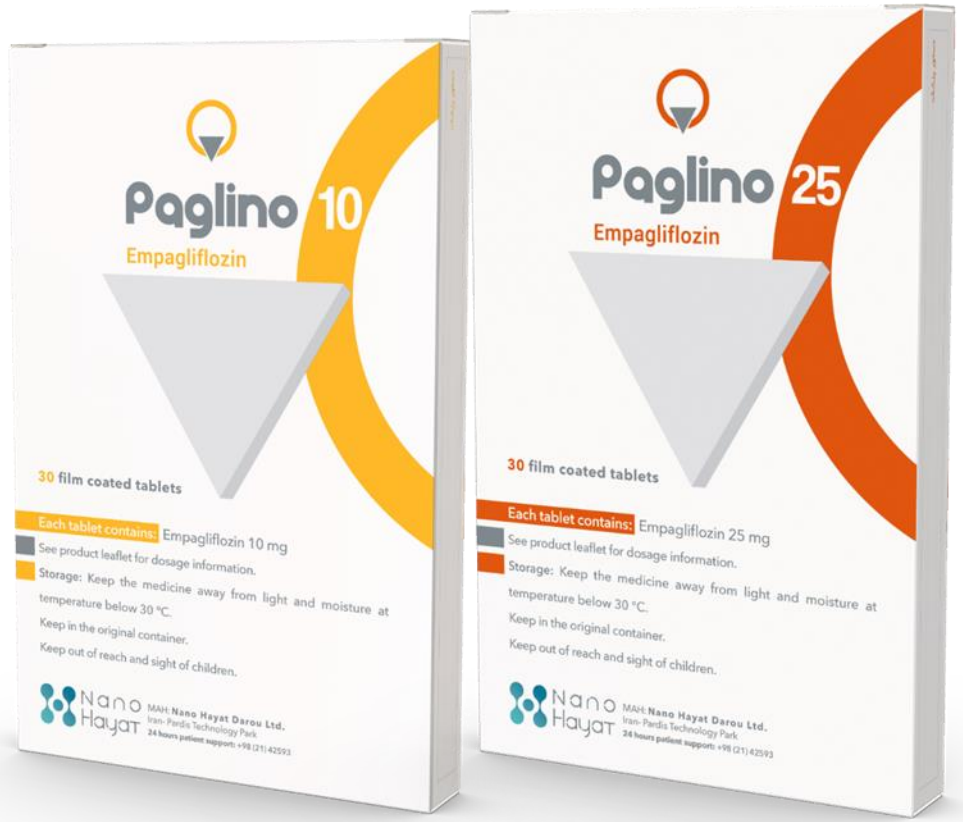
Adapted from 1. Kirby. Br J Diabetes Vasc Dis 2012;12:315–20. 2. Lantus® SPC. FDA 2015.

Paglino®
Empagliflozin

Orchid Pharmed
Sky's The Limit

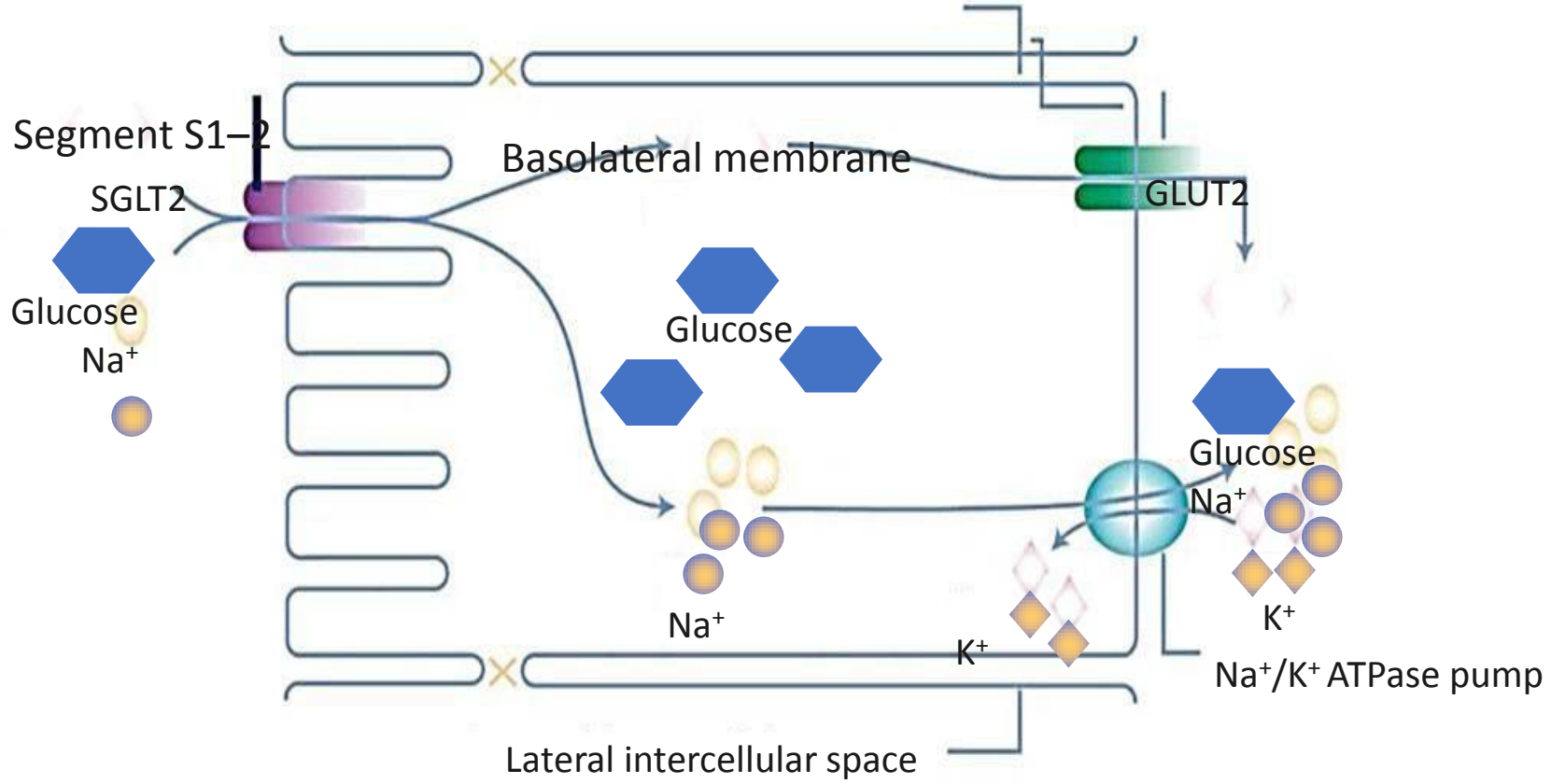
Empagliflozin

- Brand name: Paglino
- Tablet 10, 25 mg



Paglino®
Empagliflozin

SGLT2 is a sodium glucose cotransporter



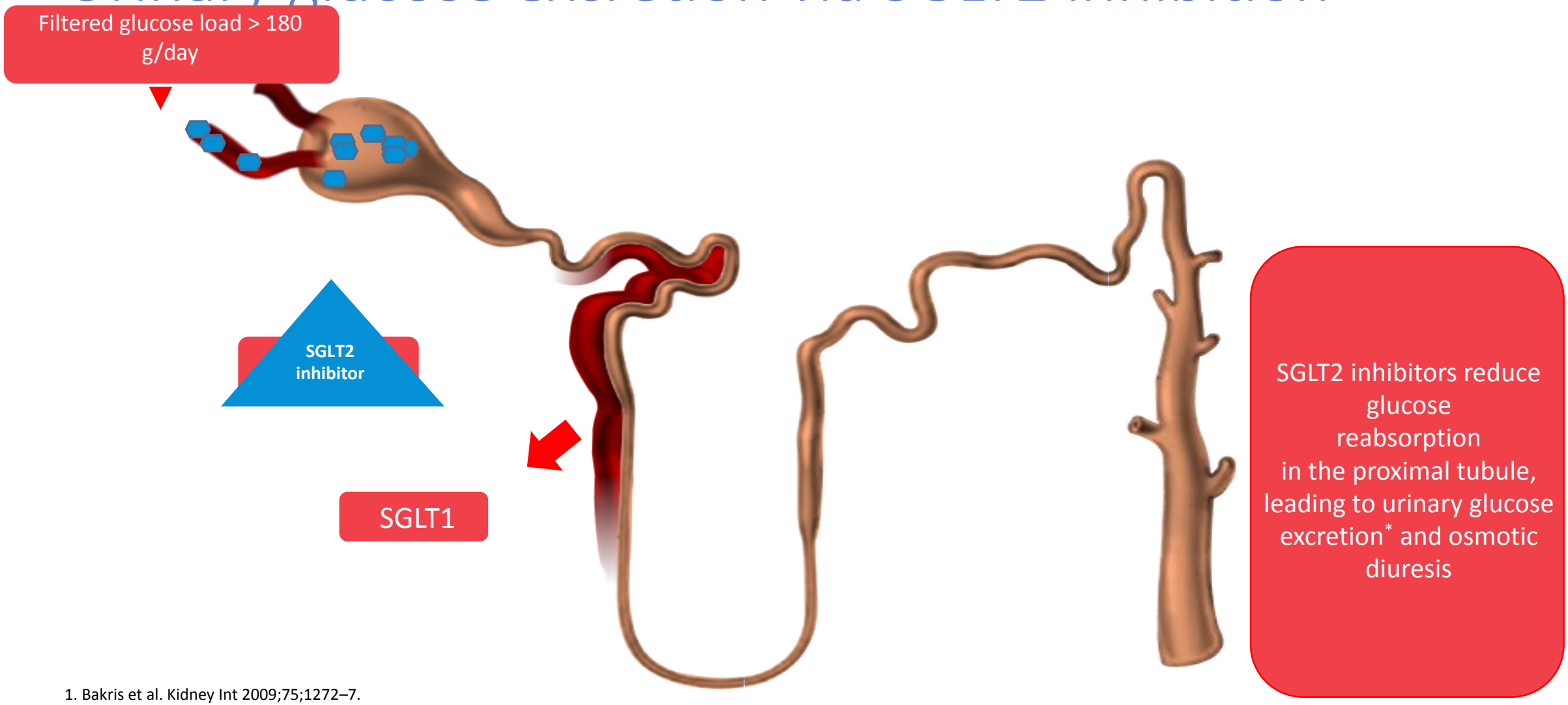
- SGLTs transfer glucose and sodium (Na^+:glucose coupling ratio for SGLT1 = 2:1 and for SGLT2 = 1:1) from the lumen into the cytoplasm of tubular cells through a secondary active transport mechanism

GLUT, glucose transporter; SGLT, sodium glucose cotransporter.

1. Wright EM, et al. *Physiology*. 2004;19:370–376. 2. Bakris GI, et al. *Kidney Int*. 2009;75:1272–1277.
3. Mather A, Pollock C. *Kidney Int Suppl*. 2011;120:S1–S6.

Paglino®
Empagliflozin

Urinary glucose excretion via SGLT2 inhibition[1]



SGLT2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

1. Bakris et al. Kidney Int 2009;75;1272–7.

Pharmacological properties of available SGLT2 inhibitors

Link to SGLT2 clinidata

	Empagliflozin	Dapagliflozin	Canagliflozin
Therapeutic dose (mg/day) Starting dose	10–25 10	5–10 10	100–300 100
Administration	QD With or without food	QD With or without food	QD Before first meal
Peak plasma concentration (hours post-dose)	1.5	Within 2	1–2
Absorption (mean oral bioavailability)	≥ 60%	~ 78%	~ 65%
Metabolism	← Primarily glucuronidation - no active metabolite →		
Elimination (half-life, hours)	Hepatic:renal 43:57 [12.4]	Hepatic:renal 22:78 [12.9]	Hepatic:renal 67:33 [13.1]*
Selectivity over SGLT1	1:5000	> 1:1400	> 1:160[1]
Glucose excretion with higher dose (g/day)	78	~ 70	119

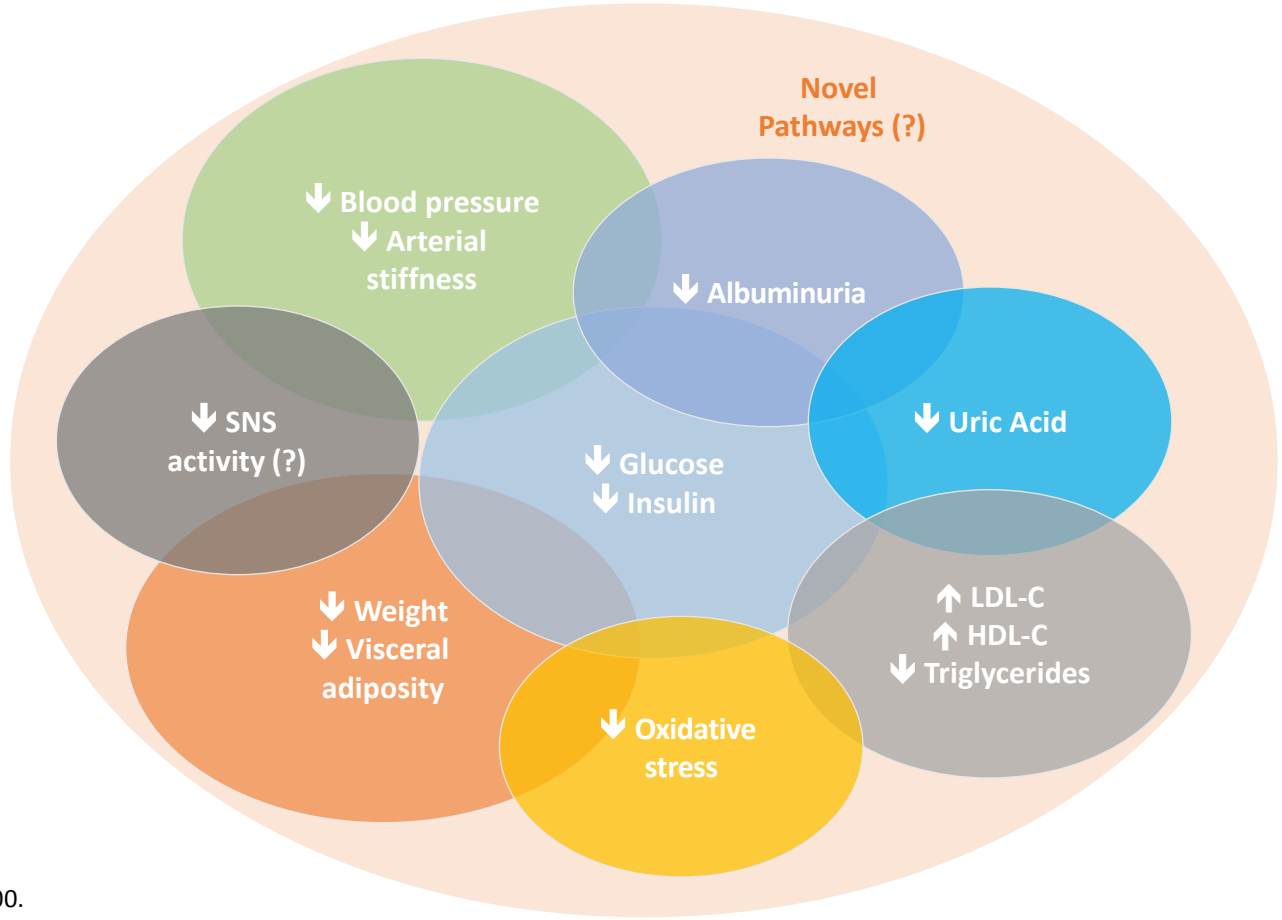
*For the 300 mg dose.

Data from http://www.ema.europa.eu/ (Jardiance SPC, Forxiga SPC , Invokana PI, Invokana SPC, all accessed June 2015); 1. Sha et al. Diab Obes Metab 2015;17:188–97.

SGLT2 inhibitors modulate a range of factors related to CV risk

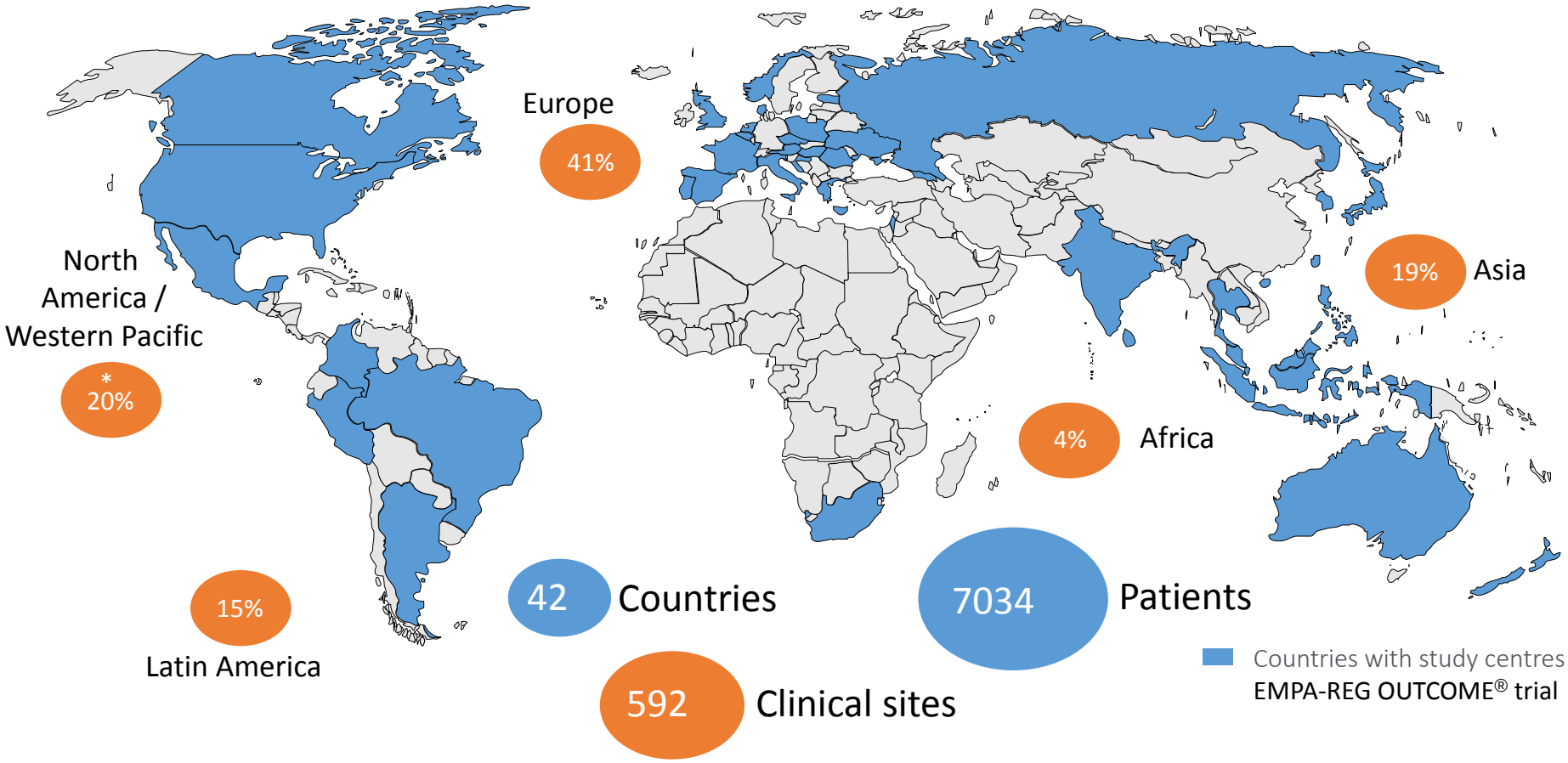
Based on clinical and mechanistic studies

Link to SGLT2 clinical data



Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100.

Long-term CV safety of empagliflozin is being evaluated in a large, multicentre Phase IV trial (EMPA-REG OUTCOME®)



*Cumulative percentage for North America, Australia and New Zealand.

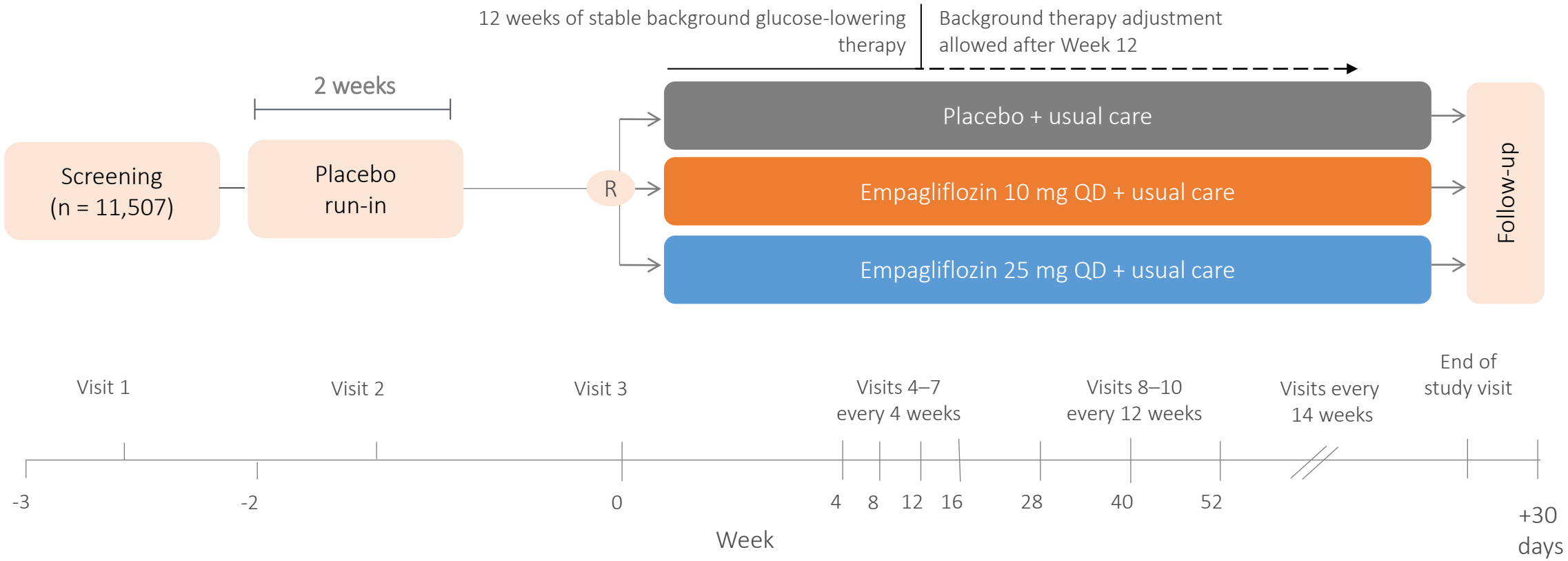
1. Zinman et al. Cardiovasc Diabetol 2014;13:102. 2. NCT01131676.

ACROSS T2D The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

EMPA-REG OUTCOME®: Study design

Aim **Compound-specific**

To determine CV safety of empagliflozin vs placebo + usual care for glycaemic control and CV risk in patients with T2D and high CV risk



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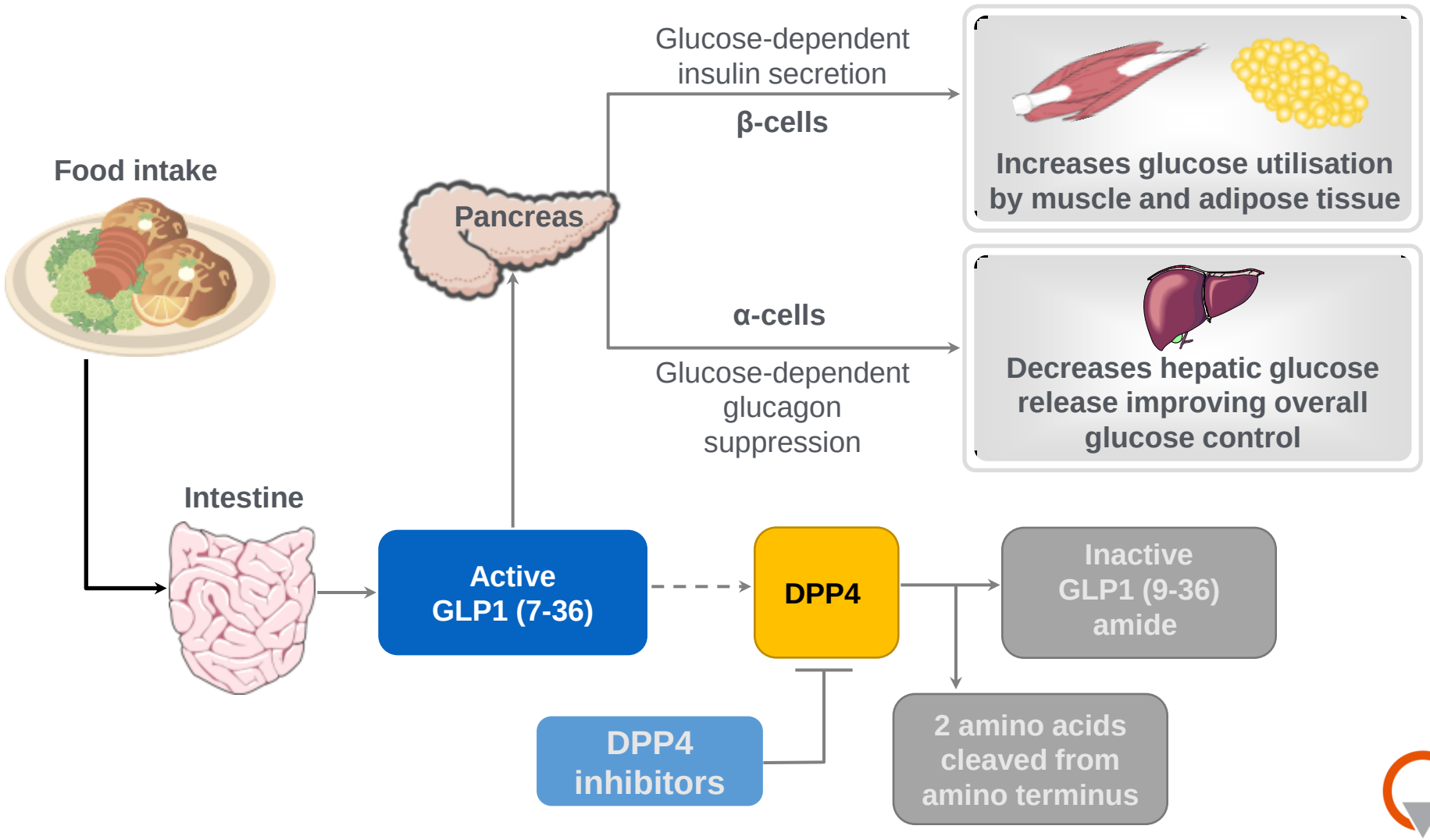
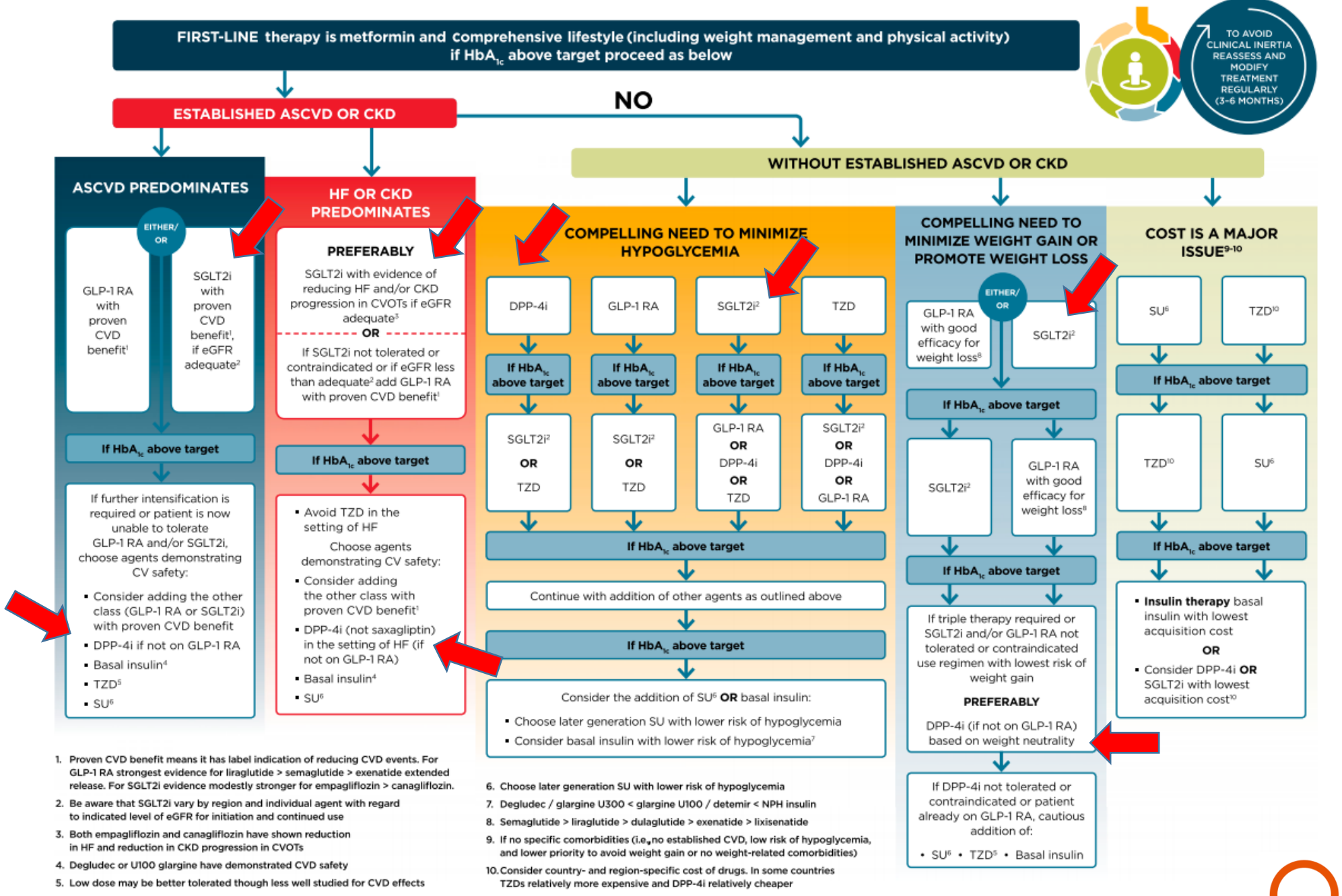
DPP4 inhibitors: Mechanism of action



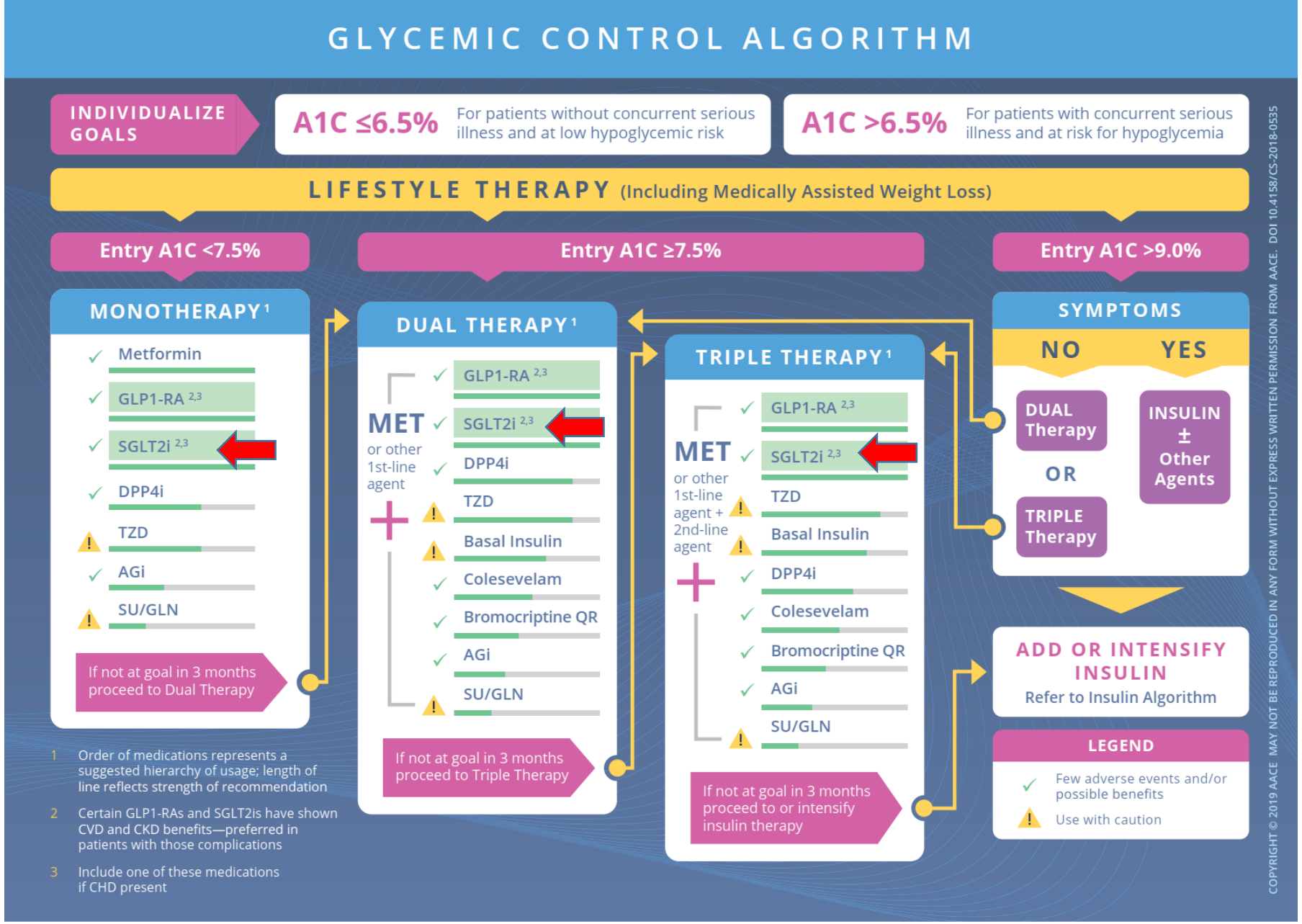
Adapted from Drucker. Expert Opin Invest Drugs 2003;12:87–100 and Ahrén Curr Diab Rep. 2003;3:365–372.

Paglino® Empagliflozin



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

2019 American Diabetes Association Standards Of Diabetes Medical Care



American Association of Clinical Endocrinologists/American College of Endocrinology

Type 2 Diabetes management algorithm

Recommendations for the treatment of patients with diabetes to reduce heart failure risk

2019 European society of cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

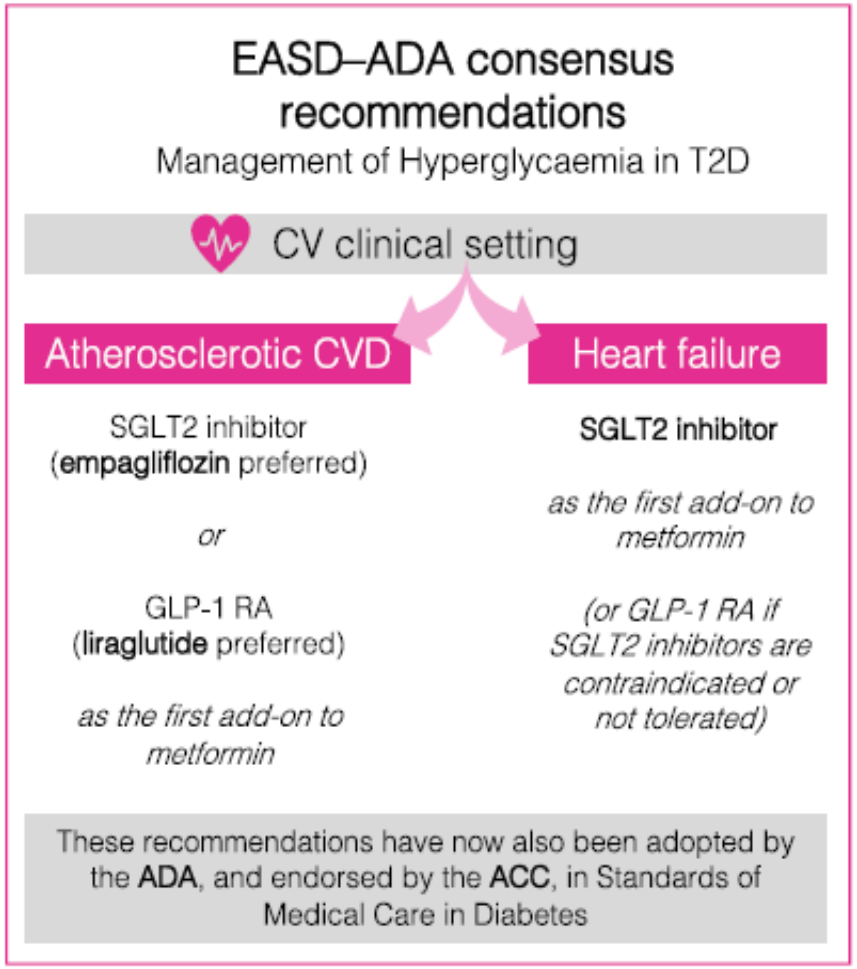
Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended.[306,311,496]	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m^2.[2,484,485]	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[158,176,297,299,300,303,498,499]	IIb	A
The DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[293,294]	IIb	B
Insulin may be considered in patients with advanced systolic HFrEF.[500]	IIb	C
Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk of HF (or with previous HF).[279,491–493]	III	A
The DPP4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization, and is not recommended for DM treatment in patients at risk of HF (or with previous HF).[291]	III	B

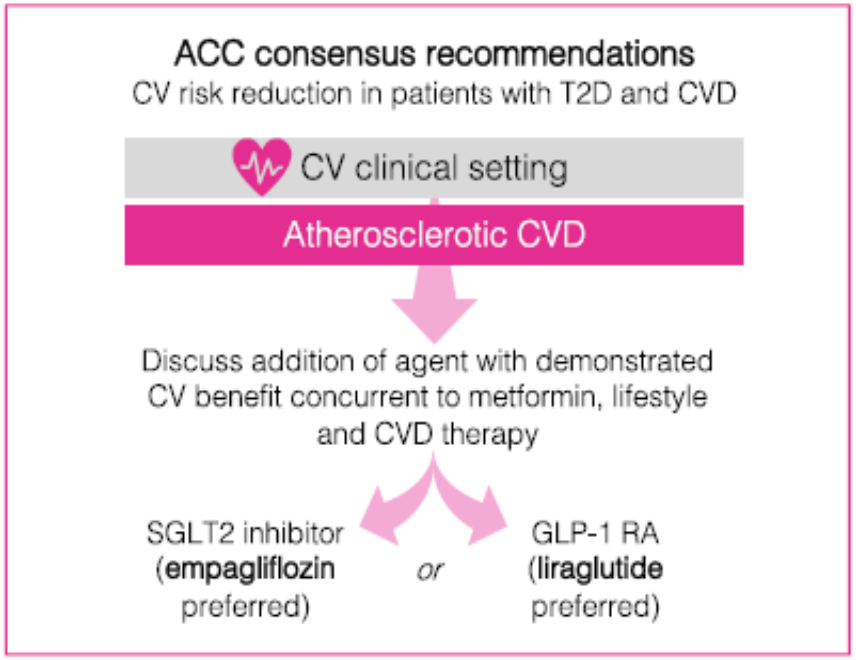
Recommendations for the prevention and management of CKD in patients with diabetes

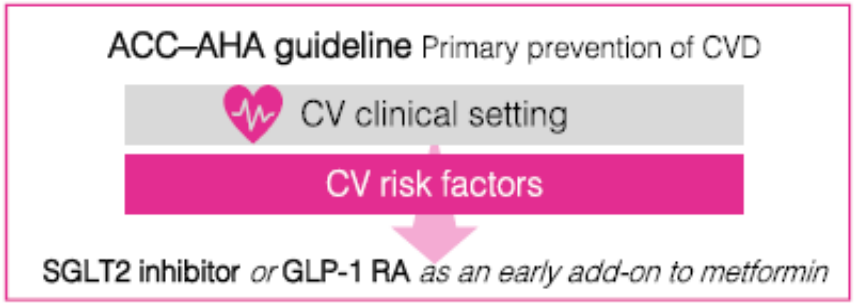
2019 European society of cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

Recommendations	Class[a]	Level[b]
It is recommended that patients with DM are screened annually for kidney disease by assessment of eGFR and urinary albumin:creatinine ratio.[543]	I	A
Tight glucose control, targeting HbA1c (<7.0% or <53 mmol/mol) is recommended to decrease microvascular complications in patients with DM.[145–149]	I	A
It is recommended that patients with hypertension and DM are treated in an individualized manner, targeting a SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years) the SBP goal is to a range of 130–139 mmHg.[155,159,181–183]	I	A
A RAAS blocker (ACEI or ARB) is recommended for the treatment of hypertension in patients with DM, particularly in the presence of proteinuria, microalbuminuria, or LVH.[167–170]	I	A
Treatment with an SGLT2 inhibitor (empagliflozin, canagliflozin, or dapagliflozin) is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to <90 mL/min/1.73 m^2).[306,311,313,496]	I	B
Treatment with the GLP1-RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints, and should be considered for DM treatment if eGFR is >30 mL/min/1.73m^2.[176,299]	IIa	B

SGLT2 inhibitors—what do guidelines say







Schernthaner et al. Cardiovasc Diabetol (2019) 18:115; 10.1186/s12933-019-0920-3

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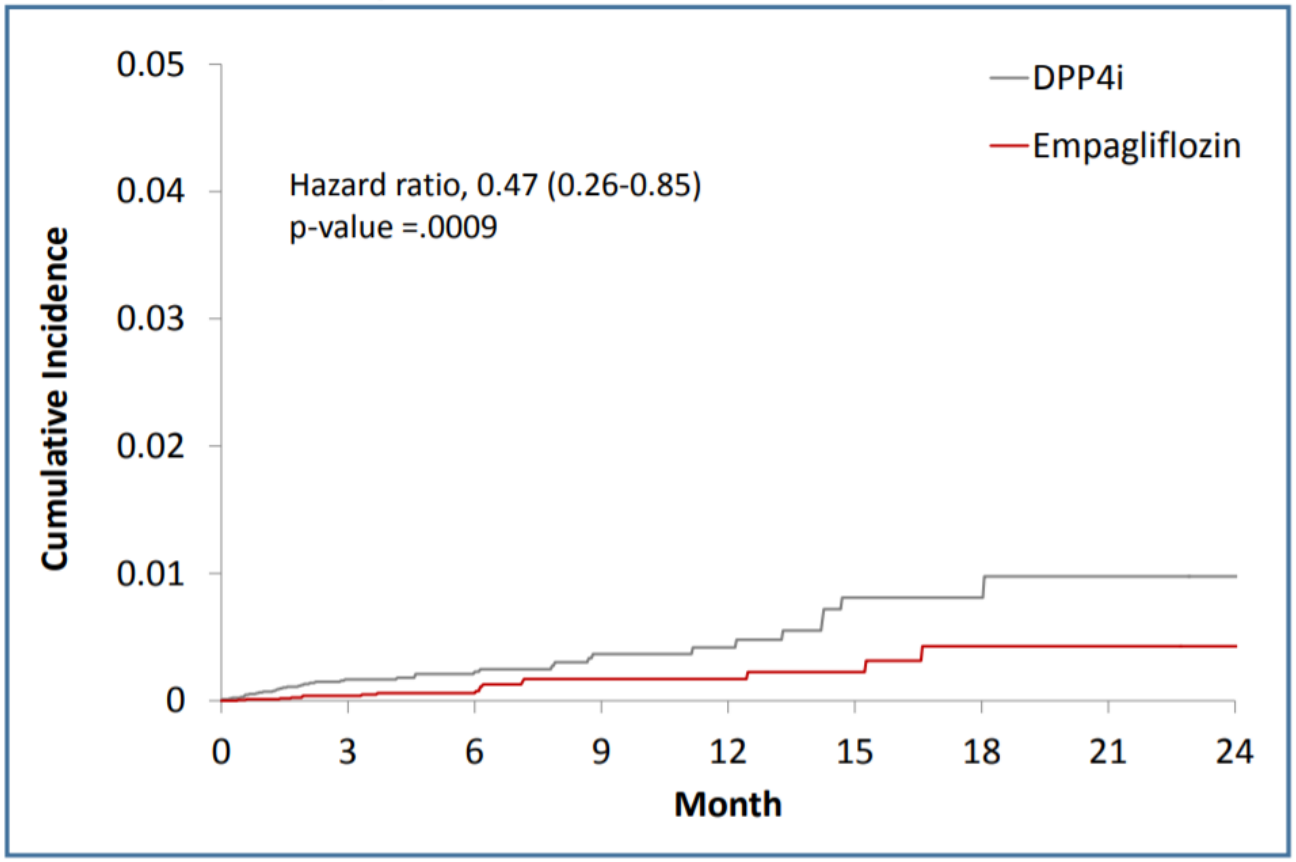
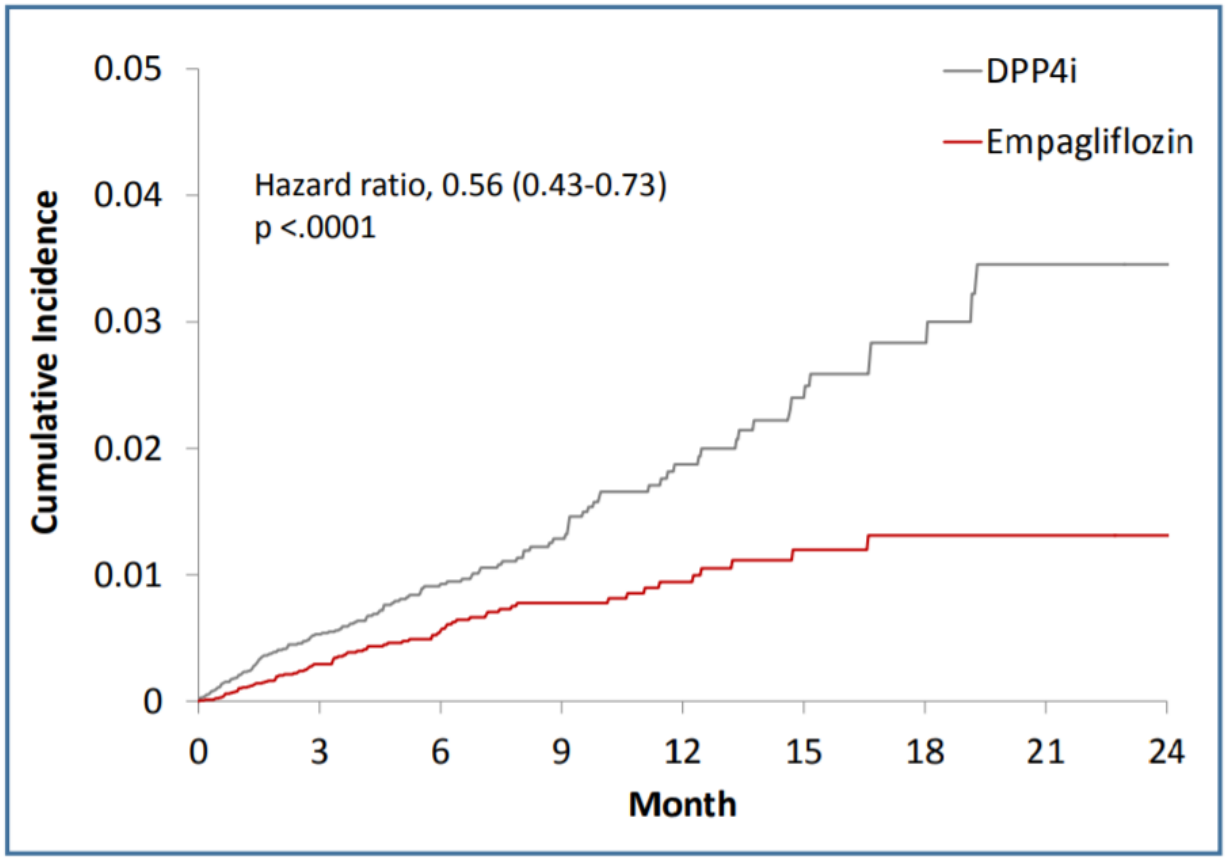
HHF risk

[redacted] PS-matched Kaplan-Meier curve for cumulative incidence of HHF-specific since treatment initiation

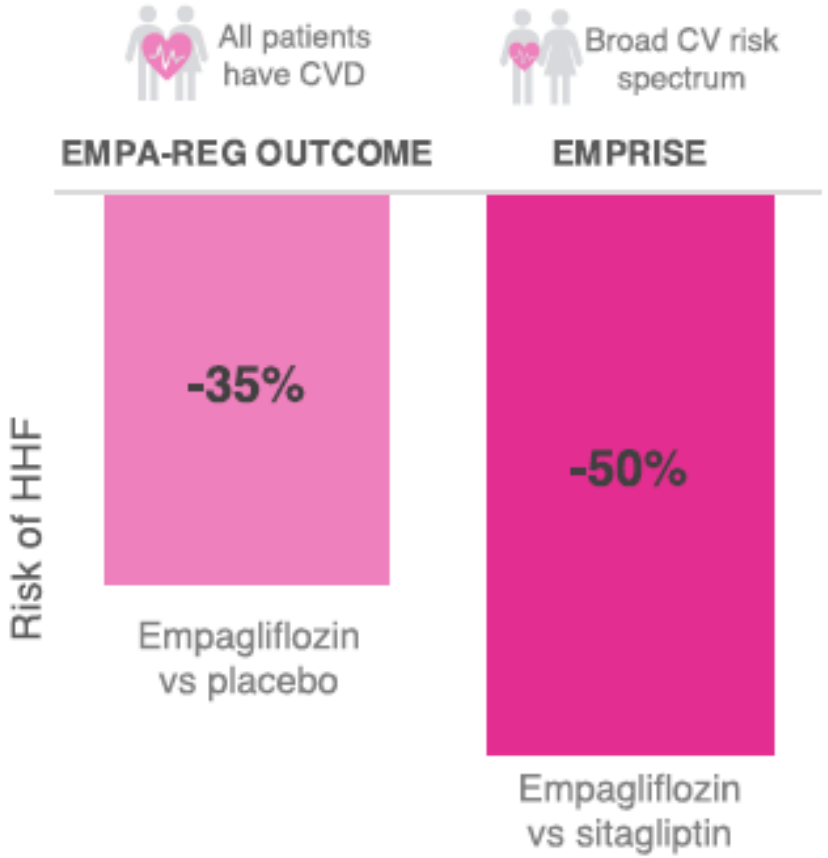


[redacted] PS-matched Kaplan-Meier curve for cumulative incidence of HHF-broad since treatment initiation



Schernthaner et al. Cardiovasc Diabetol (2019) 18:115; 10.1186/s12933-019-0920-3

Results



The relative risk reduction of HHF in the first interim analysis of EMPRISE was consistent with that seen in EMPA-REG OUTCOME, confirming the robustness of empagliflozin's HHF benefit in routine clinical practice, in a population with a broader CV risk profile, and against a DPP-4 inhibitor as an active comparator

Schernthaner et al. Cardiovasc Diabetol (2019) 18:115; 10.1186/s12933-019-0920-3

Paglino® Empagliflozin

CV death

- While hospitalization for heart failure benefit seems to be a consistent observation with SGLT2 inhibitors in patients with T2D, **empagliflozin** remains the only SGLT2 inhibitor proven to reduce CV death (38% reduction in EMPA-REG OUTCOME).
- Although **canagliflozin** did show a trend towards a reduction in both the CANVAS Program and CREDENCE, this did not meet significance, while there was no apparent effect with **dapagliflozin** in DECLARETIMI.
- **Empagliflozin** is also the only agent in the class proven to reduce death by any cause, with a 32% reduction in EMPA-REG OUTCOME

Schernthaner et al. Cardiovasc Diabetol (2019) 18:115; 10.1186/s12933-019-0920-3

THE LANCET
Diabetes & Endocrinology

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Sky's the Limit

Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial

Michael Roden, Jianping Weng*, Jens Eilbracht, Bruno Delafont, Gabriel Kim, Hans J Woerle, Uli C Broedl, on behalf of the EMPA-REG MONO trial investigators†*

Lancet Diabetes Endocrinol
۲۰۱۳; ۱: ۲۰۸–۱۹

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Empagliflozin

Study Design and participants

24 week, double-blind, parallel-group, randomized phase 3 trial, enrolled patients at 124 trial sites

- **89% Completed trial**

Lancet Diabetes Endocrinol
۲۰۱۳;۱:۲۰۸–۱۹

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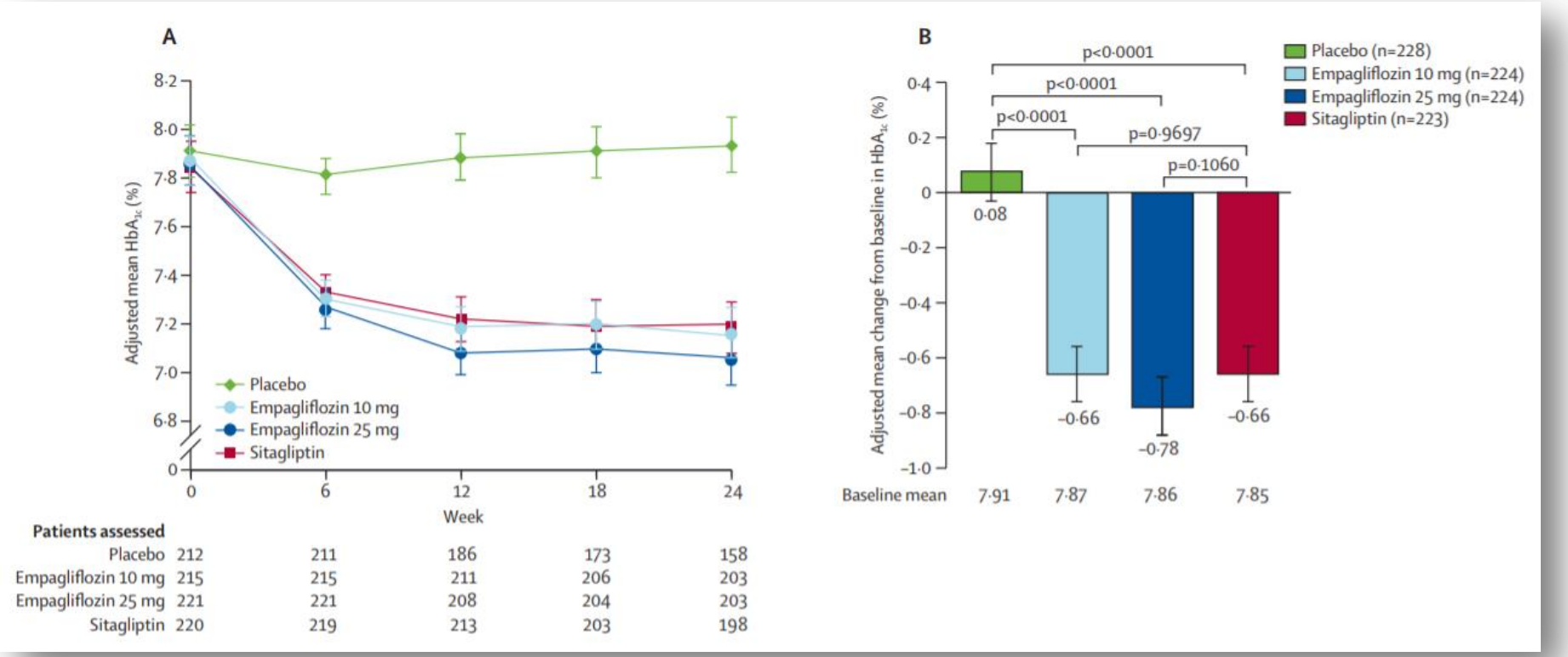
Empagliflozin

Results: HbA1C



In patients with HbA1c concentrations of at least 8·5% at baseline (mean baseline ~9·1% in all treatment groups), both doses of empagliflozin were associated with greater reductions in HbA1c at week 24 than with sitagliptin.

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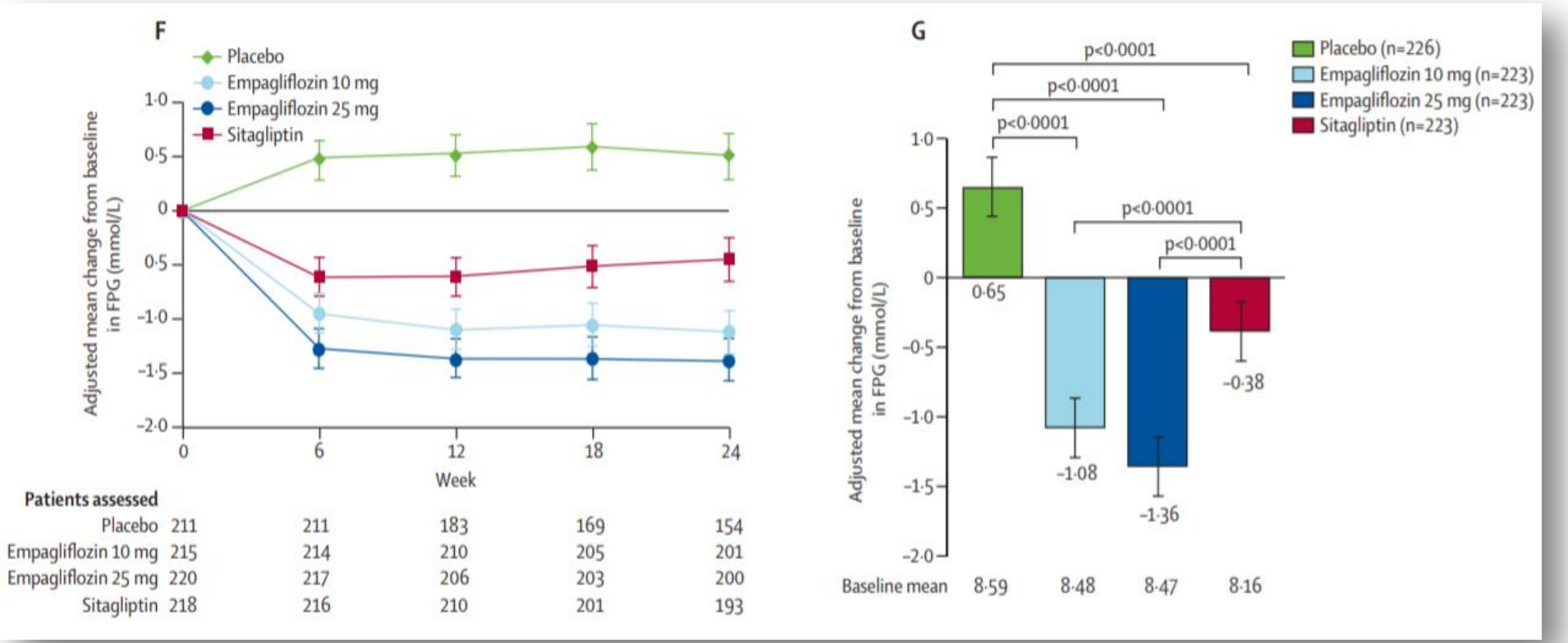
Results: FPG



At week 24, changes from baseline in FPG were greater with empagliflozin 10 mg and empagliflozin 25 mg than they were with placebo or sitagliptin

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Empagliflozin

Results: body weight

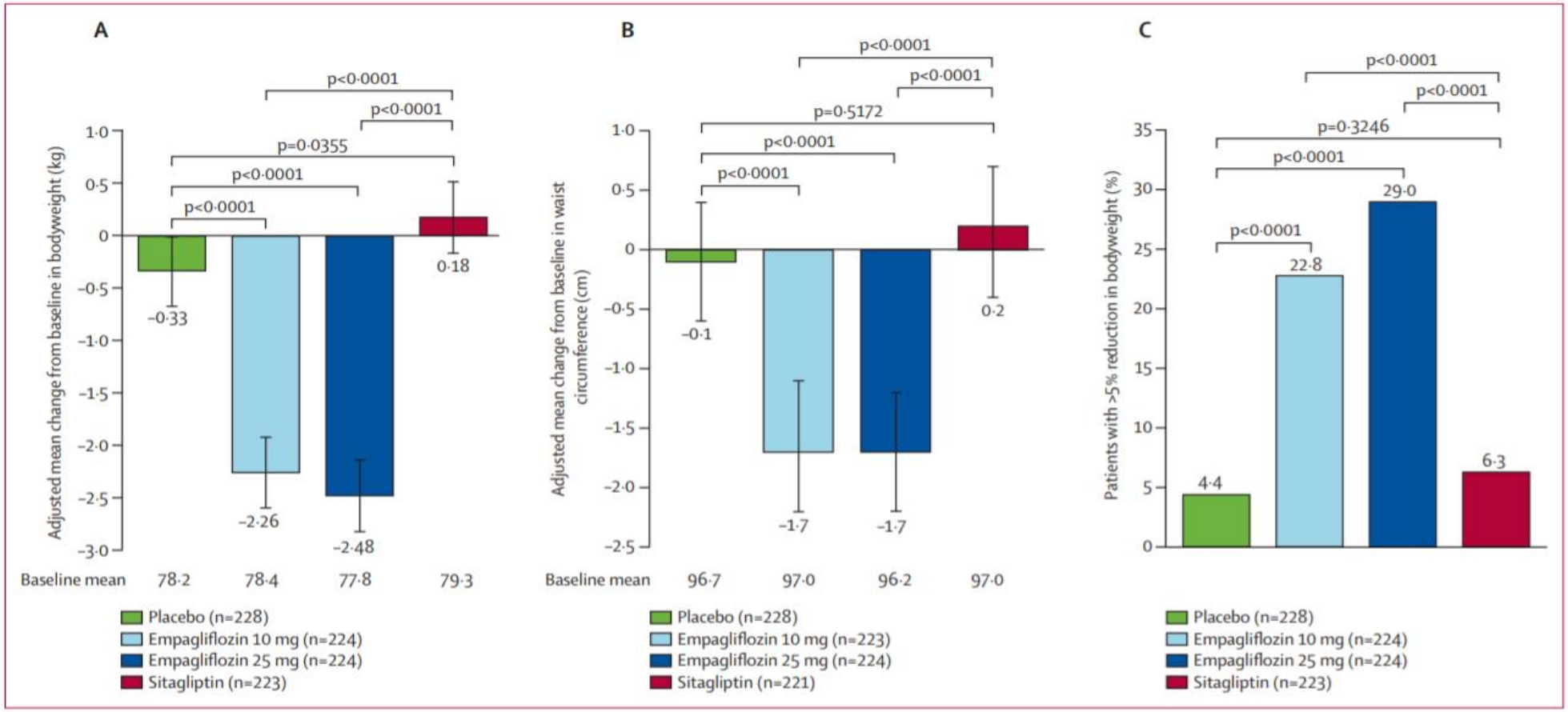
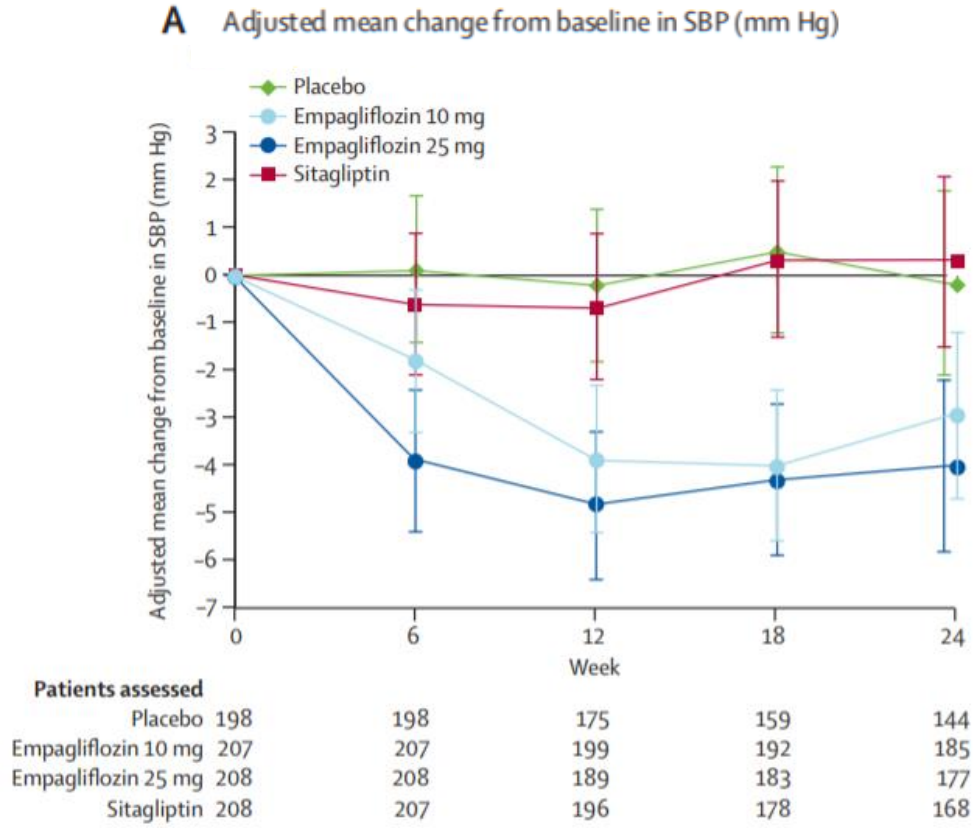
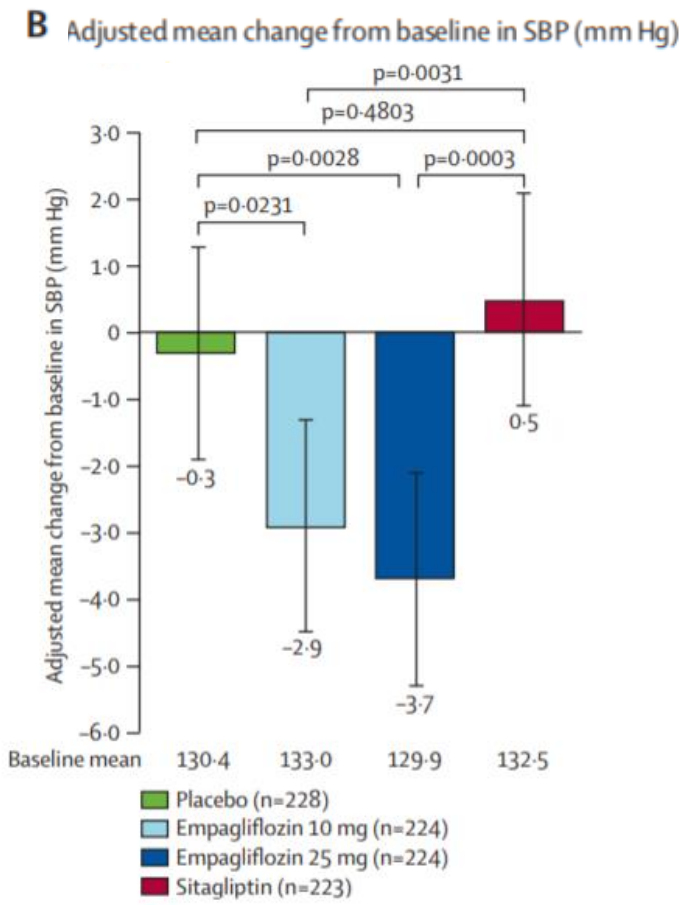
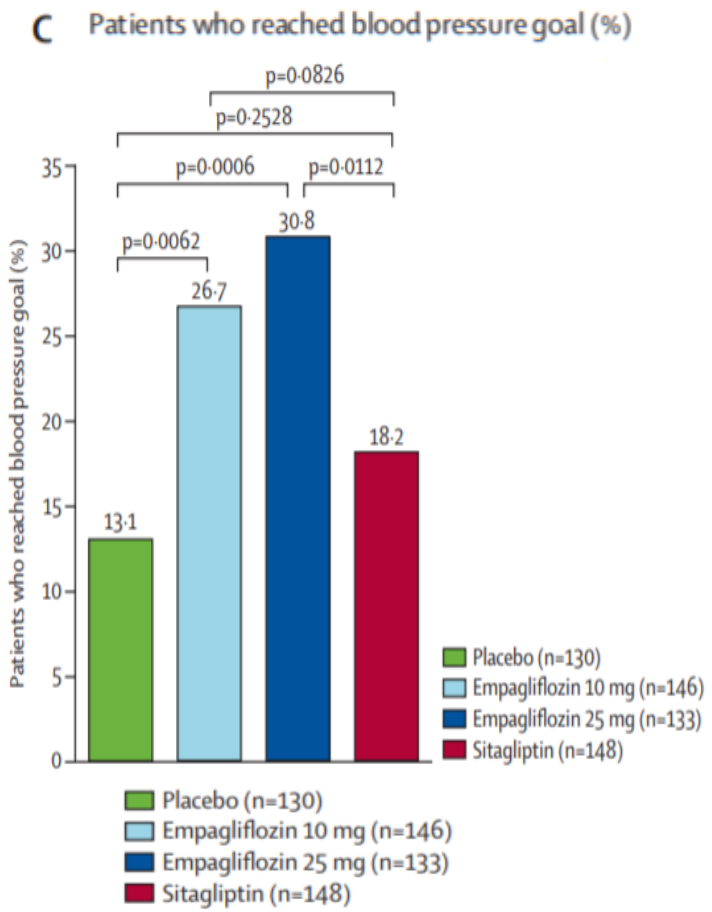


Figure 3: **Changes in bodyweight and waist circumference in the full analysis set**
Error bars show 95% CIs. (A) Adjusted mean change from baseline in bodyweight at week 24 (ANCOVA, LOCF). (B) Adjusted mean change from baseline in waist circumference at week 24 (ANCOVA, LOCF). (C) Proportion of patients with >5·0% reduction in bodyweight at week 24 (logistic regression with non-completers regarded as failures). LOCF=last observation carried forward.

Results: SBP


A
Adjusted mean change from baseline in SBP (mm Hg)
Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg
Sitagliptin
Adjusted mean change from baseline in SBP (mm Hg)
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
0
6
12
18
24
Week
Patients assessed
Placebo 198 198 175 159 144
Empagliflozin 10 mg 207 207 199 192 185
Empagliflozin 25 mg 208 208 189 183 177
Sitagliptin 208 207 196 178 168


B
Adjusted mean change from baseline in SBP (mm Hg)
p=0·0031
p=0·4803
p=0·0028
p=0·0003
p=0·0231
Adjusted mean change from baseline in SBP (mm Hg)
3·0
2·0
1·0
0
-1·0
-2·0
-3·0
-4·0
-5·0
-6·0
-0·3
-2·9
-3·7
0·5
Baseline mean 130·4 133·0 129·9 132·5
Placebo (n=228)
Empagliflozin 10 mg (n=224)
Empagliflozin 25 mg (n=224)
Sitagliptin (n=223)


C
Patients who reached blood pressure goal (%)
p=0·0826
p=0·2528
p=0·0006
p=0·0112
p=0·0062
Patients who reached blood pressure goal (%)
35
30
25
20
15
10
5
0
13·1
26·7
30·8
18·2
Placebo (n=130)
Empagliflozin 10 mg (n=146)
Empagliflozin 25 mg (n=133)
Sitagliptin (n=148)
Placebo (n=130)
Empagliflozin 10 mg (n=146)
Empagliflozin 25 mg (n=133)
Sitagliptin (n=148)

Orchid Pharmed
Sky's the Limit

Long-Term Safety and Efficacy of Empagliflozin, Sitagliptin, and Metformin

An active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes

ELE FERRANNINI, MD[1]
ANDREAS BERK, PHD[2]
STEFAN HANTEL, PHD[3]
SABINE PINNETTI, MD[3]
THOMAS HACH, MD[4]
HANS J. WOERLE, MD[4]
ULI C. BROEDL, MD[4]

[redacted]

Diabetes Care 36:4015–4021, 2013

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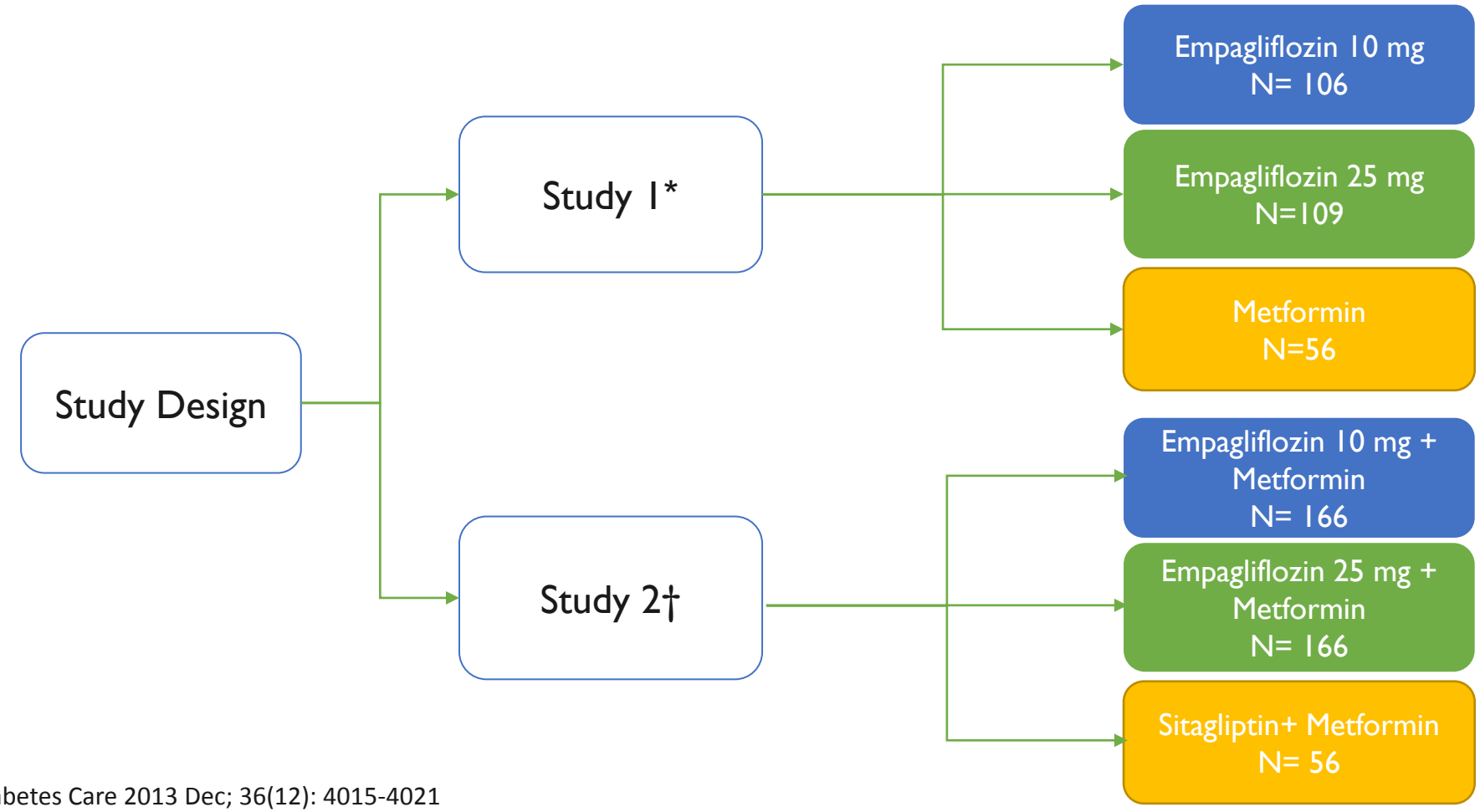
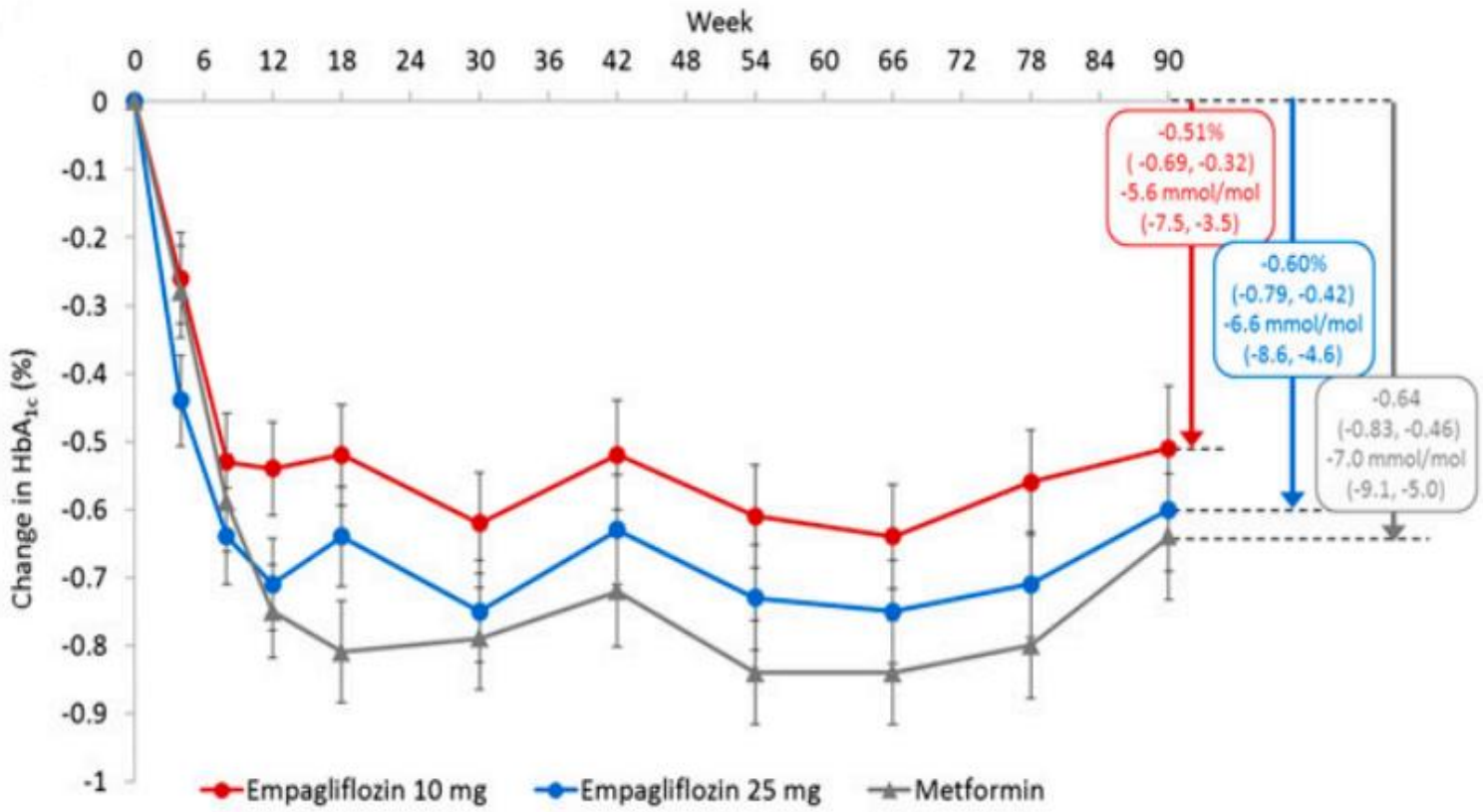
Empagliflozin

Study Design and participants



Diabetes Care 2013 Dec; 36(12): 4015-4021

Results: HbA1C



In the monotherapy groups:

Empagliflozin 10 mg : 31.9%

Empagliflozin 25 mg : 32.1%

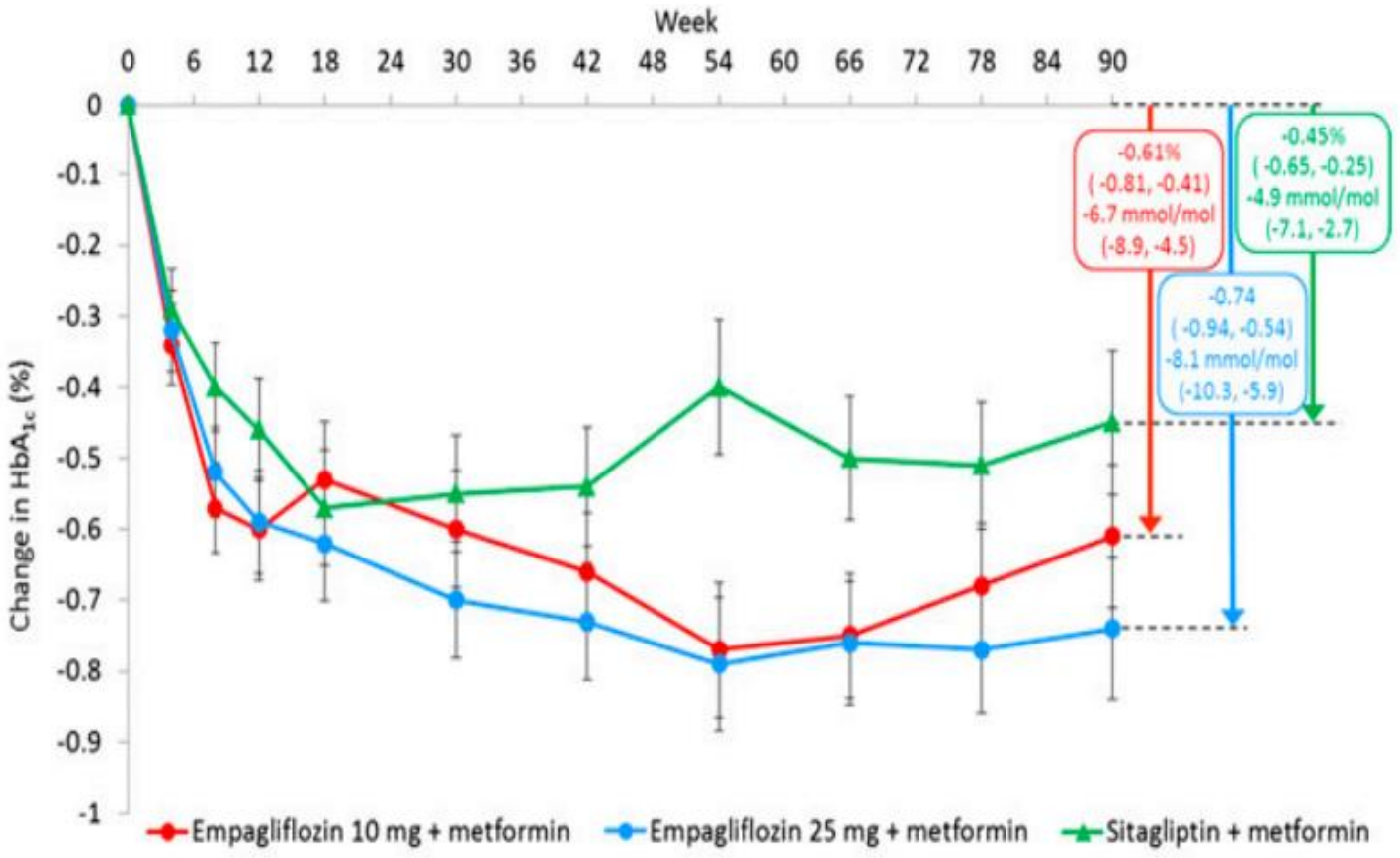
Metformin: 31.0%

of patients reached HbA1c: 7% at week 78

Diabetes Care 2013

Paglino®
Empagliflozin

Results: HbA1C



Of patients on background metformin therapy:

Empagliflozin 10 mg : 27.0%

Empagliflozin 25 mg : 44.6%

Sitagliptin 100: 36.8%

of patients reached HbA1c: 7% at week 78.

Diabetes Care 2(

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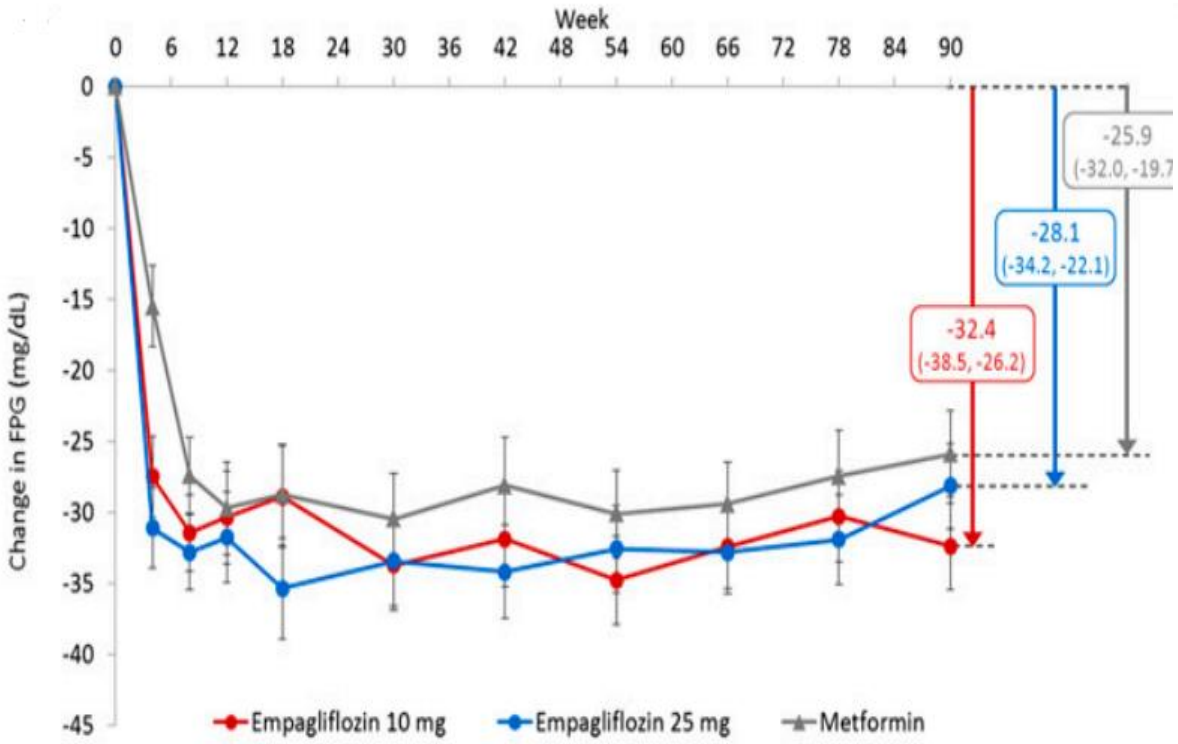
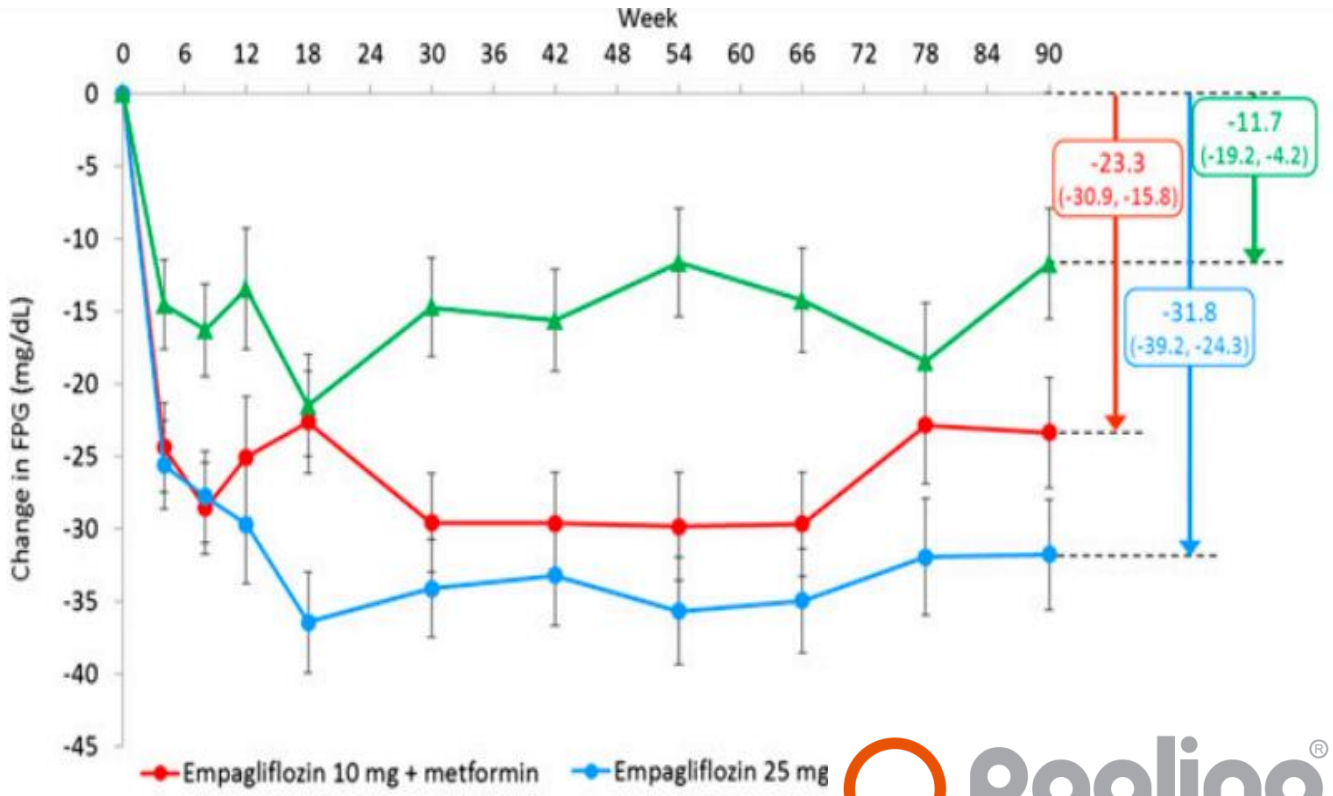
Empagliflozin

Results: FPG





Diabetes Care 2013 Dec; 36(12): 4015-4021

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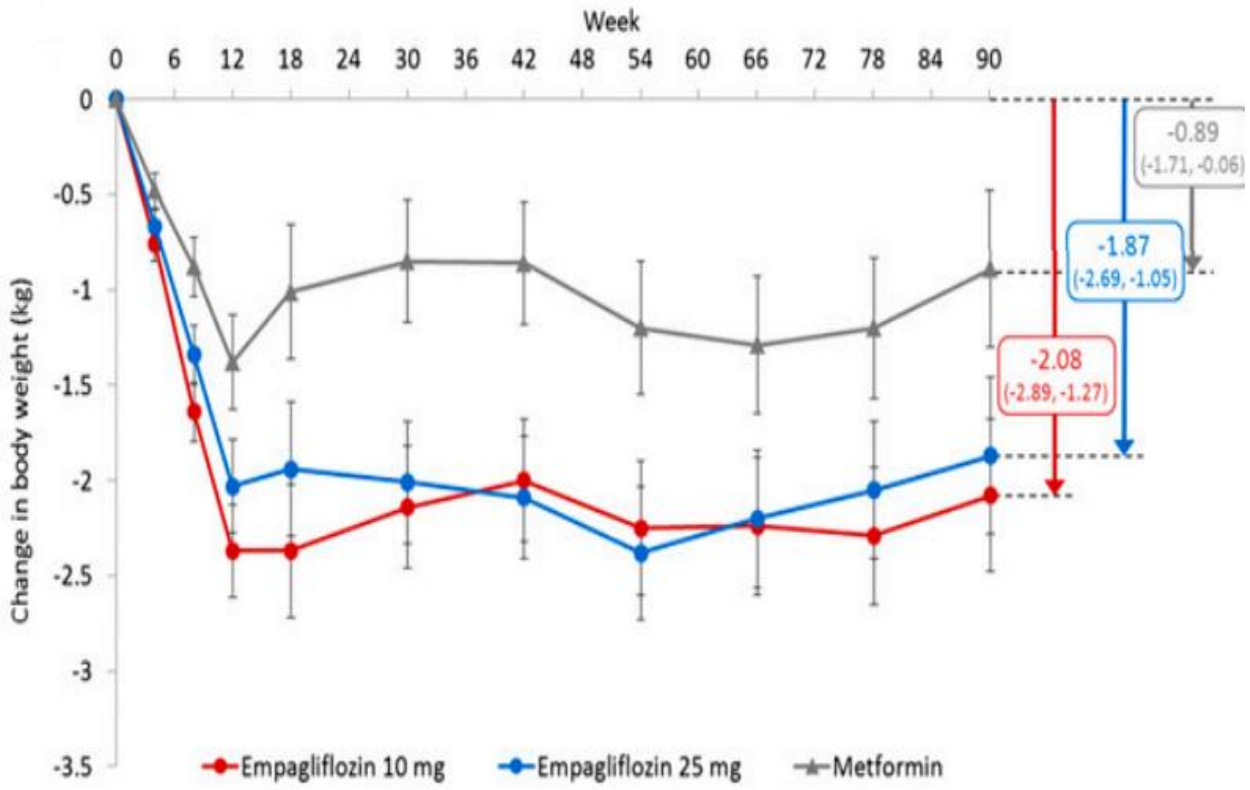
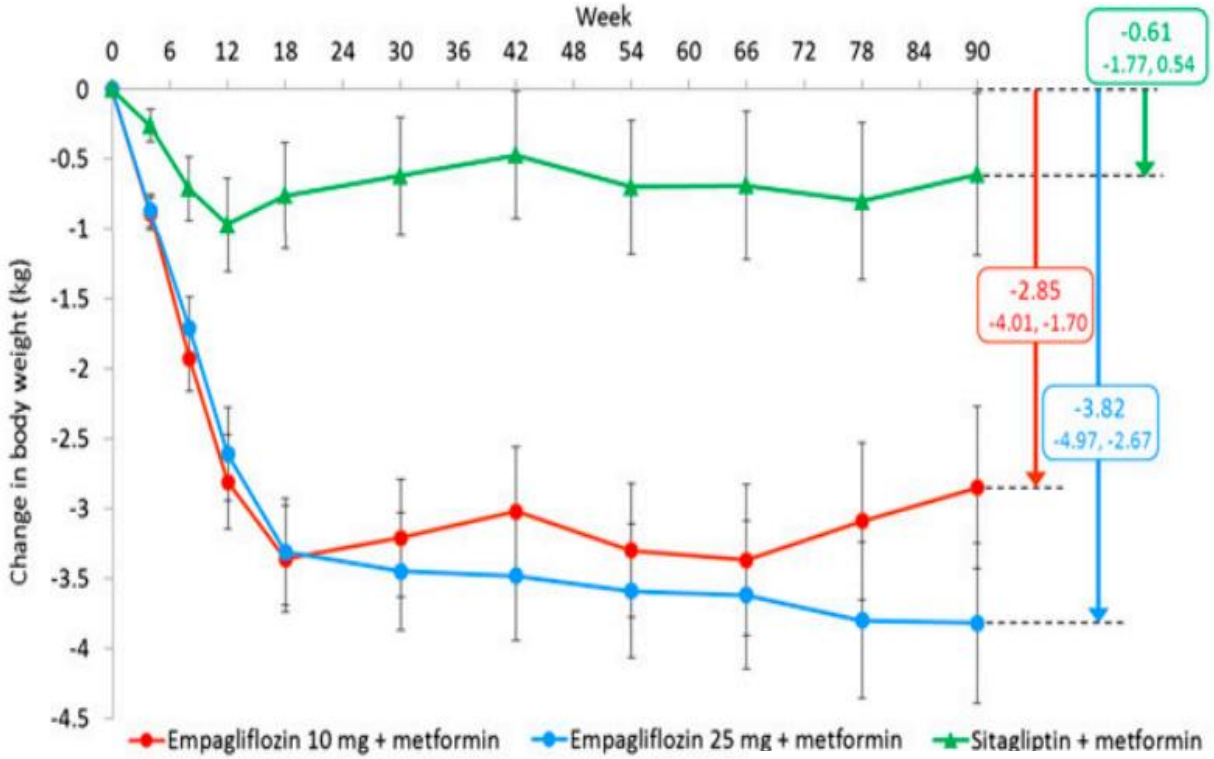
Empagliflozin

Results: Body weight





Diabetes Care 2013 Dec; 36(12): 4015-4021

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Empagliflozin

Results: Safety

- ✓ **More than 90% of AEs were mild or moderate in intensity, as assessed by the investigator.**

- ✓ **Severe AEs were reported in 2.4–6.6% of patients in empagliflozin groups, 7.1% of patients on metformin, and 8.9% of patients on sitagliptin as add-on to metformin.**

Diabetes Care 2013 Dec; 36(12): 4015-4021

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Empagliflozin

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2019

 DOI 10.4158/CS-2018-0535

TABLE OF CONTENTS

COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

 DOI 10.4158/CS-2018-0535

PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)
2.	Avoid hypoglycemia
3.	Avoid weight gain
4.	Individualize all glycemic targets (A1C, FPG, PPG)
5.	Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable
6.	Therapy choices are affected by initial A1C, duration of diabetes, and obesity status
7.	Choice of therapy reflects cardiac, cerebrovascular, and renal status
8.	Comorbidities must be managed for comprehensive care
9.	Get to goal as soon as possible—adjust at ≤3 months until at goal
10.	Choice of therapy includes ease of use and affordability
11.	A1C ≤6.5% for those on any insulin regimen as long as CGM is being used

 DOI 10.4158/CS-2018-0535

LIFESTYLE THERAPY

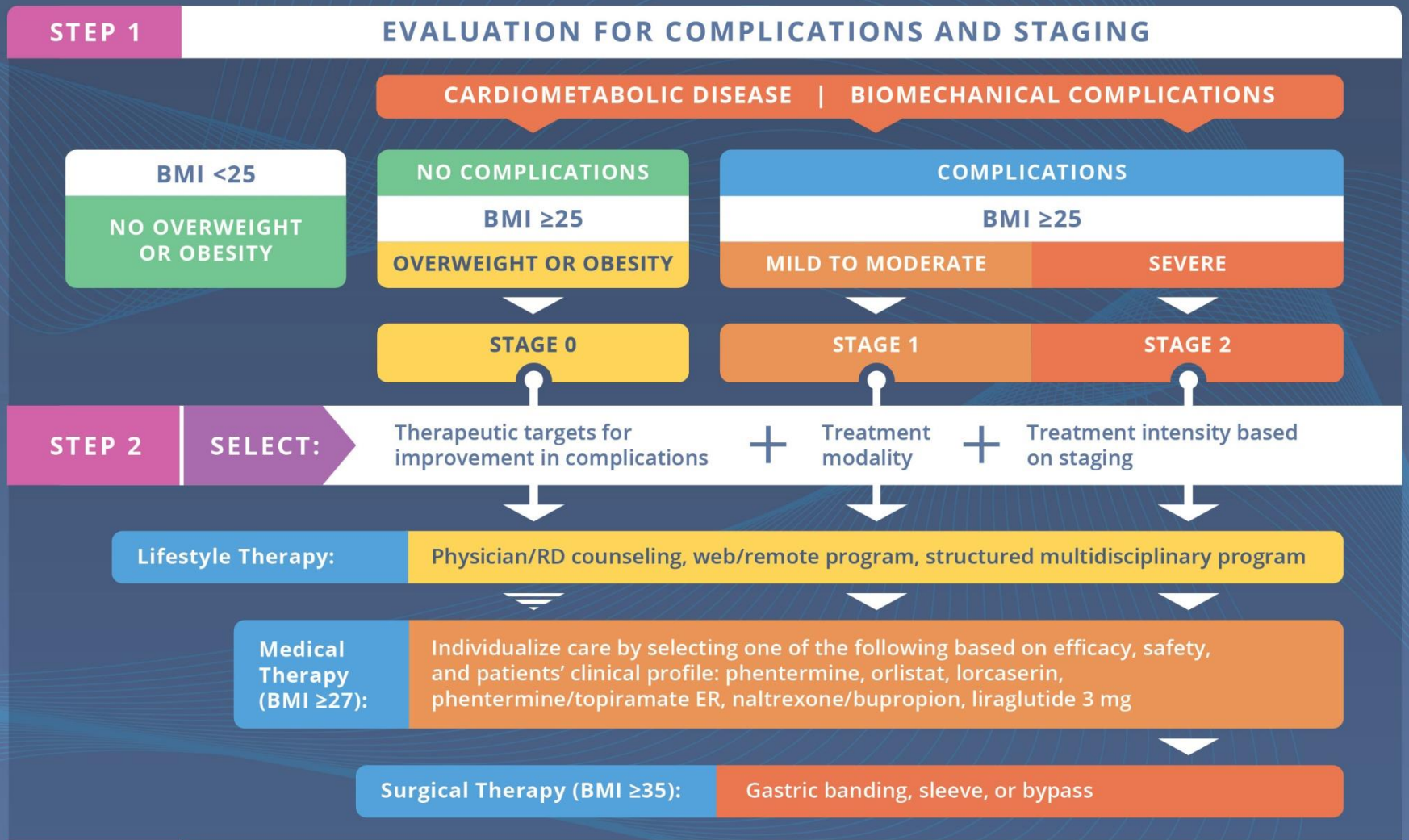
RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

Nutrition	• Maintain optimal weight • Calorie restriction (if BMI is increased) • Plant-based diet; high polyunsaturated and monounsaturated fatty acids	• Avoid *trans* fatty acids; limit saturated fatty acids	• Structured counseling • Meal replacement
Physical Activity	• 150 min/week moderate exertion (e.g., walking, stair climbing) • Strength training • Increase as tolerated	• Structured program • Wearable technologies	• Medical evaluation/ clearance • Medical supervision
Sleep	• About 7 hours per night • Basic sleep hygiene	• Screen OSA • Home sleep study	• Referral to sleep lab
Behavioral Support	• Community engagement • Alcohol moderation	• Discuss mood with HCP	• Formal behavioral therapy
Smoking Cessation	• No tobacco products	• Nicotine replacement therapy	• Referral to structured program

 DOI 10.4158/CS-2018-0535

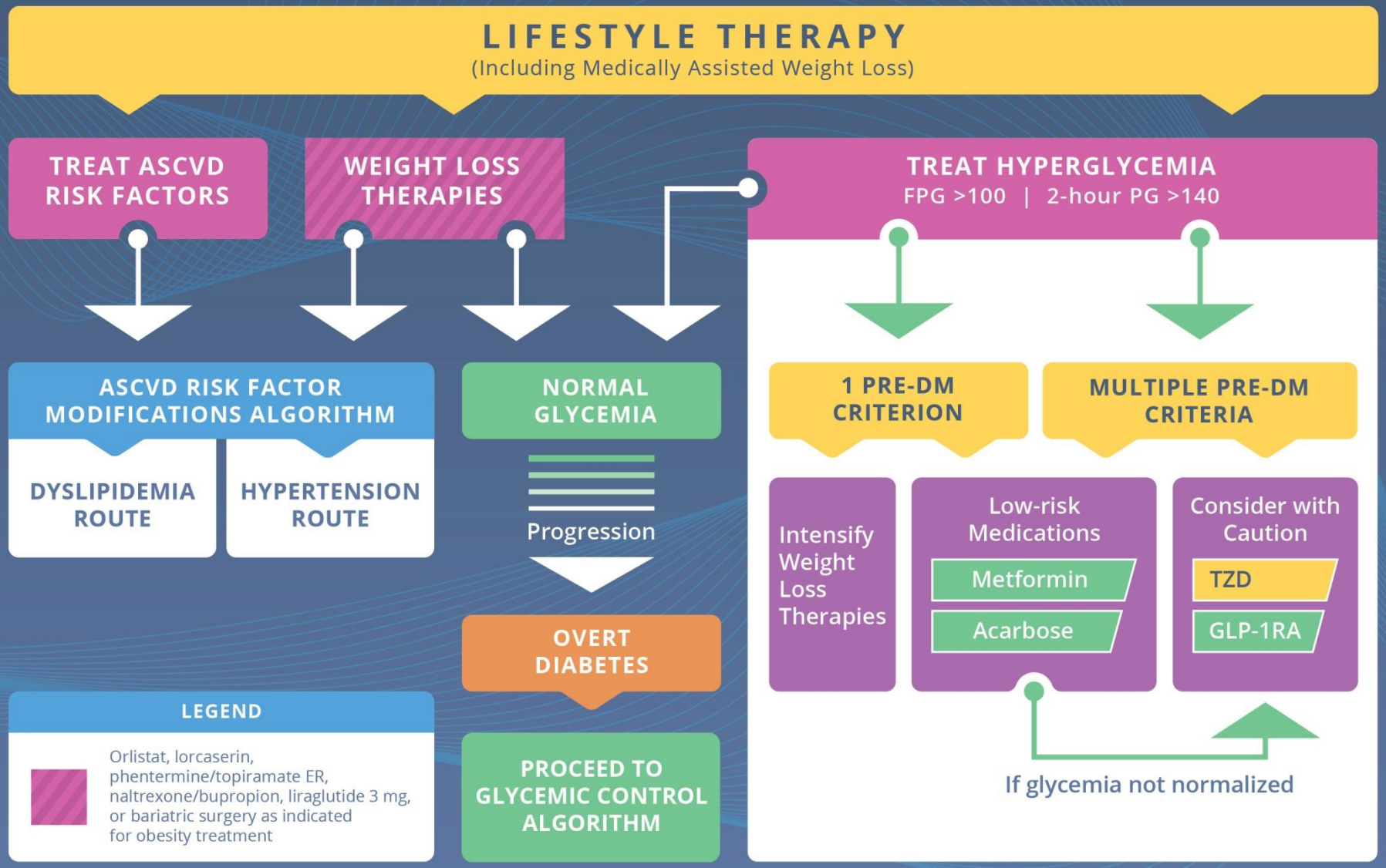
COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESITY



 DOI 10.4158/CS-2018-0535

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



 DOI 10.4158/CS-2018-0535

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:
- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C: Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG: Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P: Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:** Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

 DOI 10.4158/CS-2018-0535

GLYCEMIC CONTROL ALGORITHM

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

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C <7.5%

MONOTHERAPY[1]

- ✓ Metformin
- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥7.5%

DUAL THERAPY[1]

MET or other 1st-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ✓ DPP4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY[1]

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP1-RA [2,3]
- ✓ SGLT2i [2,3]
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ DPP4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C >9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

2 Certain GLP1-RAs and SGLT2is have shown CVD and CKD benefits—preferred in patients with those complications

3 Include one of these medications if CHD present

PROGRESSION OF DISEASE

 DOI 10.4158/CS-2018-0535

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 GLP1-RA

Or SGLT2i
Or DPP4i

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%

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PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	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	Contra-indicated if eGFR <30 mL/min/1.73 m^2	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/min/1.73 m^2 Genital Mycotic Infections Possible CKD Benefit	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
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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2019 European society of Cardiology (ESC) Guidelines on diabetes, pre-diabetes, and CVD

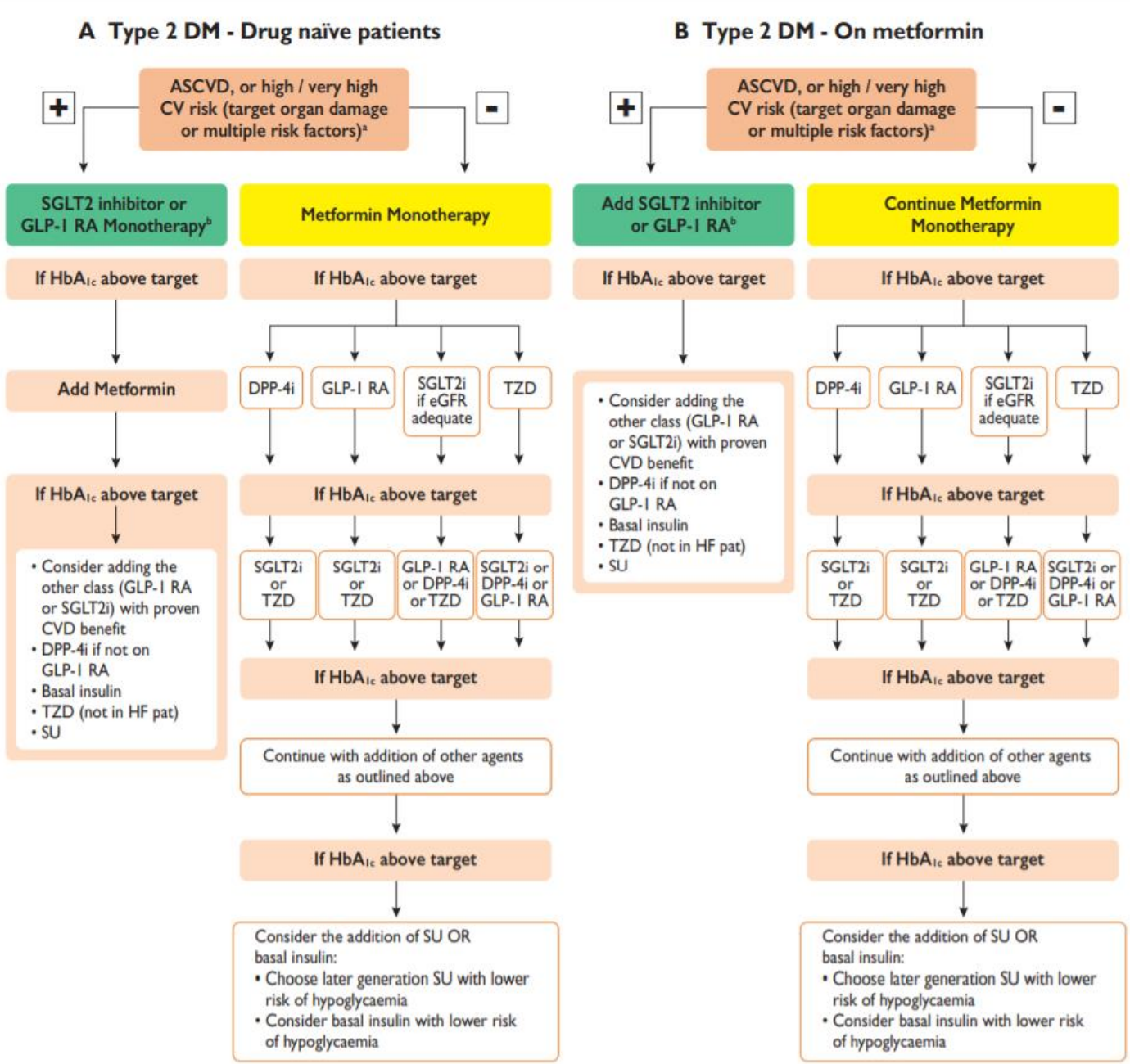
What's new in 2019 ESC guidelines?

Change in recommendations	
2013	**2019**
BP targets	
BP target <140/85 mmHg is recommended for all	Individualized BP targets are recommended SBP to 130 mmHg and, if well tolerated, <130 mmHg, but not <120 mmHg In older people (>65 years) target SBP to a range of 130 - 139 mmHg DBP to <80 mmHg but not <70 mmHg
	On-treatment SBP to <130 mmHg should be considered for patients at high risk of cerebrovascular events or diabetic kidney disease
Lipid targets	
In DM at high CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) In DM at very high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) is recommended	In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended
Antiplatelet therapy	
Aspirin for primary prevention is not recommended in DM at low CVD risk	Aspirin (75 - 100 mg/day) for primary prevention may be considered in patients with DM at very high/high risk in the absence of clear contraindications
	Aspirin for primary prevention is not recommended in patients with DM at moderate CV risk
Glucose-lowering treatment	
Metformin should be considered as first-line therapy in patients with DM	Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk
Revascularization	
DES rather than BMS is recommended in DM	Same techniques are recommended in patients with and without DM (see 2018 ESC/EACTS myocardial revascularization Guidelines)
PCI may be considered as an alternative to CABG in patients with DM and less complex CAD (SYNTAX score ≤22)	One- or two-vessel CAD, no proximal LAD
	CABG / PCI
	One- or two-vessel CAD, proximal LAD
	CABG / PCI
	Three-vessel CAD, low complexity
	CABG / PCI
	Left main CAD, low complexity
	CABG / PCI
CABG recommended in complex CAD (SYNTAX score >22)	Three-vessel CAD, intermediate or high complexity
	CABG / PCI
	Left main CAD, intermediate complexity
	CABG / PCI
	High complexity
	CABG / PCI
Management of arrhythmias	
Oral anticoagulation in AF (paroxysmal or persistent)	
VKAs or NOACs (e.g. dabigatran, rivaroxaban, or apixaban) are recommended	It is recommended to give preference to NOACs (e.g. dabigatran, rivaroxaban, apixaban, or edoxaban)

Ia IIa IIb III

Recommendations for lifestyle modifications in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM.[27,117]	I	A
Lifestyle intervention is recommended to delay or prevent the conversion of pre-DM states, such as IGT, to T2DM.[85,86]	I	A
Reduced calorie intake is recommended for lowering excessive body weight in individuals with pre-DM and DM.[c] [82,83,89,90]	I	A
Moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise, for ≥150 min/week is recommended for the prevention and control of DM, unless contraindicated, such as when there are severe comorbidities or a limited life expectancy.[d] [110,111–113,119]	I	A
A Mediterranean diet, rich in polyunsaturated and monounsaturated fats, should be considered to reduce CV events.[96,97]	IIa	B
Vitamin or micronutrient supplementation to reduce the risk of DM, or CVD in patients with DM, is not recommended.[79,120]	III	B


A Type 2 DM - Drug naïve patients
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
SGLT2 inhibitor or GLP-1 RA Monotherapy[b]
Metformin Monotherapy
If HbA1c above target
Add Metformin
If HbA1c above target
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin
• TZD (not in HF pat)
• SU
If HbA1c above target
DPP-4i
GLP-1 RA
SGLT2i if eGFR adequate
TZD
If HbA1c above target
SGLT2i or TZD
SGLT2i or TZD
GLP-1 RA or DPP-4i or TZD
SGLT2i or DPP-4i or GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia
B Type 2 DM - On metformin
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
Add SGLT2 inhibitor or GLP-1 RA[b]
Continue Metformin Monotherapy
If HbA1c above target
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin
• TZD (not in HF pat)
• SU
If HbA1c above target
DPP-4i
GLP-1 RA
SGLT2i if eGFR adequate
TZD
If HbA1c above target
SGLT2i or TZD
SGLT2i or TZD
GLP-1 RA or DPP-4i or TZD
SGLT2i or DPP-4i or GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

Recommendations for the treatment of patients with diabetes to reduce heart failure risk

2019 European society of cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

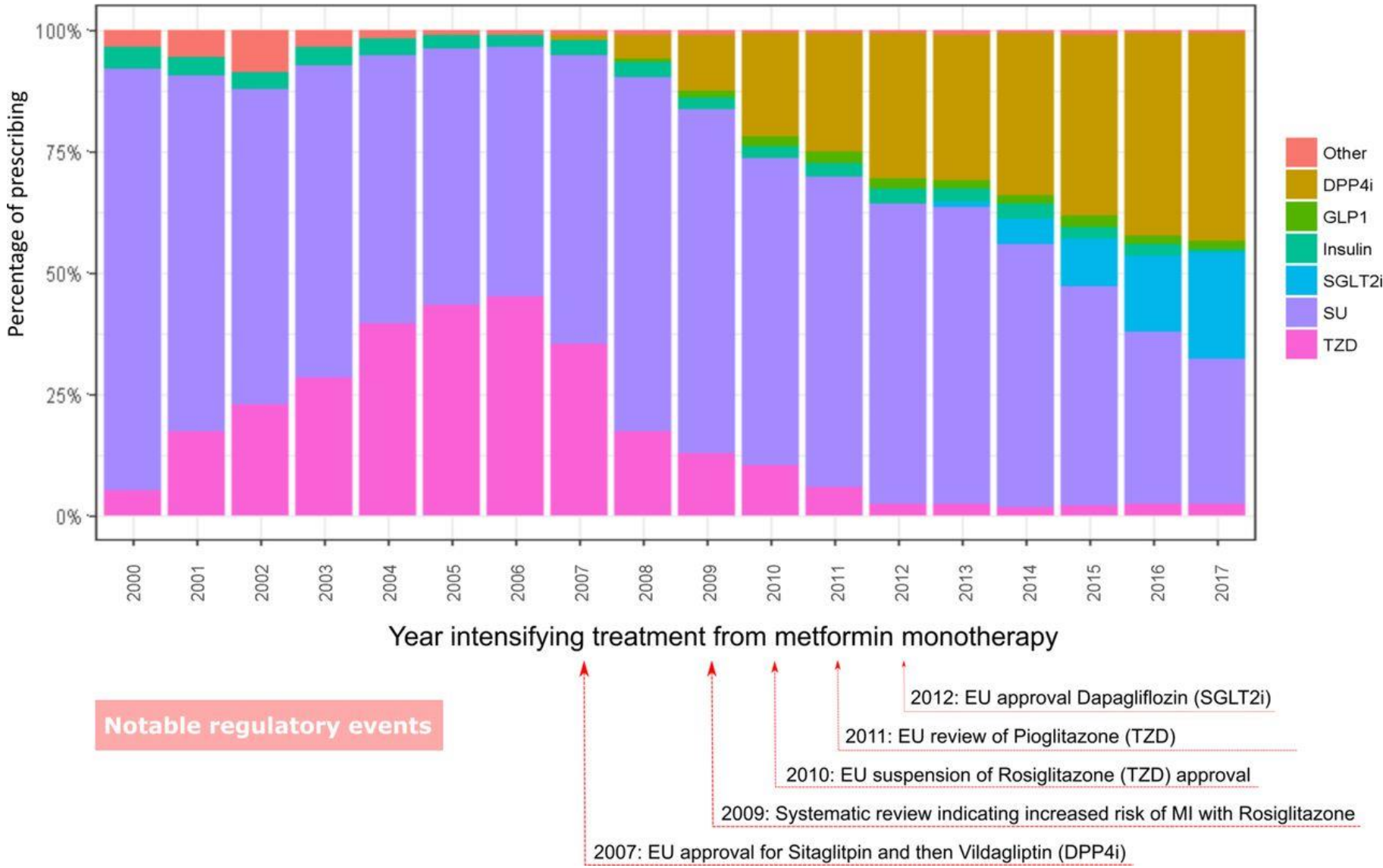
Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended.[306,311,496]	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m^2.[2,484,485]	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[158,176,297,299,300,303,498,499]	IIb	A
The DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[293,294]	IIb	B
Insulin may be considered in patients with advanced systolic HFrEF.[500]	IIb	C
Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk of HF (or with previous HF).[279,491–493]	III	A
The DPP4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization, and is not recommended for DM treatment in patients at risk of HF (or with previous HF).[291]	III	B

Recommendations for the prevention and management of CKD in patients with diabetes

2019 European society of cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

Recommendations	Class[a]	Level[b]
It is recommended that patients with DM are screened annually for kidney disease by assessment of eGFR and urinary albumin:creatinine ratio.[543]	I	A
Tight glucose control, targeting HbA1c (<7.0% or <53 mmol/mol) is recommended to decrease microvascular complications in patients with DM.[145–149]	I	A
It is recommended that patients with hypertension and DM are treated in an individualized manner, targeting a SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years) the SBP goal is to a range of 130–139 mmHg.[155,159,181–183]	I	A
A RAAS blocker (ACEI or ARB) is recommended for the treatment of hypertension in patients with DM, particularly in the presence of proteinuria, microalbuminuria, or LVH.[167–170]	I	A
Treatment with an SGLT2 inhibitor (empagliflozin, canagliflozin, or dapagliflozin) is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to <90 mL/min/1.73 m^2).[306,311,313,496]	I	B
Treatment with the GLP1-RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints, and should be considered for DM treatment if eGFR is >30 mL/min/1.73m^2.[176,299]	IIa	B

Percentage of Intensifying diabetes medication based on prescribing information in UK: 2000-2017

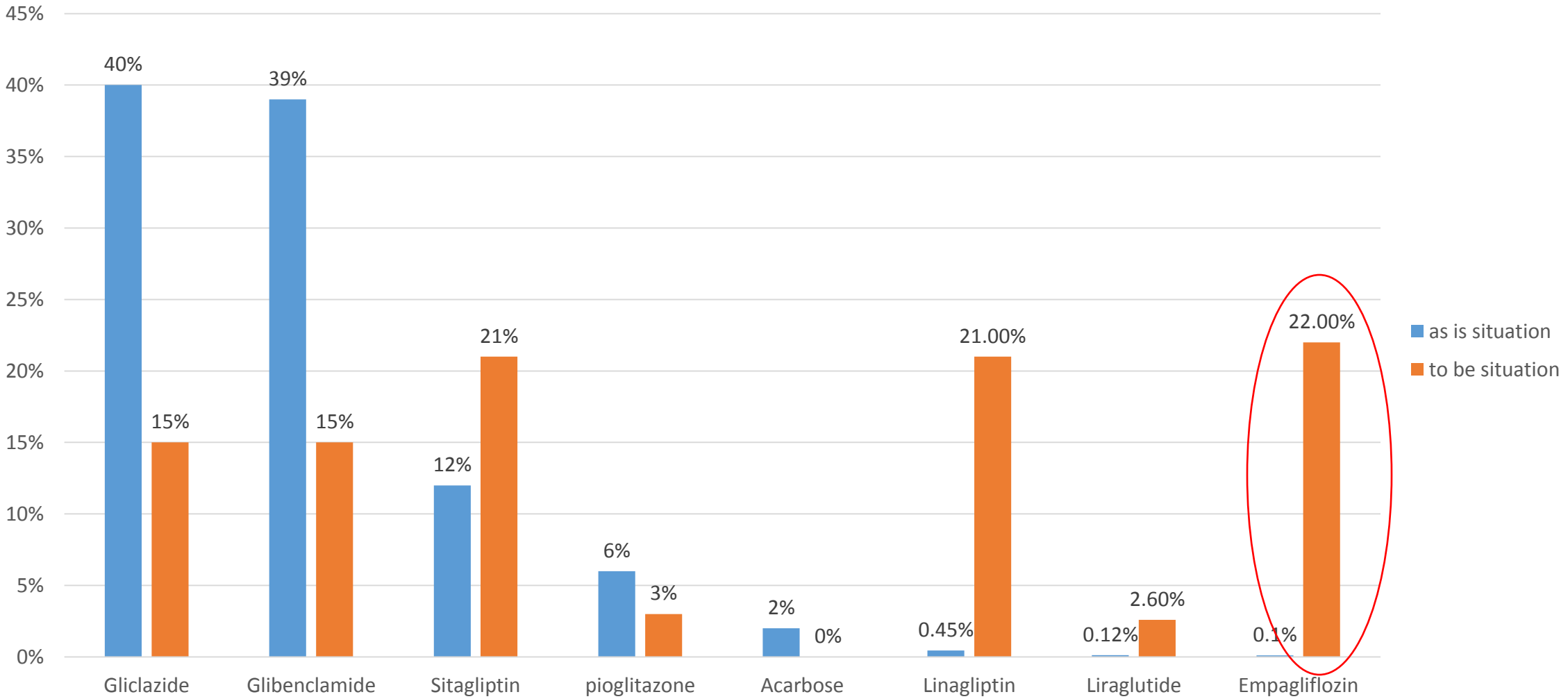


Wilkinson S, Douglas I, Stirnadel-Farrant H, et al Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017 BMJ Open 2018;8:e022768

Choice of Treatment to Use along Metformin in Iran

As is situation: based on Based on Iranian Pharmaceutical Sales Data

To be situation: based on UK trends article



What should you remember?

- Screen for DM – it's an EPIDEMIC!

- Treat glucose, BP and lipids early, aggressively, and to goal; use ASA when appropriate; insist on smoking cessation; and watch for complications.

- Empower patients to be involved in their DM management.
- Remember that DM is a progressive disease, so expect to change therapy over time – let patients know this at diagnosis.
- Stay informed about the current management of DM – it's changing constantly!

UKPDS 1977 – 2007 Global Conclusions

A. " Our results show a sustained legacy effect of an intensive glucose control strategy".

B. " How well you are treated now, and how well you were treated in the past, determines the long-term health outcomes as far as glycaemic control is concerned ".

[Prof Rury Holman Principal investigator UKPDS]

UKPDS 81 N Engl J Med 2008; 359:1577-89
EASD 2008 UKPDS Press Release

Thanks For Your Attention