4 Reasons to Use SGLT-2 Inhibitors Early in Type 2 Diabetes Treatment Paradigm

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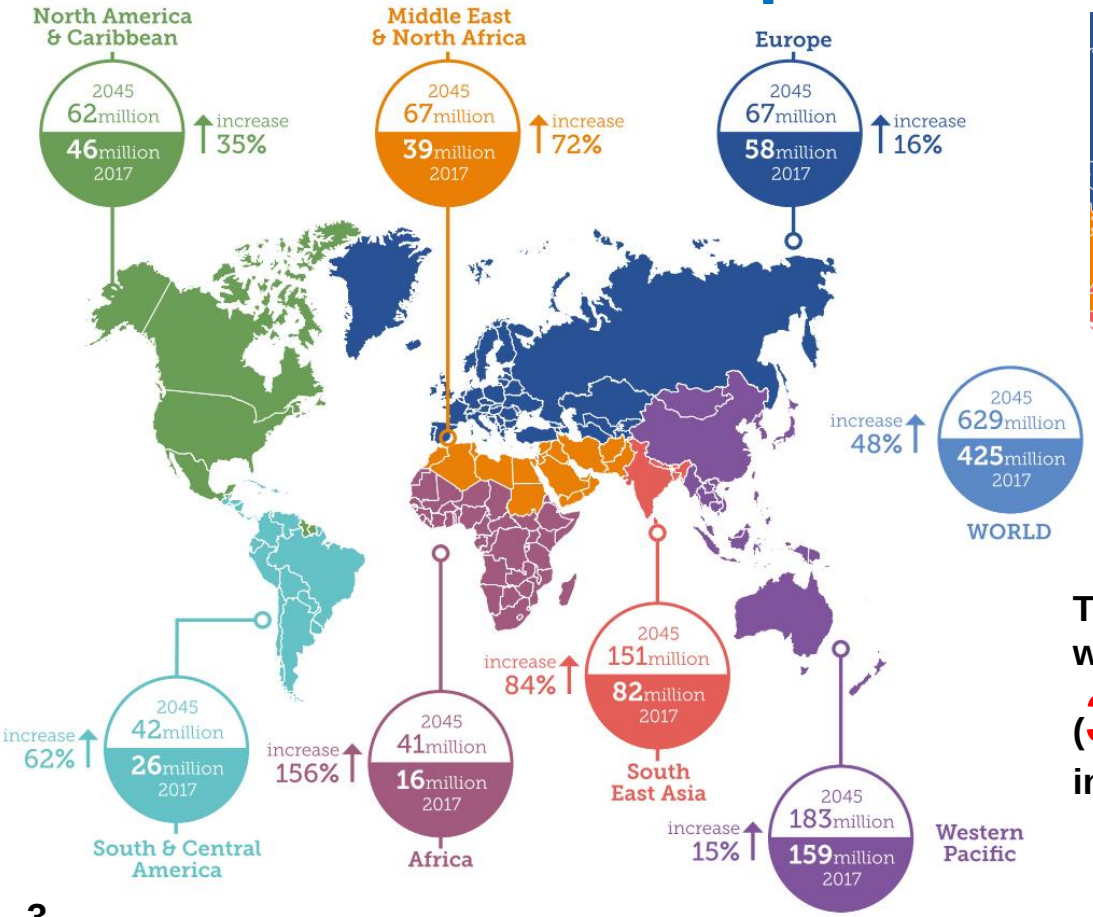
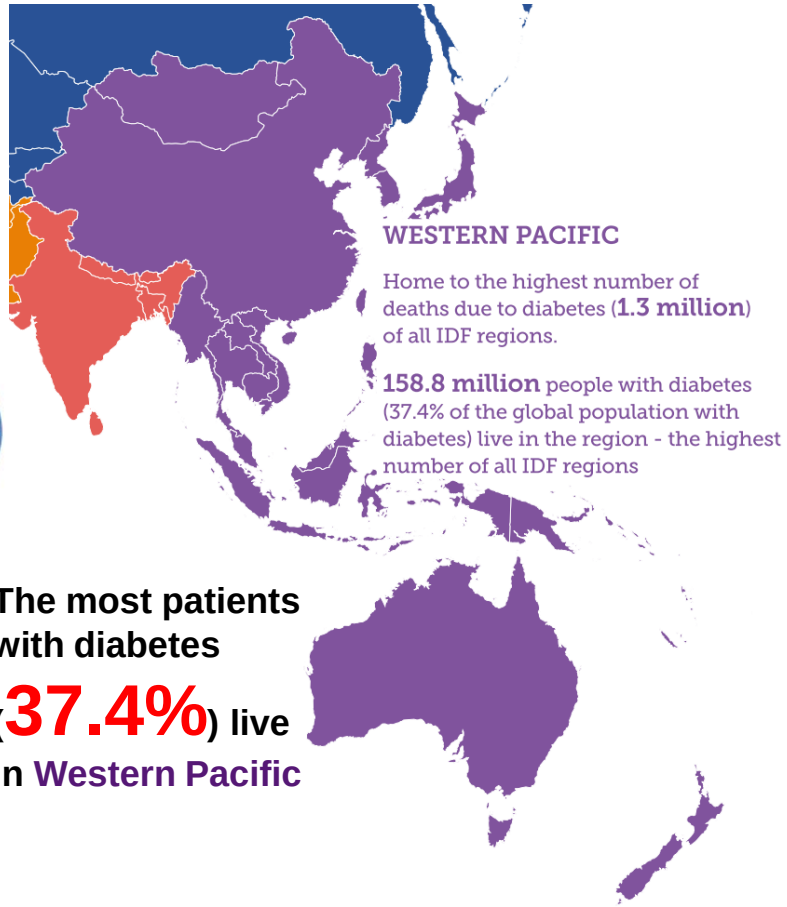
Outline

- **Introduction**
- **4 Reasons to Use SGLT-2 Inhibitors Early in T2DM**
  - Effect on CVD & Death in non-CVD patients
  - β-cell function & Insulin resistance
  - Fat mass & fatty liver
  - Renal function
- **Conclusion**

Diabetes Population is still Rising





WESTERN PACIFIC

Home to the highest number of deaths due to diabetes (**1.3 million**) of all IDF regions.

158.8 million people with diabetes (37.4% of the global population with diabetes) live in the region - the highest number of all IDF regions

The most patients with diabetes

(37.4%) live in Western Pacific

2017 IDF Diabetes Atlas 8th Edition: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html

Prevalence of diabetes in Taiwan for 2017[1]

Western Pacific

International Diabetes Federation

IDF DIABETES ATLAS
Eighth edition 2017

Country/territory	Adults with diabetes (20-79) in 1,000s [Confidence interval]	Diabetes (20-79) national prevalence (%) [Confidence interval]	Diabetes age-adjusted (20-79) comparative prevalence (%) [Confidence interval]
Japan	7,234.2 [6,155.2-9,489.8]	7.7 [6.6-10.1]	5.7 [4.7-8.6]
Republic of Korea	3,465.4 [2,631.3-4,349.9]	8.8 [6.7-11.1]	6.8 [5.3-8.7]
Malaysia	3,492.6 [3,124.2-4,024.6]	16.9 [15.1-19.4]	16.7 [14.9-19.3]
New Zealand	326.1 [250.5-405.2]	10.1 [7.8-12.6]	8.1 [6.3-10.1]
Philippines	3,721.9 [2,980.4-4,695.2]	6.3 [4.9-7.8]	7.1 [5.6-8.9]
Singapore	606.0 [527.9-682.2]	13.7 [12.0-15.5]	11.0 [9.5-12.5]
Taiwan	1,958.0 [1,467.1-2,524.2]	10.9 [8.1-14.0]	8.8 [6.5-11.6]
Thailand	4,208.6 [3,235.1-4,838.8]	8.3 [6.4-9.5]	7.0 [5.5-8.2]

1,781,100 adults with diabetes in 2015[2]

1,958,000 adults with diabetes in 2017

838,000 adults with undiagnosed diabetes

10%

1. 2017 IDF Diabetes Atlas 8th Edition: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html
2. 2015 IDF Diabetes Atlas 7th Edition: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html

Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

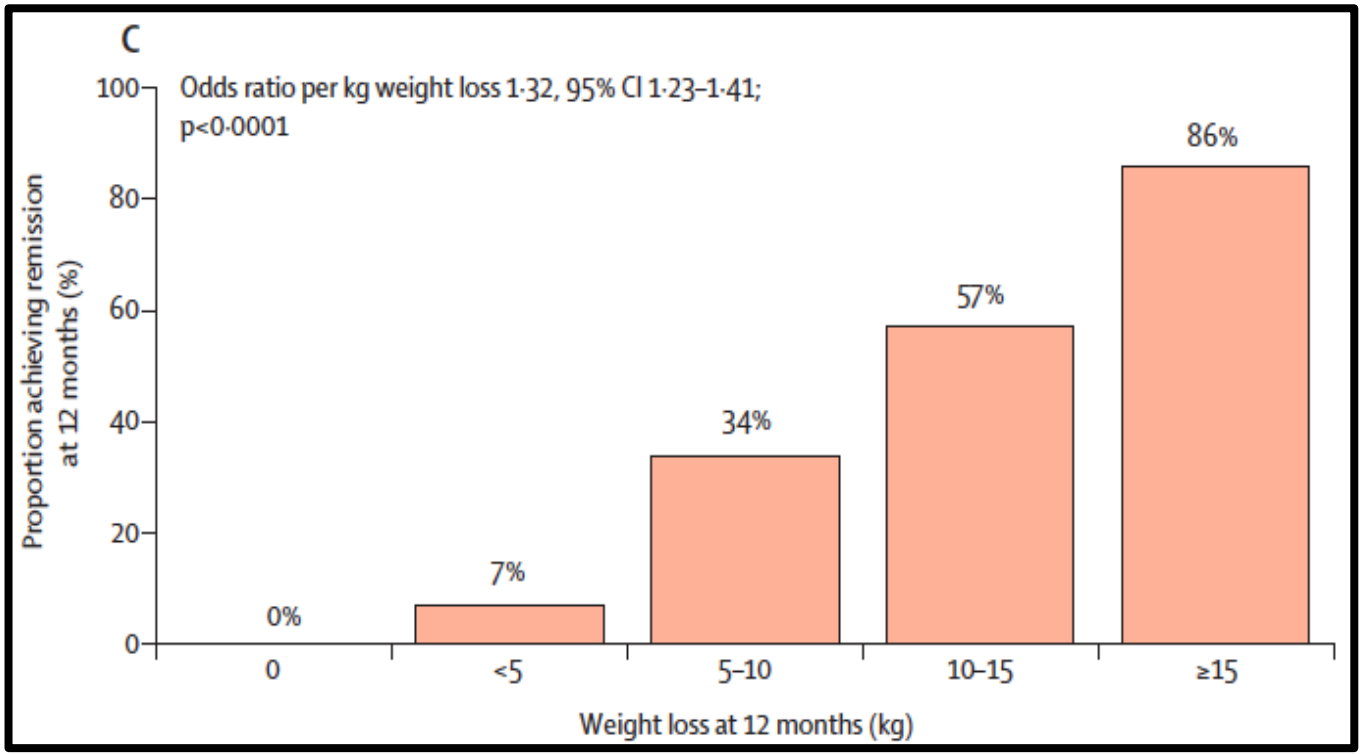
The majority of lifestyle weight-loss interventions in overweight or obese adults with type 2 diabetes resulted in weight loss <5% and did not result in beneficial metabolic outcomes.

A weight loss of >5% appears necessary for beneficial effects on HbA1c, lipids, and blood pressure

J Acad Nutr Diet. 2015 Sep;115(9):1447-63. doi: 10.1016/j.jand.2015.02.031. Epub 2015 Apr 29.

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Scotland

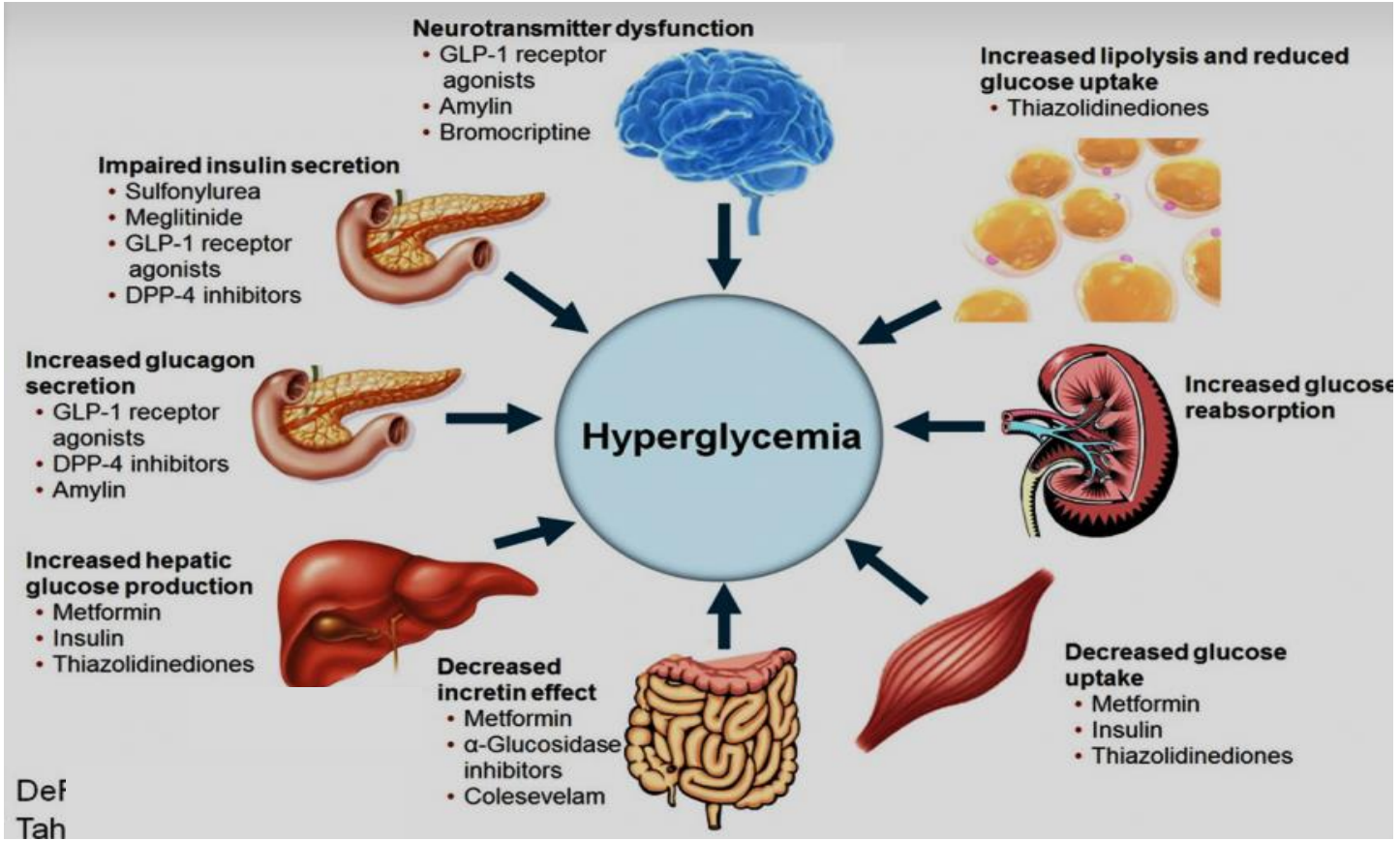


Weight 100kg
BMI 35kg/m^2
HbA1c 7.7%
DM duration: 3 years

Remission of diabetes
-HbA1c<6.5%
-Off antidiabetic medication for 2 months

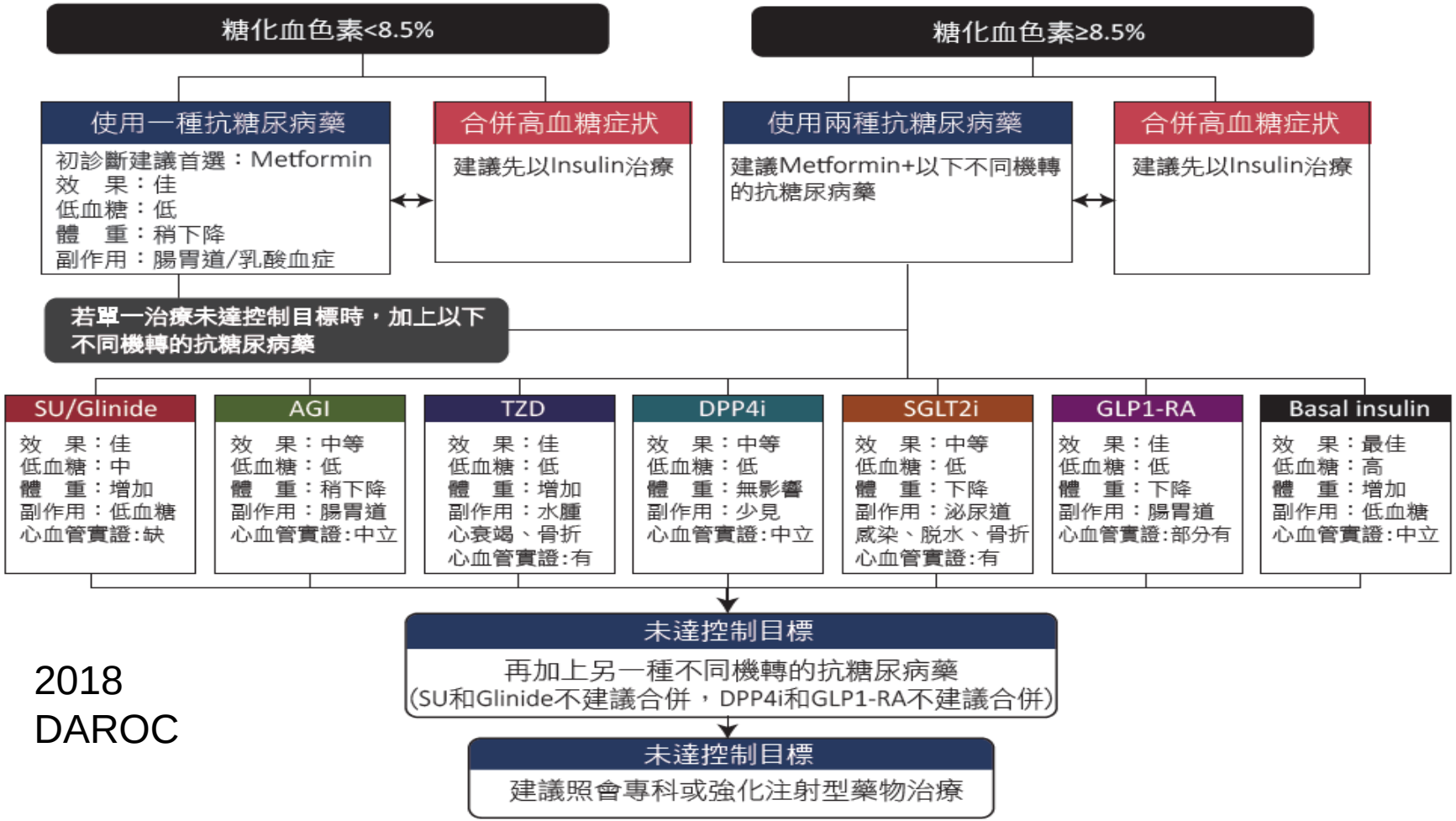
Lancet. 2017 Dec 4. pii: S0140-6736(17)33102-1. doi: 10.1016/S0140-6736(17)33102-1.

Where Diabetes Medications Work



DeFronzo RA. *Diabetes.* 2009;58:773-795.

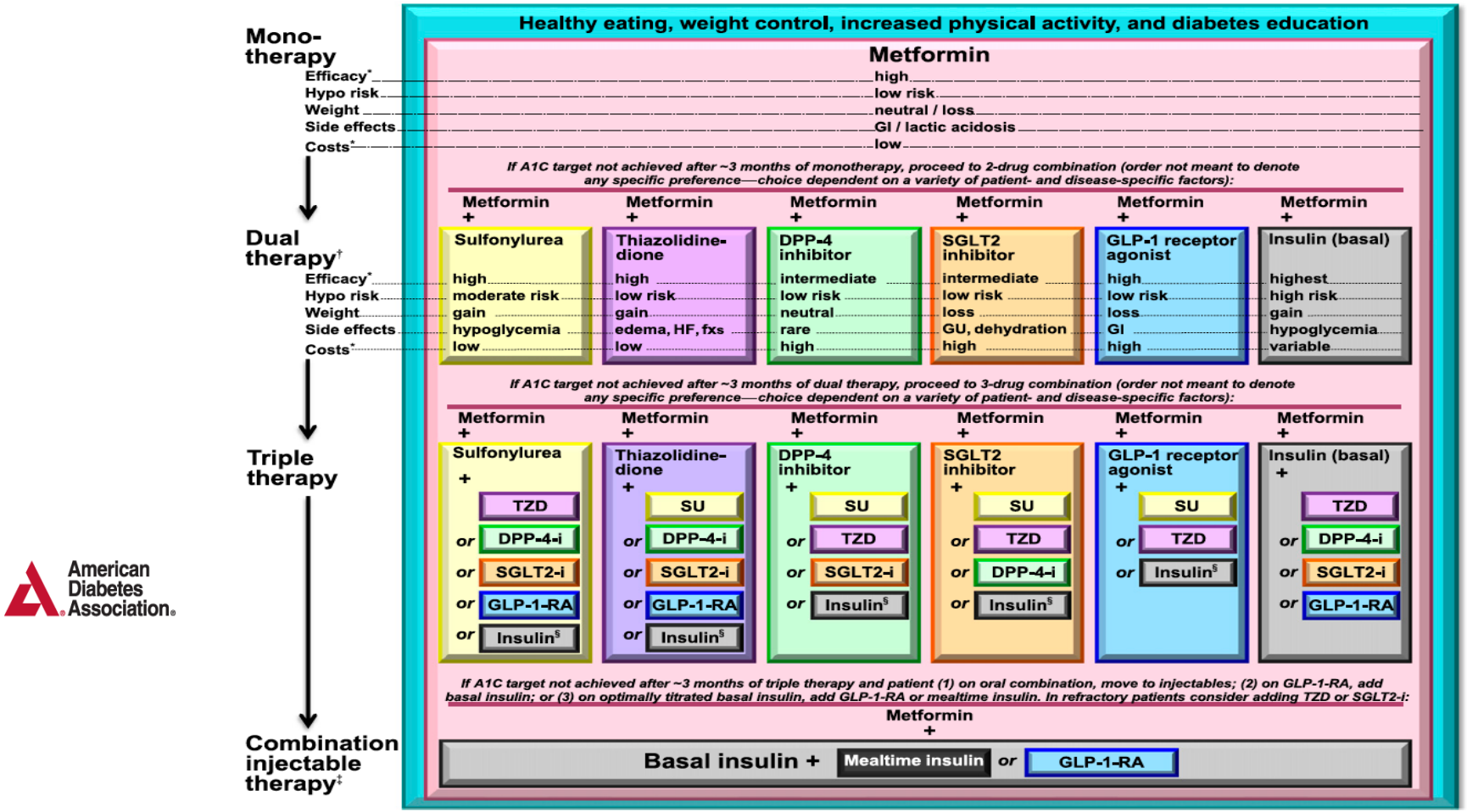
第2型糖尿病人高血糖的處理流程圖



健康生活型態的飲食和運動

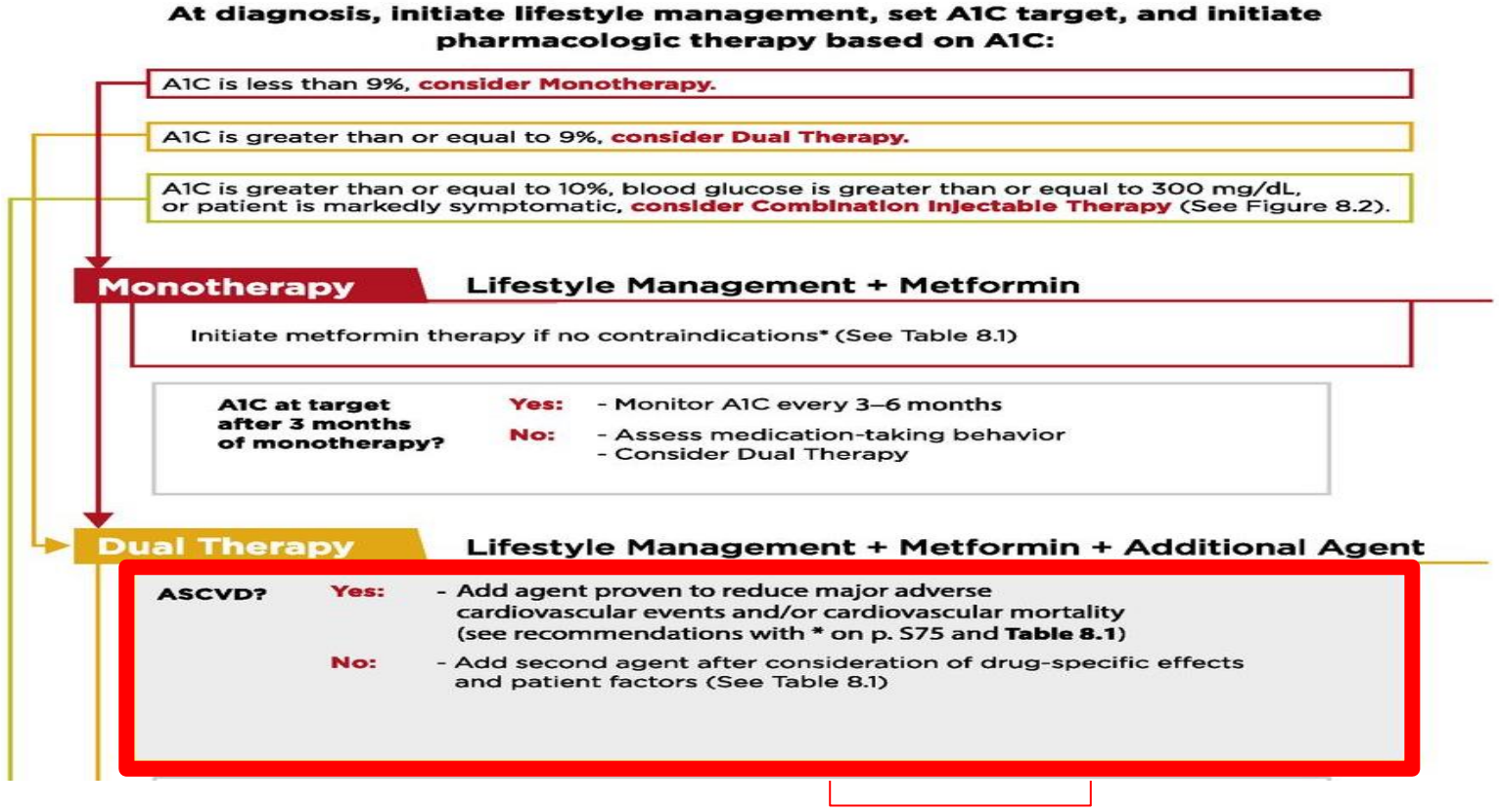
2018
DAROC

American Diabetes Association, Standards of Medical Care in Diabetes 2017



American Diabetes Association.

American Diabetes Association, Standards of Medical Care in Diabetes 2018



SGLT-2i: Associated with lower CVD event rate and mortality in patients with T2DM and CVD (EMPA-REG OUTCOME)
FDA recently added a new indication for empagliflozin to reduce the risk of CV death in adults with T2DM and CV disease.

Diabetes Care Volume 40, Supplement 1, January 2017

Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 189–222

www.jcma-online.com

Guidelines

2018 consensus of the Taiwan Society of Cardiology and the Diabetes Association of Republic of China (Taiwan) on the pharmacological management of patients with type 2 diabetes and cardiovascular diseases

Chern-En Chiang [a,b,c,*], Shih-Yi Lin [d,e], Tsung-Hsien Lin [f,g], Tzung-Dau Wang [h], Hung-I Yeh [i], Jung-Fu Chen [j], Chia-Ti Tsai [k], Yi-Jen Hung [l], Yi-Heng Li [m], Ping-Yen Liu [n,o], Kuan-Cheng Chang [p,q], Kang-Ling Wang [a,c], Ting-Hsing Chao [r], Kou-Gi Shyu [s], Wei-Shiung Yang [t,u], Kwo-Chang Ueng [v], Pao-Hsien Chu [w], Wei-Hsian Yin [x,y], Yen-Wen Wu [c,z], Hao-Min Cheng [aa,ab], Shyi-Jang Shin [ac,ad], Chien-Ning Huang [ae,af], Lee-Ming Chuang [u], Shing-Jong Lin [ag,ah], San-Jou Yeh [w], Wayne Huey-Herng Sheu [c,e,ai,aj,**], Jiunn-Lee Lin [ak,***]

Table 2

Treatment algorithm in diabetic patients with hypertension.

Target HbA1c	<7%			
Monotherapy	Metformin			
Dual therapy	Metformin + SGLT-2 i			
Triple therapy	Metformin + SGLT-2 i + GLP-1 RA[a]	Metformin + SGLT-2 i + TZD[b]	Metformin + SGLT-2 i + DPP-4 i	Metformin + SGLT-2 i + SU or Glinide or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

Table 3

Treatment algorithm in diabetic patients with CHD.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + SGLT-2 i	Metformin + GLP-1 RA[b]
Triple therapy	Metformin + TZD[a] + SGLT-2 i	Metformin + TZD[a] + GLP-1 RAs[b]	Metformin + SGLT-2 i + GLP-1 RAs[b]
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents		

Table 4

Treatment algorithm in diabetic patients with stage 3 CKD.

Target HbA1c	<7%			
Monotherapy	Metformin			
Dual therapy	Metformin + SGLT-2 i			
Triple therapy	Metformin + SGLT-2 i + GLP-1 RA[a]	Metformin + SGLT-2 i + TZD[b]	Metformin + SGLT-2 i + DPP-4 i	Metformin + SGLT-2 i + SU or Glinide or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

Table 5

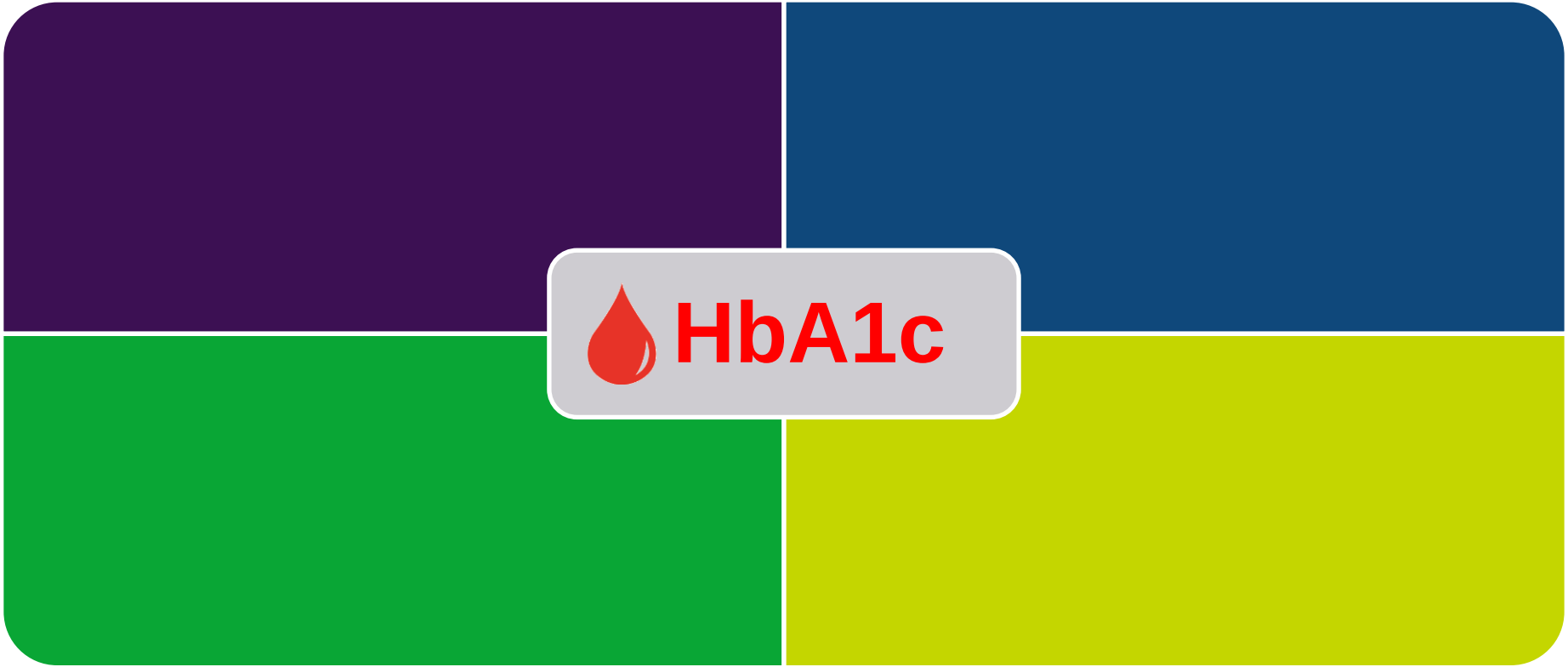
Treatment algorithm in diabetic patients with a history of stroke.

Target HbA1c	<7%		
Monotherapy	Metformin		
Dual therapy	Metformin + TZD[a]	Metformin + GLP-1 RA[b]	Metformin + SGLT-2 i
Triple therapy	Metformin + TZD[a] + GLP-1 RA[b]	Metformin + TZD[a] + SGLT-2 i	Metformin + GLP-1 RA[b] + SGLT-2 i
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents		

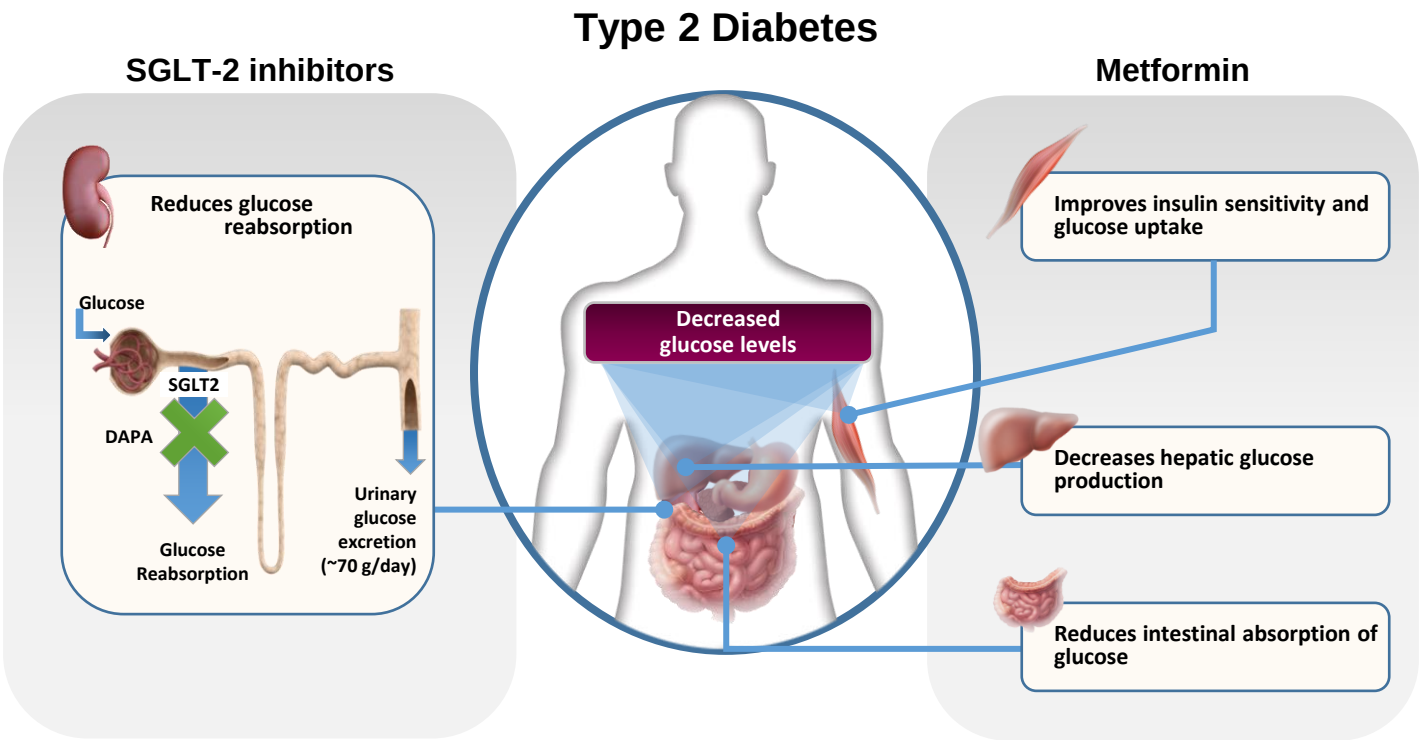
Table 6
Treatment algorithm in diabetic patients with heart failure.

Target HbA1c	<8%			
Monotherapy	SGLT-2 i or metformin			
Dual therapy	SGLT-2 i + metformin			
Triple therapy	SGLT-2 i + metformin + GLP-1 RA	SGLT-2 i + metformin + DPP-4 i (except saxa., alo., and vilda.)	SGLT-2 i + metformin + SU or AGI	SGLT-2 i + metformin + Glinide
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents			

4 Reasons to Use SGLT-2 Inhibitors Early in T2DM



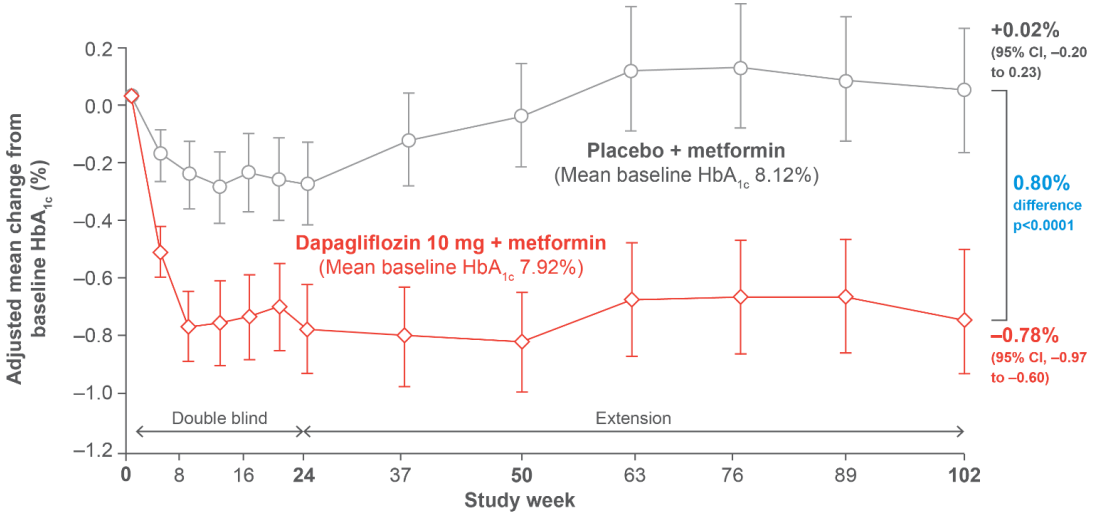
Glycemic control through insulin-independent mechanisms with metformin and SGLT2i can address multiple defects in T2DM



SGLT-2: sodium-glucose cotransporter-2; T2DM: type 2 diabetes mellitus.

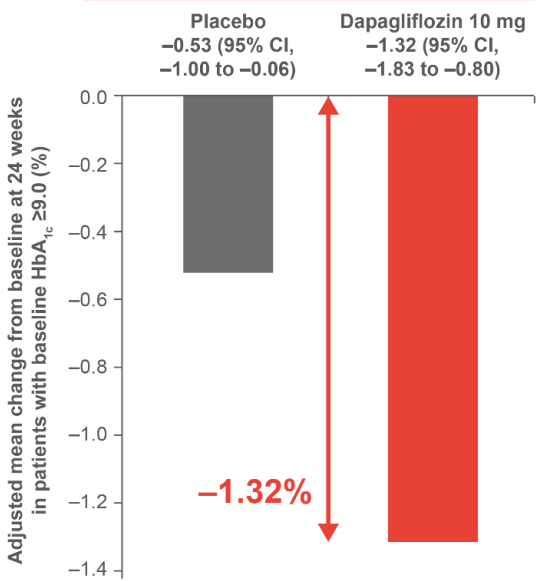
1. Drugs 72:2289-2312 (2012); 2. Diabetes Care 13:696-704 (1990)

Dapagliflozin as add-on to metformin demonstrated significant HbA1c reductions, sustained over 2 years versus placebo



Sample size (including data after rescue)				
Dapagliflozin + metformin	132	117	102	57
Placebo + metformin	133	100	74	28

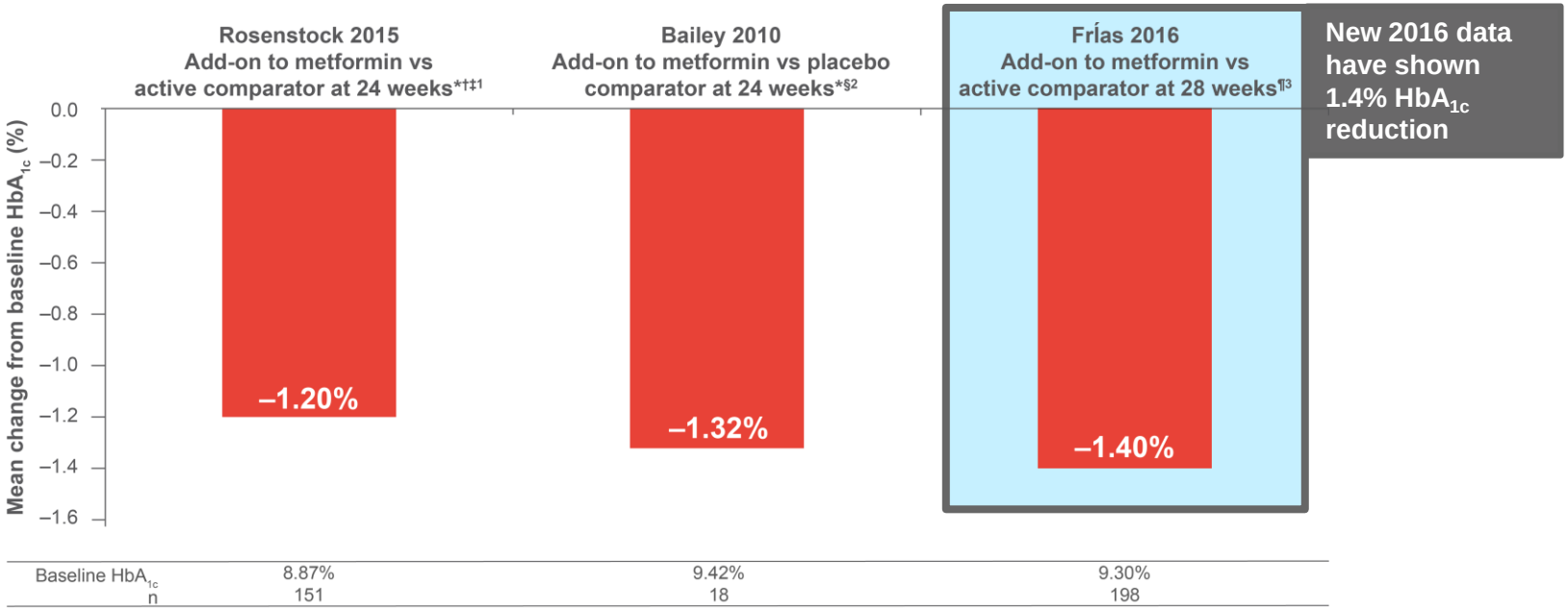
A1c reduction in patient with baseline A1c ≥ 9%



At the 24-week primary endpoint, dapagliflozin delivered HbA_{1c} reductions of –0.80% versus –0.30% with placebo (p<0.0001)[2]

Data are mean change from baseline after adjustment for baseline value. Data after rescue are excluded. Analyses were obtained by longitudinal repeated-measures analyses. A Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week clinical study with a 78-week, double-blind extension in adult patients with Type 2 diabetes who had inadequate glycaemic control (HbA_{1c} ≥7% and ≤10%) on metformin alone. Primary endpoint: HbA_{1c} reduction at 24 weeks.
CI, confidence interval.
1. Bailey CJ, *et al. BMC Med* 2013;**11**:43; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

Dapagliflozin as add-on to metformin demonstrated HbA_{1c} reductions of 1.2% or more in patients with high baseline HbA_{1c}

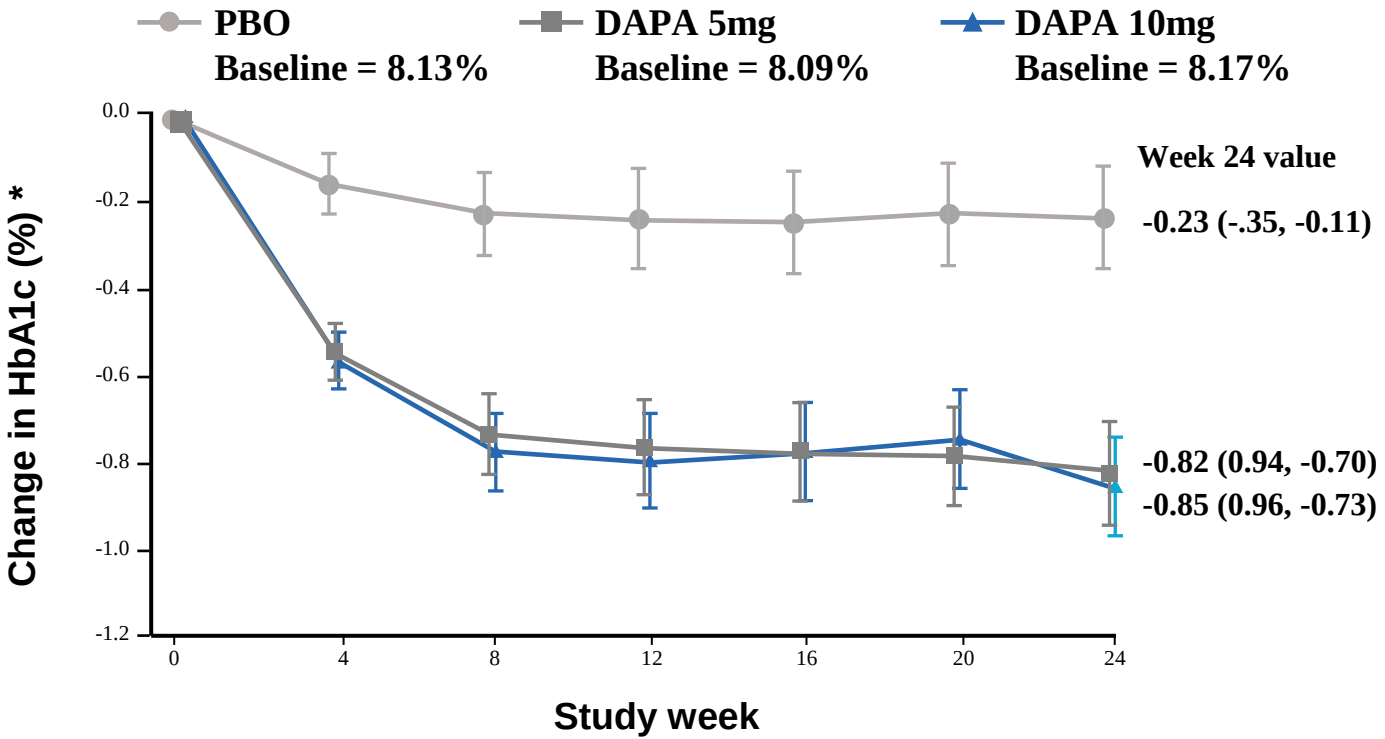


*Clinical trial data from patients with high baseline HbA_{1c} who had dapagliflozin added to metformin or metformin XR. †Adjusted mean change from baseline HbA_{1c} (%). ‡Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-weeks clinical study to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (≥1500 mg/day) versus glycaemic control (HbA_{1c} ≥7% and ≤10%) on metformin alone.[1]

§Phase III, 24-week, multicentre, randomised, double-blind, active controlled, parallel-group study to compare the efficacy and safety of the dual add-on of saxagliptin 5 mg and dapagliflozin 10 mg with either saxagliptin 5 mg or dapagliflozin 10 mg added on alone in adult patients with Type 2 diabetes who had inadequate glycaemic control (HbA_{1c} ≥8% to ≤12%) on metformin alone. The study met its primary endpoint. This is a retrospective post hoc analysis of the data. ¶Phase III, 28-week, multicentre double-blind, randomised, active-controlled trial to compare the efficacy and safety of exenatide (2 mg/day) plus dapagliflozin (10 mg/day) with exenatide or dapagliflozin alone in patients with Type 2 diabetes inadequately controlled by metformin (HbA_{1c} ≥8% to ≤12%). The primary endpoint was change in HbA_{1c} from baseline to week 28.[3] XR, extended release. This combination is not indicated in the current licence of exenatide.

1. Rosenstock J, *et al. Diabetes Care* 2015;**38**:376–83; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Frìas JP, *et al. Lancet Diabetes Endocrinol* 2016. Epub ahead of print.

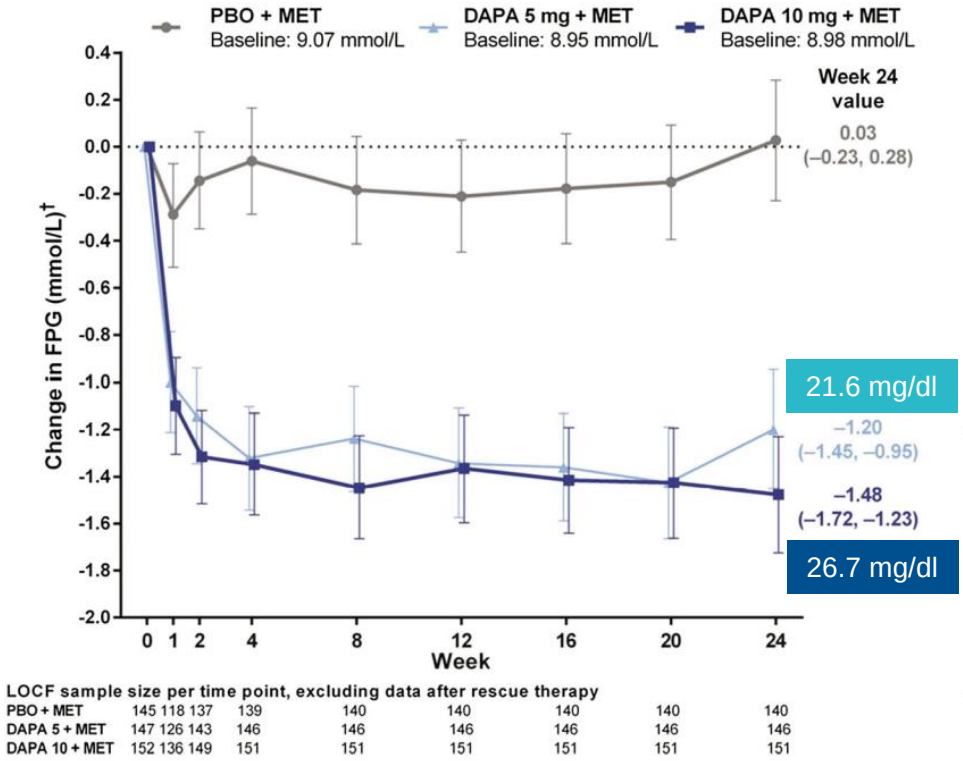
Dapagliflozin demonstrated significant HbA1c reductions in Asian patients with T2DM after metformin failure

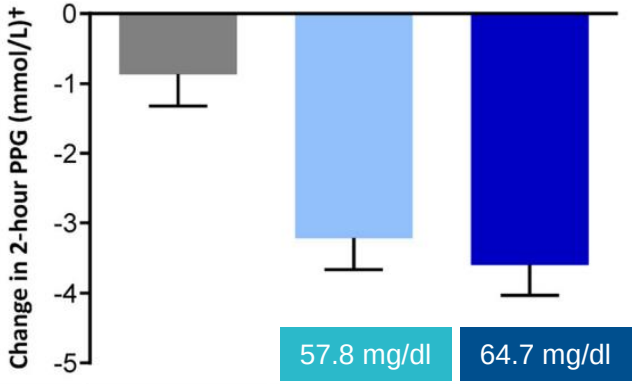


24-week RCT, included Asian T2DM patients with inadequately controlled by metformin (HbA1c 7.5%-10.5%) randomized to receive placebo (n = 145) or dapagliflozin 5 (n = 147) or 10 mg (n = 152)
Most participants were Chinese (86.0%), with mean age of 53.8 years and mean T2D duration of 4.9 years

Yang W et al. J Diabetes. 2016 Nov;8(6):796-808.

Dapagliflozin demonstrated significant FPG and PPG reductions in Asian patients with T2DM after metformin failure





	Placebo + MET (n=117)	DAPA 5 mg + MET (n=117)	DAPA 10 mg + MET (n=124)
Baseline 2-hour PPG (mmol/L)	14.15	14.07	14.10
Change from baseline (95% CI)	–0.86 (–1.31, –0.41)	–3.21 (–3.66, –2.75)	–3.59 (–4.03, –3.15)
Difference versus placebo (95% CI of difference)		–2.35 (–2.99, –1.71)	–2.73 (–3.36, –2.09)
p value		<0.0001	<0.0001

FPG: fasting plasma glucose, PPG: postprandial plasma glucose

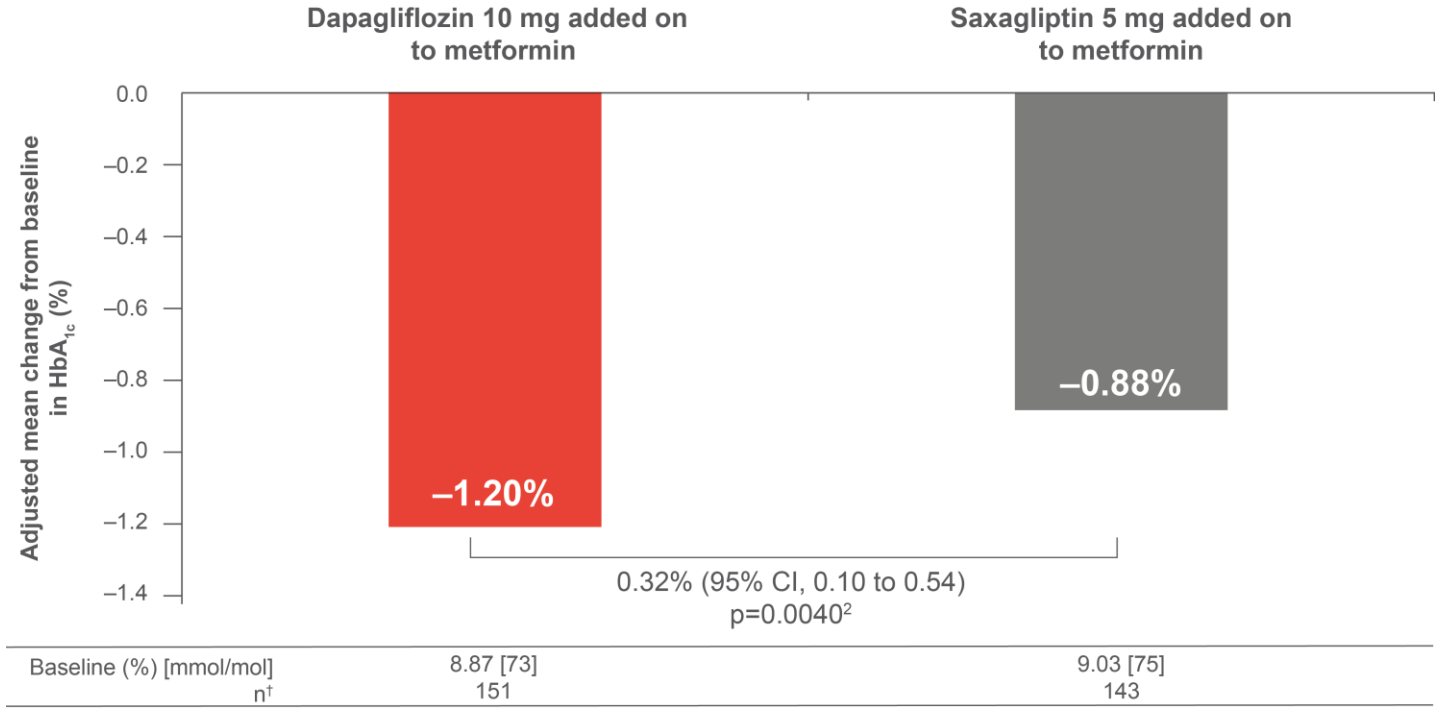
Yang W et al. J Diabetes. 2016 Nov;8(6):796-808.

Second-line medications of diabetes treatment

The glycemic efficacy consideration

SGLT-2 inhibitors **vs** DPP-4 inhibitors ?

Dapagliflozin as add-on to metformin demonstrated significantly greater reductions in HbA1c at 24 weeks versus saxagliptin

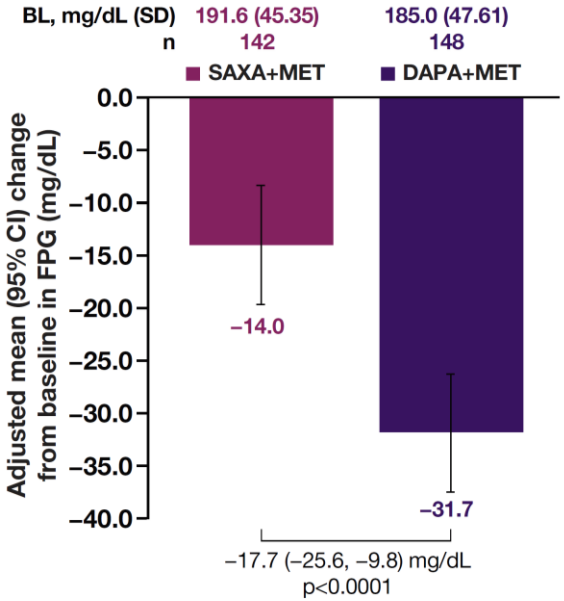


*Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual add-on of saxagliptin and dapagliflozin with either saxagliptin 5 mg or dapagliflozin 10 mg added alone in adults with Type 2 diabetes who had inadequate glycaemic control (HbA1c ≥8% to ≤12%) on metformin.

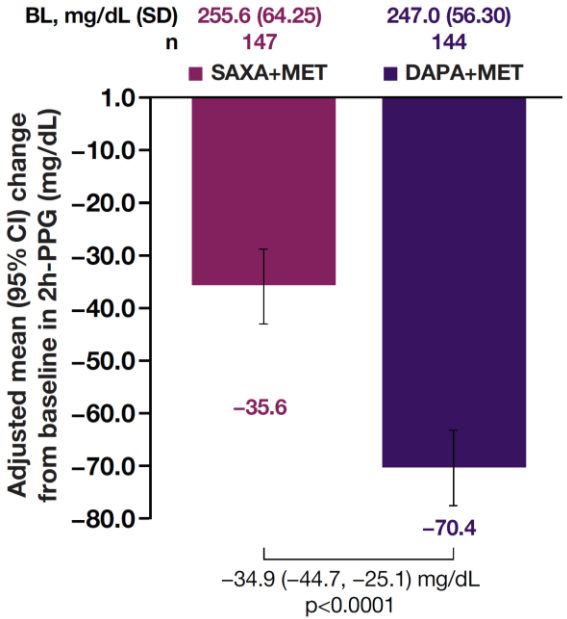
1. Diabetes Care 38:376-83 (2015); 2. Presented at the 14th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC), Los Angeles, CA, USA; Dec 1–3 (2016)

Dapagliflozin as add-on to metformin demonstrated significantly greater reductions in FPG, PPG and BW at 24 weeks versus saxagliptin

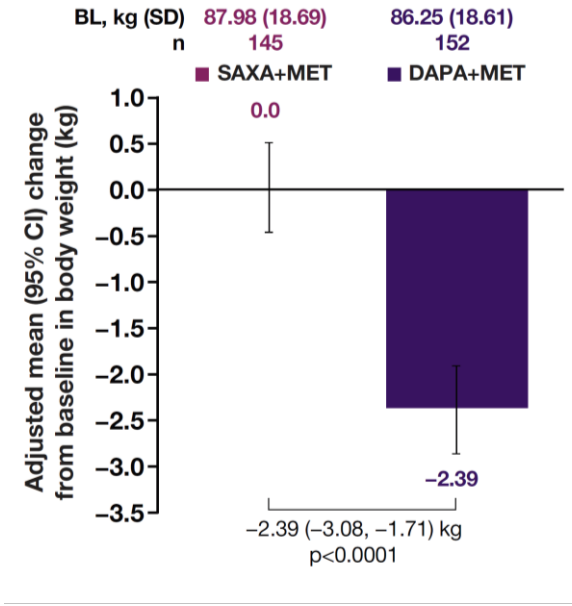
Fasting plasma glucose



Postprandial plasma glucose



Body weight



*Phase III, 24-week, randomised, double-blind, active-controlled, parallel-group study to compare the efficacy and safety of the dual add-on of saxagliptin and dapagliflozin with either saxagliptin 5 mg or dapagliflozin 10 mg added alone in adults with Type 2 diabetes who had inadequate glycaemic control (HbA1c ≥8% to ≤12%) on metformin.

1. Diabetes Care 38:376-83 (2015); 2. Presented at the 14th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC), Los Angeles, CA, USA; Dec 1–3 (2016)

Greatest glucose-lowering effect in high baseline eGFR and high baseline HbA1c levels in Asian patients

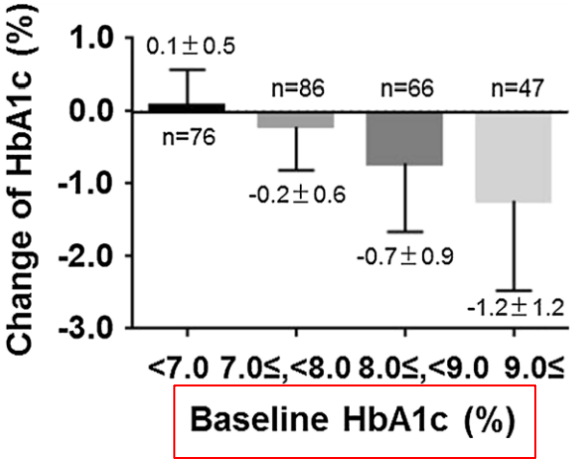
Adv Ther
https://doi.org/10.1007/s12325-017-0639-z

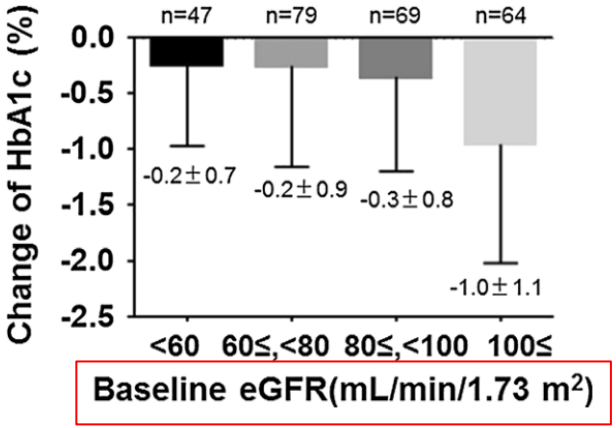
ORIGINAL RESEARCH

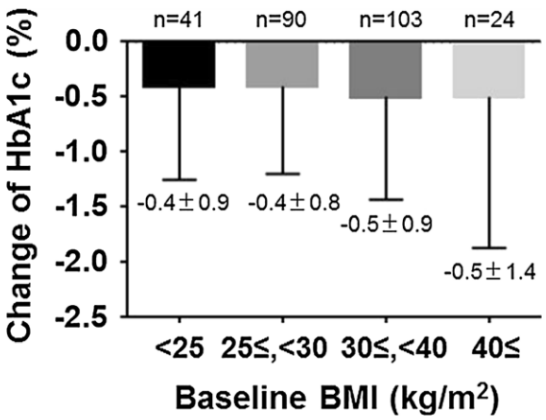
Predictors for the Treatment Effect of Sodium Glucose Co-transporter 2 Inhibitors in Patients with Type 2 Diabetes Mellitus

3 months

275 patients in Japan by measuring HbA1c levels before and 3 months after treatment of SGLT2 inhibitors: ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, or empagliflozin







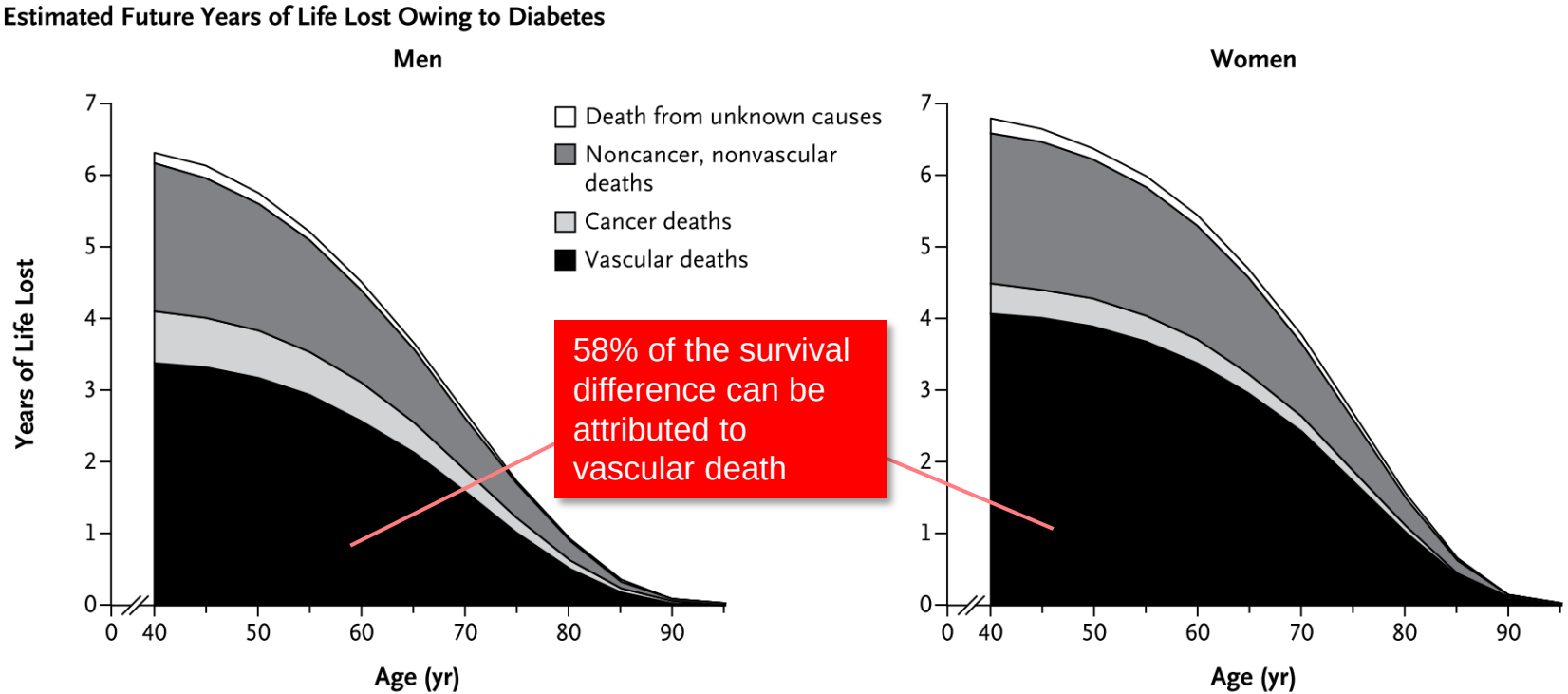
Adv Ther. 2018 Jan;35(1):124-134. doi: 10.1007/s12325-017-0639-z. Epub 2017 Nov 28.

4 Reasons to Use SGLT-2 Inhibitors Early in T2DM

Effect on CVD & Death in non-CVD patients

HbA1c

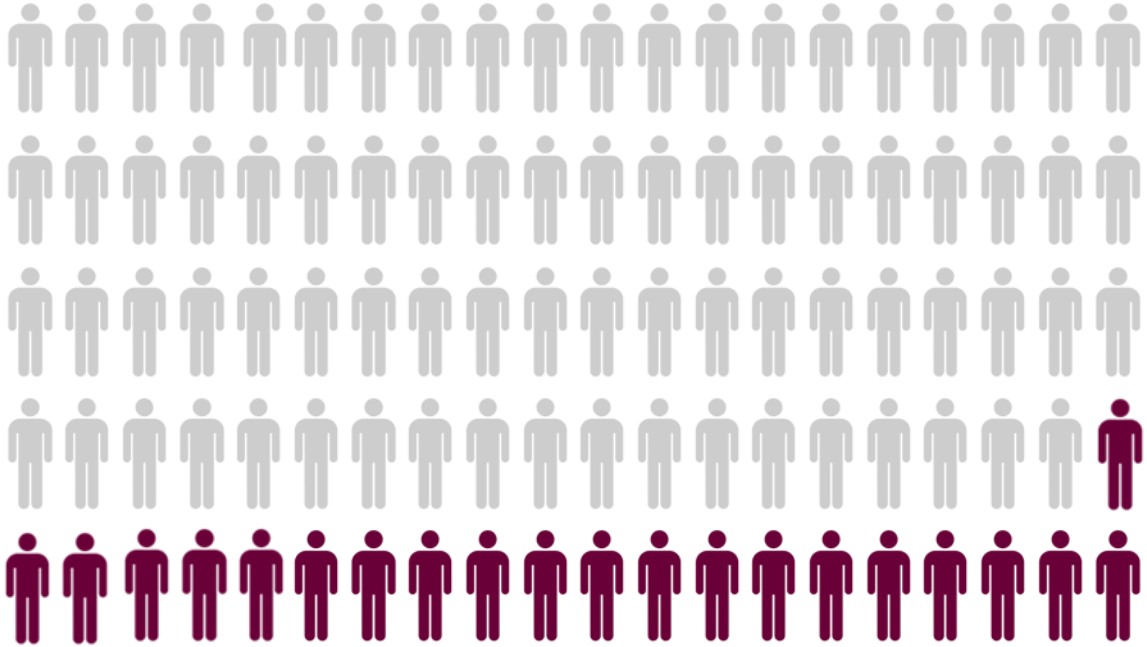
Diabetes is associated with significant loss of life years



At 40, 50, and 60 years of age, men with diabetes would incur about 6.3, 5.8, and 4.5 years of life lost.
At 40, 50, and 60 years of age, women with diabetes would incur about 6.8, 6.4, and 5.4 years of life lost

Seshasai et al. N Engl J Med 2011;364:829-41

Co-prevalence of CV comorbidities in T2DM

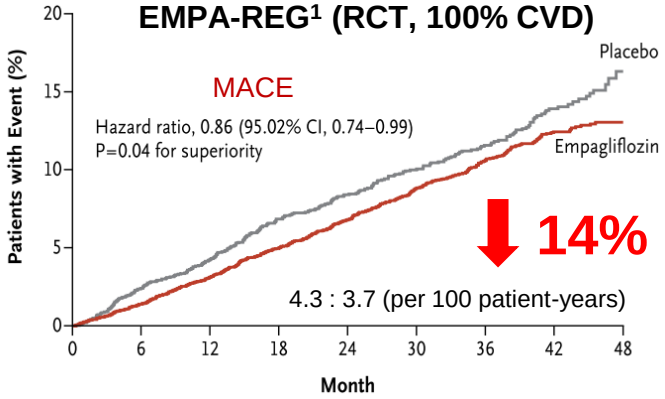


21% of patients with T2DM had CV presentation

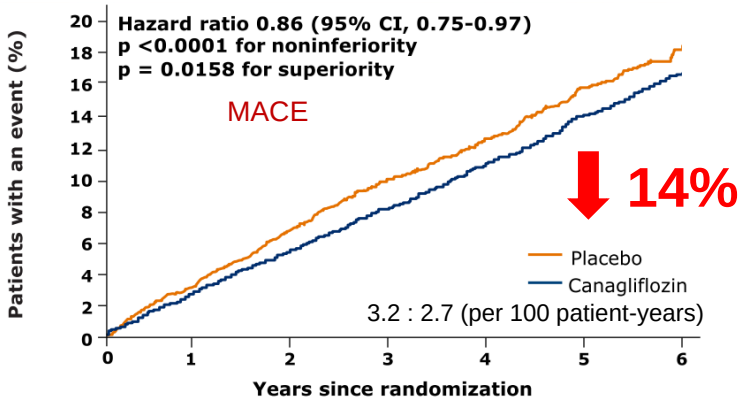
T2DM, Type 2 diabetes mellitus
A retrospective study was conducted using the Quintiles Electronic Medical Record database. N=1.39 million
Iglay K et al. Curr Med Res Opin. 2016 Jul;32(7):1243-52.

CV effects of SGLT-2 inhibitors

EMPA-REG[1] (RCT, 100% CVD)

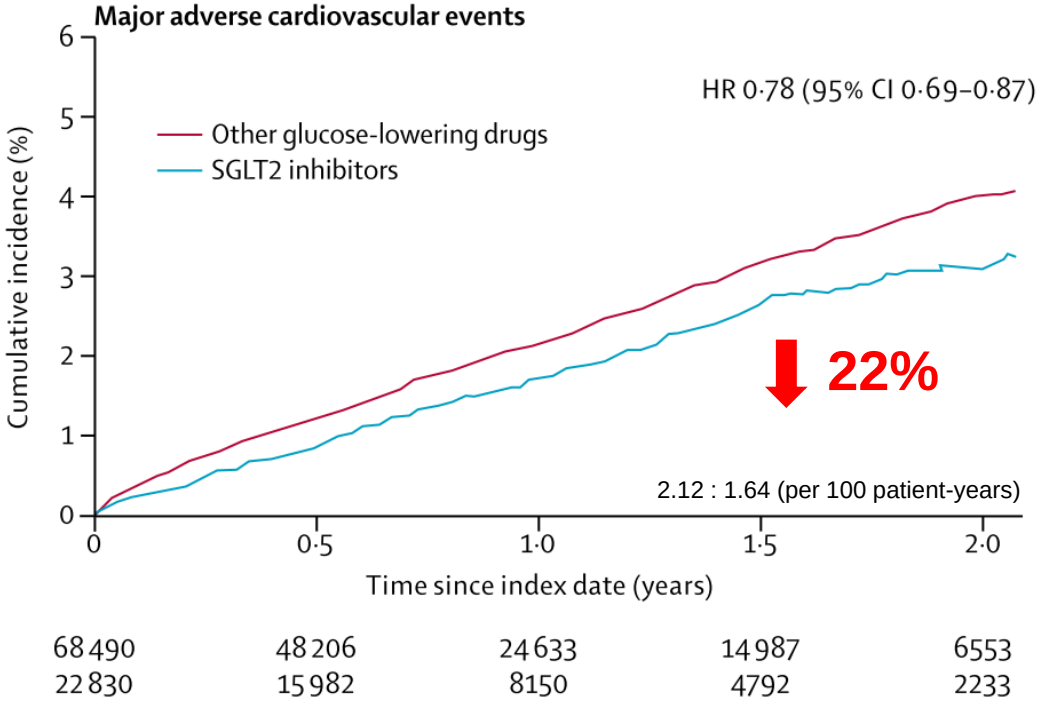


CANVAS[2] (RCT, 66% CVD)



CVD-REAL Nordic[3]

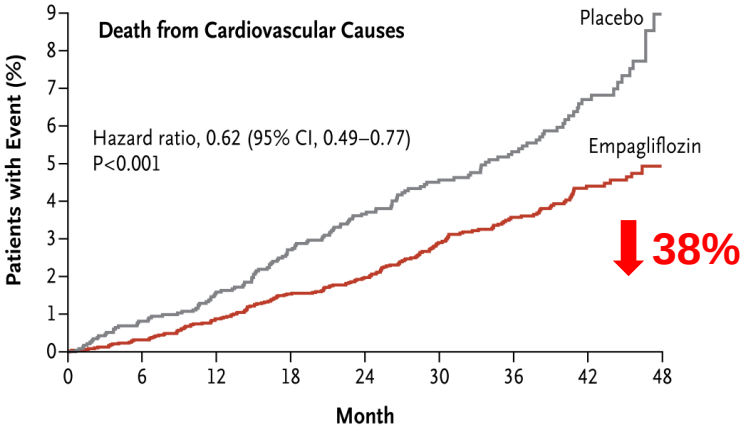
(real-world evidence, 24% CVD)



1. N Engl J Med 373:2117-28 (2015); 2. N Engl J Med Jun 12 (2017). doi: 10.1056/NEJMoa1611925. 3. Lancet Diabetes Endocrinol. 2017 Sep;5(9):709-717.

Lower CV death incidence of SGLT2i in RCT and RWE

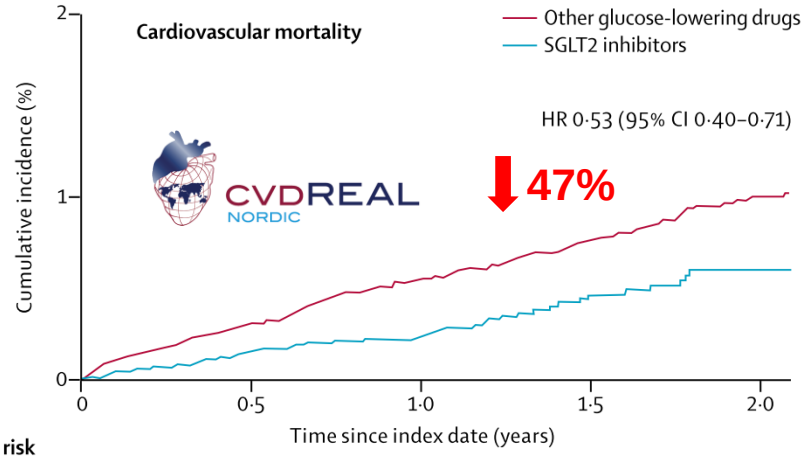
EMPA-REG[1] (RCT, 100% CVD)



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

2.0 : 1.2 events per 100 patient-years

CVD-REAL Nordic[2] (real-world evidence, 24% CVD)



Number at risk					
Other glucose-lowering drugs	68 490	48 338	24 582	15 314	6434
SGLT2 inhibitors	22 830	16 051	7760	4687	1610

0.53 : 0.27 events per 100 patient-years

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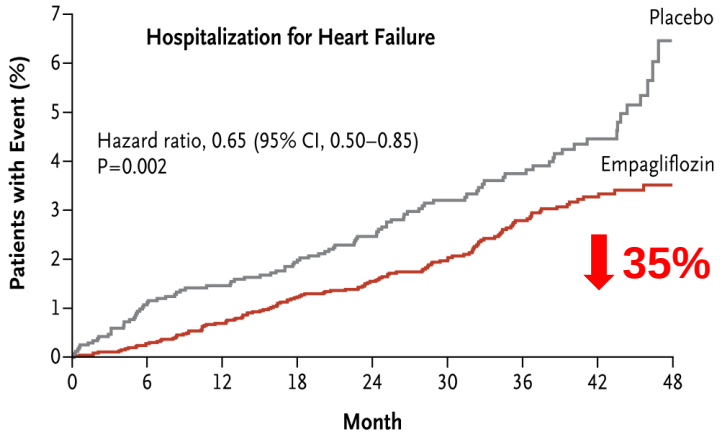
RWE: real-world evidence

1. N Engl J Med 373:2117-28 (2015); 2. Lancet Diabetes Endocrinol. 2017 Sep;5(9):709-717.

Lower HF hospitalization incidence of SGLT2i in RCT and RWE

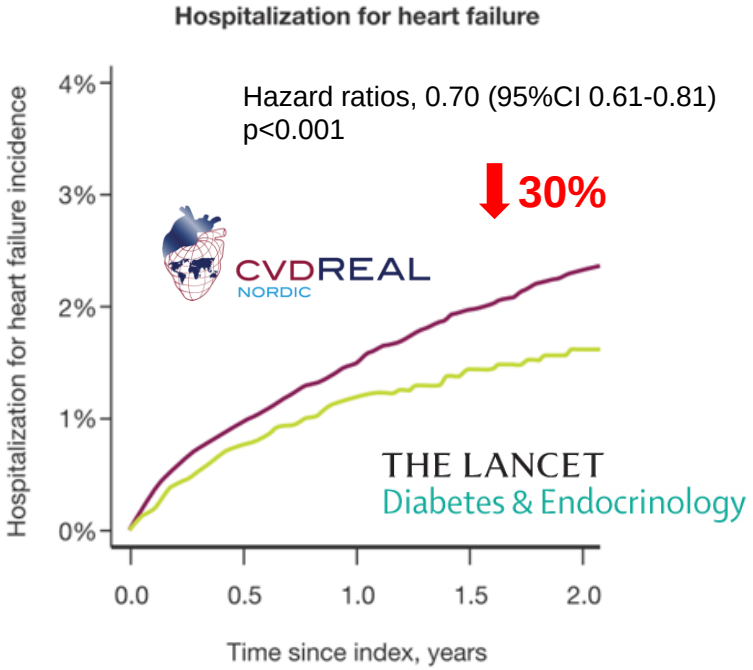
EMPA-REG[1] (RCT, 100% CVD)



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

1.5 vs 0.9 events per 100 patient-years

CVD-REAL Nordic[2] (real-world evidence, 24% CVD)



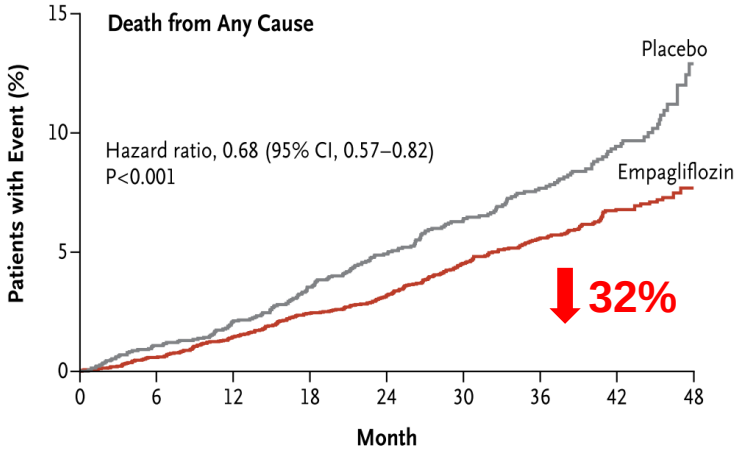
1.4 vs 0.98 events per 100 patient-years

RWE: real-world evidence

1. N Engl J Med 373:2117-28 (2015); 2. 2. Lancet Diabetes Endocrinol. 2017 Sep;5(9):709-717.

Lower All-cause Mortality of SGLT2i in RCT and RWE

EMPA-REG[1] (RCT, 100% CVD)



CVD-REAL Nordic[2] (real-world evidence, 24% CVD)

	SGLT-2i		oGLD		Hazard ratios (HR)		
	no. events	Rate/100-patient-yr	no. events	Rate/100 patient-yr	HR	95% CI	p-value
CV mortality	56	0.27	340	0.53	0.53	(0.40–0.71)	<0.001
All-cause mortality	289	1.05	1768	2.09	0.51	(0.45–0.58)	<0.001
HHF ↓49%	224	0.98	984	1.40	0.70	(0.61–0.81)	<0.001
MACE	339	1.64	1349	2.12	0.78	(0.69–0.87)	<0.001
Stroke	144	0.70	514	0.80	0.86	(0.72–1.04)	0.113
Myocardial infarction	161	0.78	574	0.90	0.87	(0.73–1.03)	0.112

CVDREAL NORDIC

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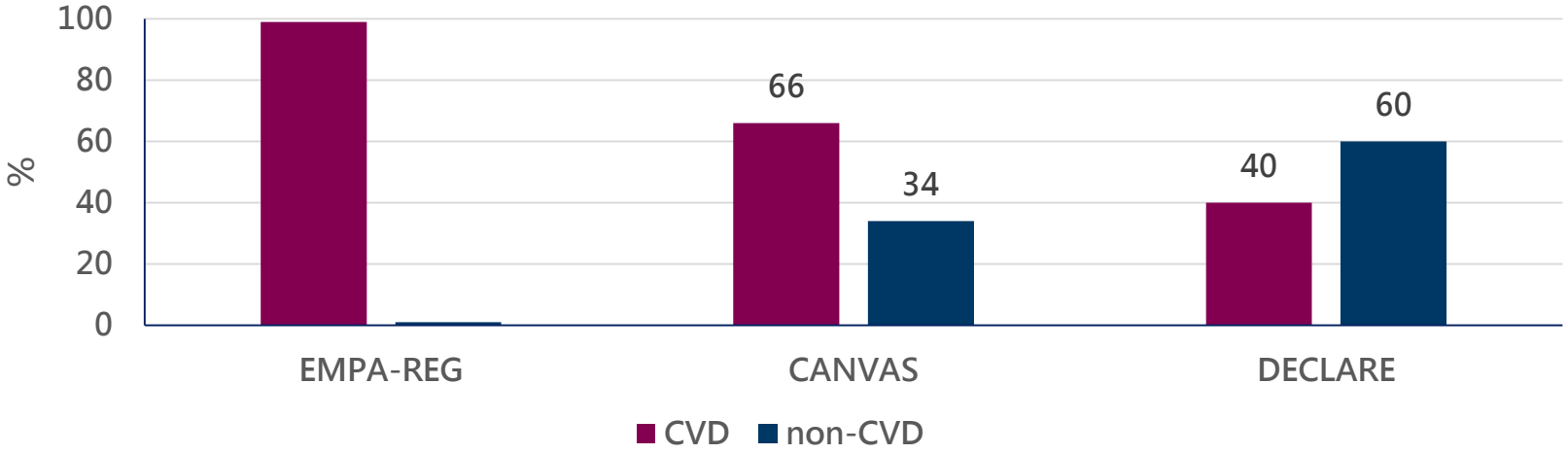
RWE: real-world evidence

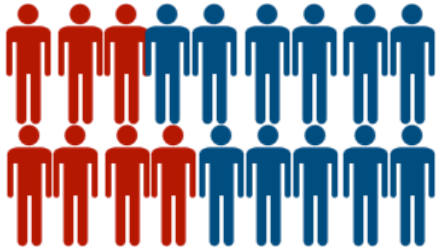
1. N Engl J Med 373:2117-28 (2015); 2. 2. Lancet Diabetes Endocrinol. 2017 Sep;5(9):709-717.

CVD and Non-CVD proportion in 3 CVOTs of SGLT-2 inhibitors



CVD 7,020 pt's

CVD 6,656 pt's
Non-CVD 3,486 pt's
Total 10,142 pt's

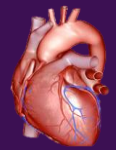


CVD 6,971 pt's
Non-CVD 10,189 pt's
Total 17,160 pt's

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Bruce Neal et al. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925.; 3. Itamar Raz et al. The 77th Scientific Sessions of the American Diabetes Association, San Diego, California, June 9-13, 2017; 1245-P

4 Reasons to Use SGLT-2 Inhibitors Early in T2DM

Effect on CVD & Death in non-CVD patients

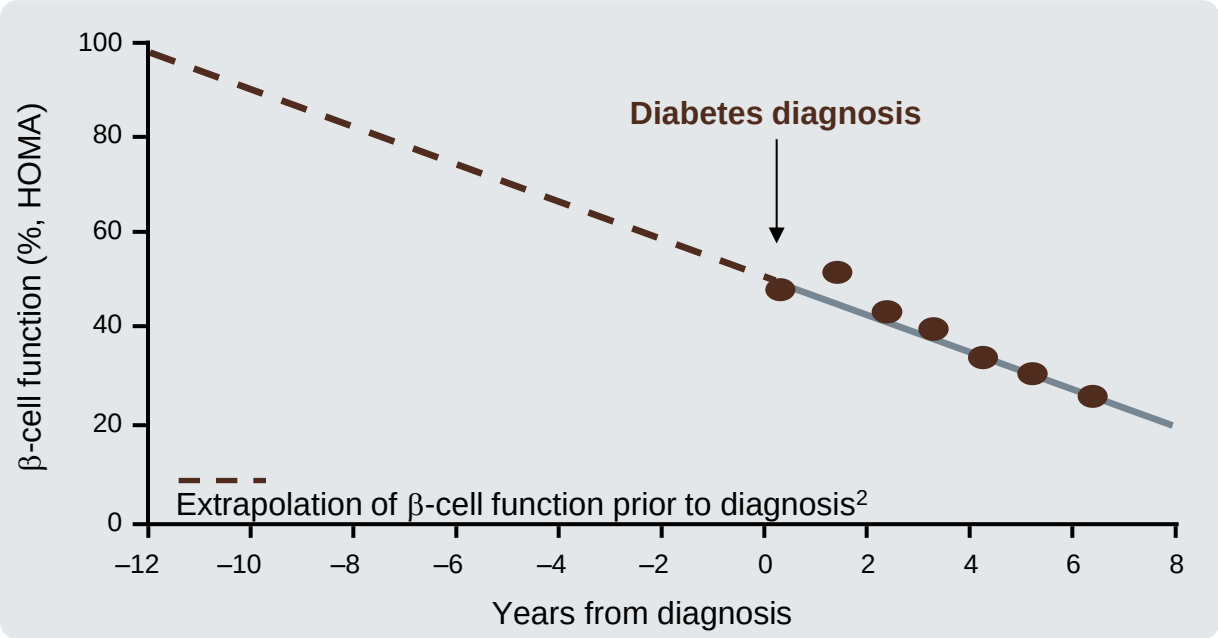


β-cell function & Insulin resistance

HbA1c

β-cell function progressively declines in T2DM

UKPDS demonstrated progressive β-cell through HOMA correlations



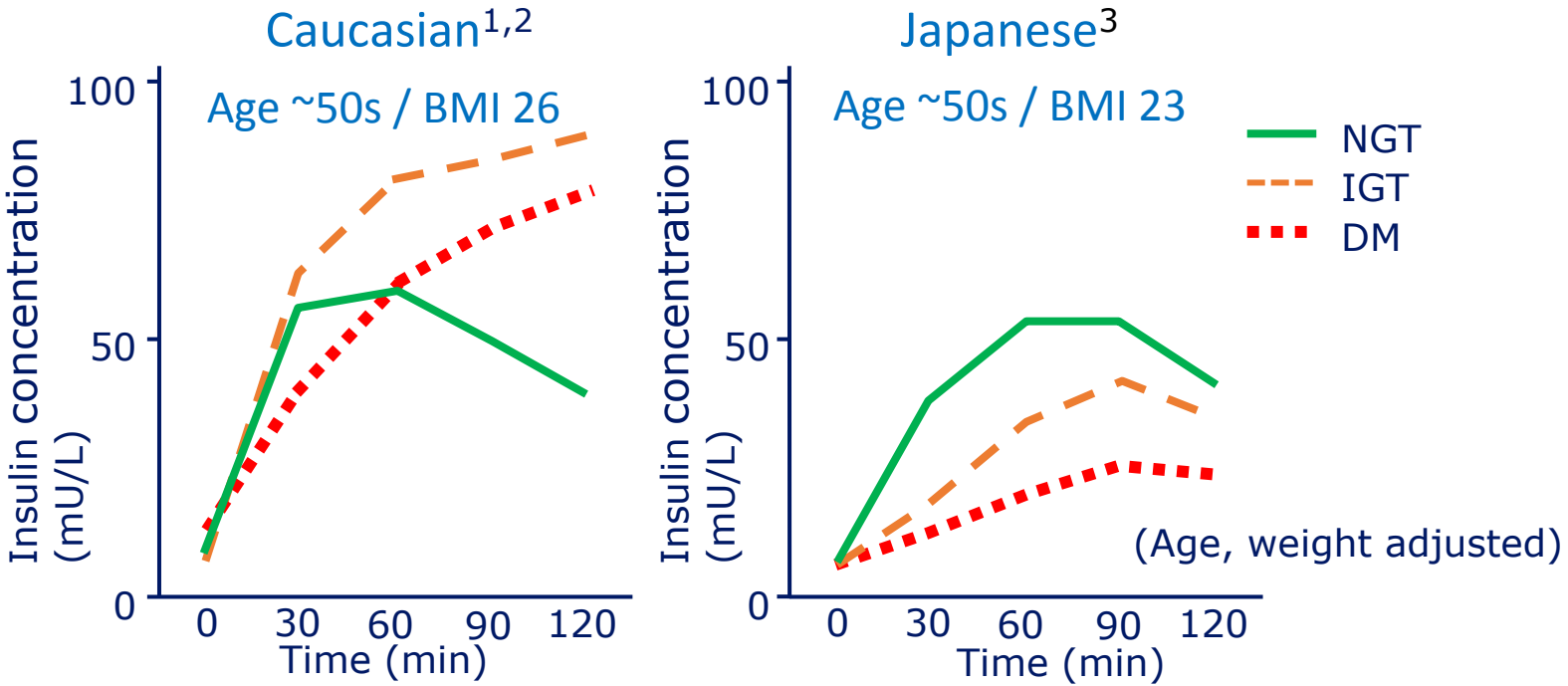
- Progressive ß-cell failure from prolonged hyperglycaemia / glucotoxicity is a key driver of disease progression in T2DM[1].
- Agents which preserve or restore ß-cell function are likely to have significant benefits[3].
- Some older agents, e.g. sulfonylureas, may promote ß-cell apoptosis[4].
- Sulfonylureas do not shorten time to insulin dependence[5].

*This graph has been drawn and adapted from data presented in UKPDS 16 . Data points relate to β-cell function in patients allocated to sulfonyurea treatment and remaining on this therapy after 6 years (n=511). HOMA=homeostasis model assessment.

1. Diabetes Care 13(6):610-30 (1990); 2. Adapted from UKPDS 16. Diabetes 44:1249-58 (1995); 3. Diabetes & metabolism journal. 38(6):426-36 (2014); 4. PLoS Medicine. 5(10) (2008); 5. Diabetes Care 37(5):1338-45 (2014)

Ethnic Differences in Pathophysiology (β-cell function)

Japanese individuals with NGT, IGT, and DM had lower insulin response to glucose ingestion than in white people



NGT: normal glucose tolerance; IGT: impaired glucose tolerance; DM: diabetes mellitus

1. Adapted from Diabetes 49;975-80 (2000); 2. Adapted from Metabolism 53;831-5 (2004); 3. Adapted from Diabetes Res Clin Pract 66(Suppl. 1);S37-43 (2004); 4. Curr Diab Rep 15:36 (2015)

Dapagliflozin can increase insulin sensitivity and improve beta cell function

Professor of Medicine and Chief of the Diabetes Division at the University of Texas Health Science Center Deputy Director of the Texas Diabetes Institute, San Antonio, Texas

nature REVIEWS NEPHROLOGY

SGLT2 inhibitors improve glycemic control and reduce the plasma glucose level through two distinct mechanisms:

1. Increasing the removal of plasma glucose by augmenting glucose excretion
2. Ameliorating glucotoxicity, which leads to improved **insulin sensitivity** in peripheral tissues and enhanced **β cell function**

Insulin sensitivity b-cell function

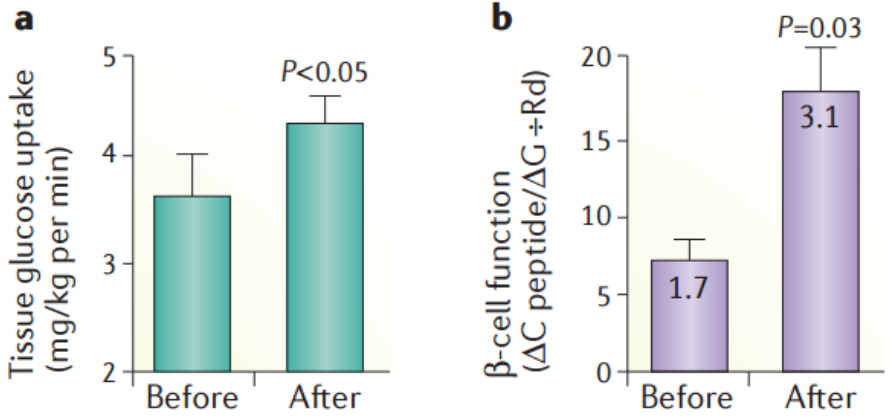
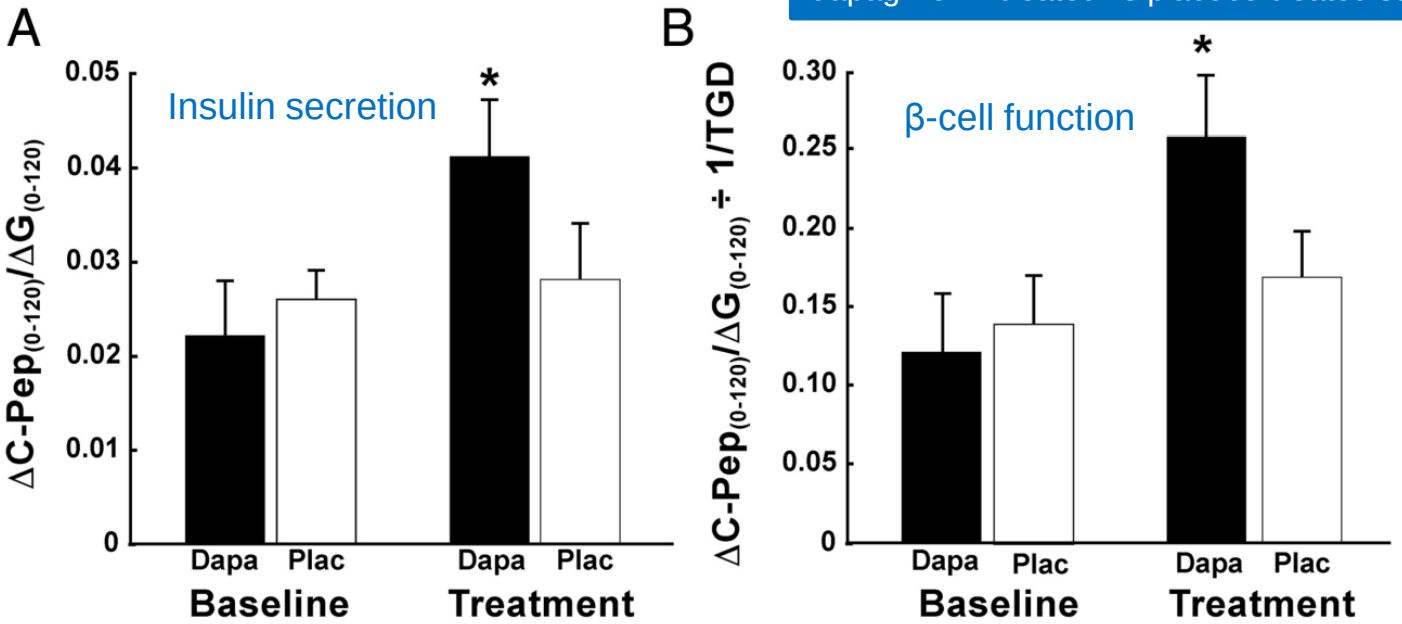


Figure 5 | **Effect of dapagliflozin on tissue sensitivity to insulin and β-cell function.** Treatment of patients with type 2 diabetes mellitus with dapagliflozin for 14 days led to a 25–30% improvement in muscle sensitivity to insulin (part **a**) and a nearly twofold increase in β-cell function (part **b**).

1. DeFronzo et.al. Nat Rev Nephrol. 13(1):11-26 (2017)

Dapagliflozin can improve insulin secretion and beta-cell function

β-cell function increased by **2-fold** (P<0.01) in dapagliflozin-treated vs placebo-treated subjects



24 subjects with T2DM received dapagliflozin (n=16) or placebo (n=8) for 2 weeks, 75-g OGTT and euglycemic hyperinsulinemic clamp were performed before and after treatment.

Figure 2. Insulin secretion (A) and β-cell function (B), measured as $\Delta C\text{-}Pep_{0-120}/\Delta G_{0-120} \div IR$, in dapagliflozin-treated and placebo-treated T2DM patients at baseline and after 2 weeks of treatment. *, $P < .05$ vs baseline and vs placebo. Dapa, dapagliflozin; Plac, placebo.

IR: insulin resistance, inverse of TGD; TGD: total body glucose disposal; OGTT: oral glucose tolerance test

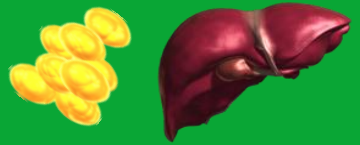
Merovci A et al. J Clin Endocrinol Metab. 2015 May;100(5):1927-32.

4 Reasons to Use SGLT-2 Inhibitors Early in T2DM

Effect on CVD & Death in non-CVD patients

β-cell function & Insulin resistance

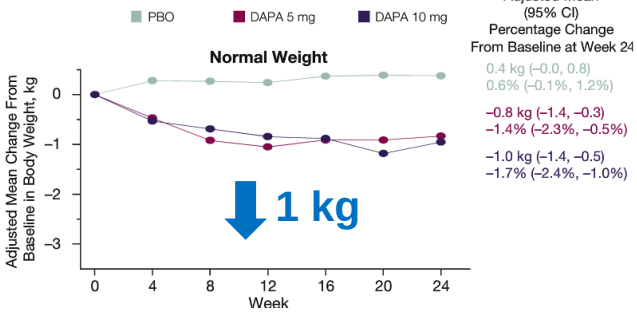
HbA1c



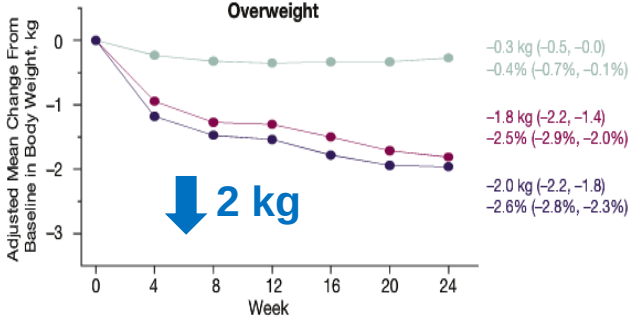
Fat mass & fatty liver

Reduction in body weight with dapagliflozin was greater in patients with higher BMI

BMI 18.5- <25

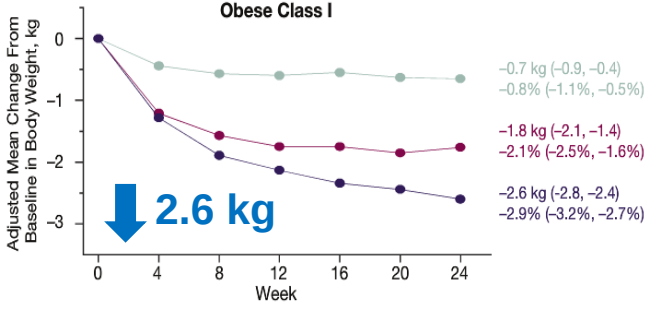


BMI 25-<30



- Normal weight: 18.5–<25 kg/m^2
- Overweight: 25–<30 kg/m^2
- Obese Class I: 30–<35 kg/m^2
- Obese Class II: 35–<40 kg/m^2
- Obese Class III: ≥40 kg/m^2

BMI 30-<35



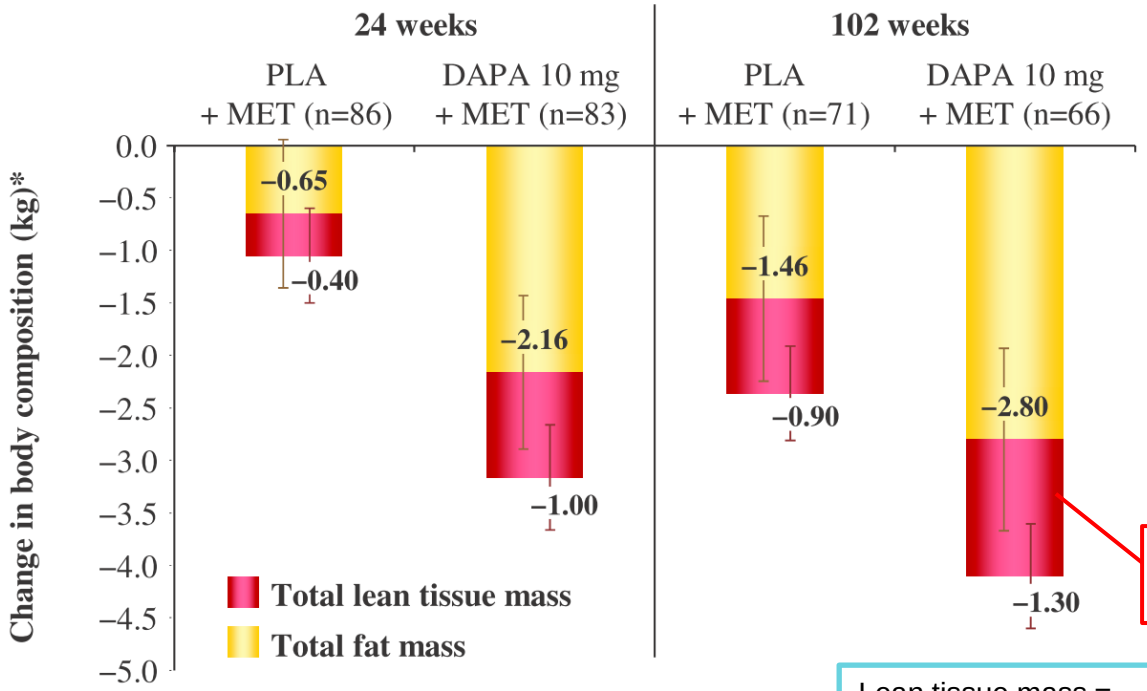
BMI 35-<40

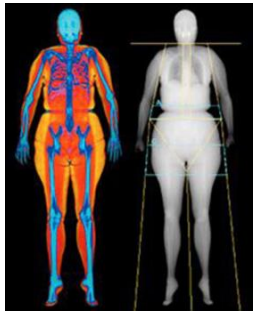
BMI >=40

ADA 76th Scientific Sessions, 1141-P, June 10 - 14, 2016, New Orleans

The reduction in total fat mass with Dapagliflozin[1]

Analysis showed dapagliflozin reduced fat mass rather than lean tissue or fluid loss, sustained up to 2 years





Whole body DXA (dual-energy X-ray absorptiometry) was used for the estimation of body composition.

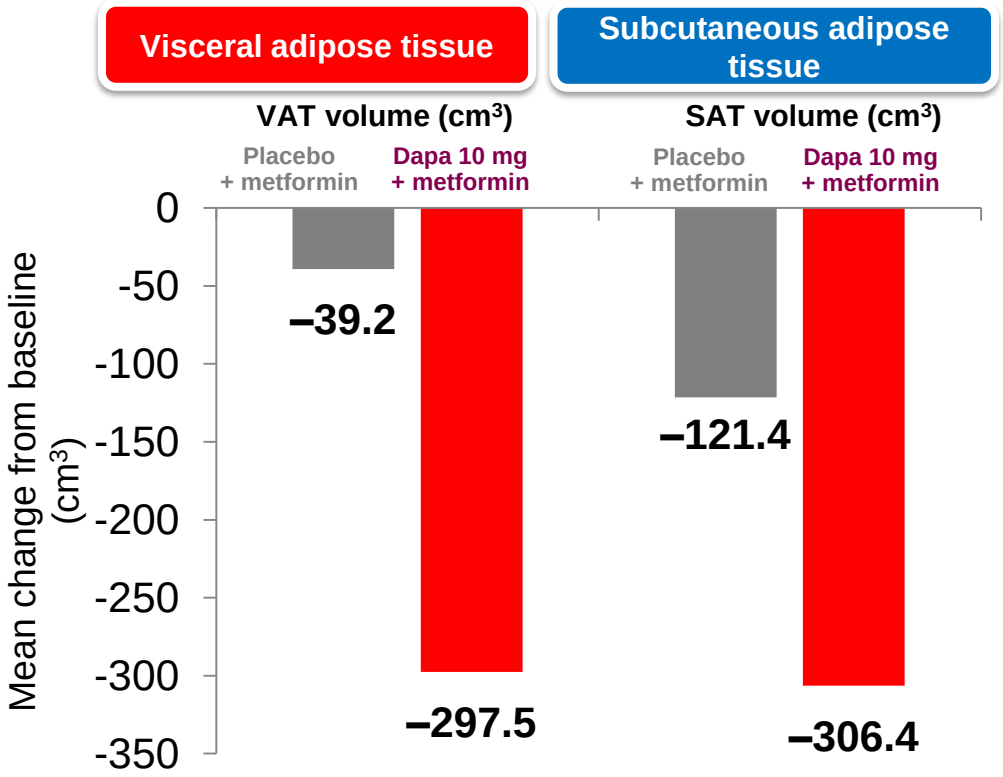
incorporating the fluid component[1]

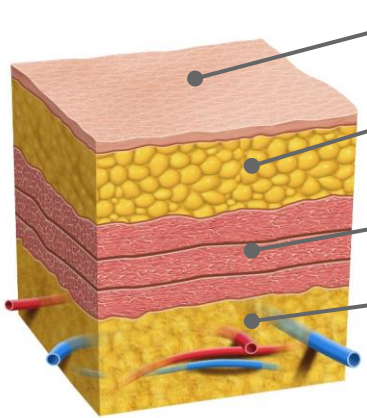
Lean tissue mass =
body weight − fat mass
= muscle mass + total body water

Dapagliflozin is not indicated for the management of weight loss.

1. Diabetes Obes Metab 16:159-69 (2014); 2. Nature Cell Biol 16:367-5. (2014)

The reduction in visceral adipose tissue and subcutaneous adipose tissue with Dapagliflozin at 24 weeks





Increased **fat mass** is associated with metabolic dysfunction[2]

Increased **lean tissue** is protective[2]

MR: magnetic resonance; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue.

J Clin Endocrinol Metab 97:1020-31 (2012)

Effect of Dapagliflozin in patients with T2DM and NASH

- In this single-arm, nonrandomized, open-label study, 11 patients with percutaneous liver biopsy-confirmed NASH and T2DM were prescribed with dapagliflozin 5mg/day for 24 weeks.

Effects of dapagliflozin on liver tests and metabolic laboratory variables (n = 11).

	Week 0 (baseline)	Week 2	Week 4	Week 8	Week 16	Week 24
	Median (interquartile range)					
AST (U/L)	52 (43–55)	50 (48–60)	48 (41–53)	39 (32–42)**	33 (23–38)**	26 (24–38)**
ALT (U/L)	59 (48–69)	65 (49–76)	55 (47–73)	47 (36–50)**	30 (26–40)**	30 (20–37)**
γ-GTP (U/L)	64 (47–94)	57 (37–86)**	49 (36–81)**	50 (30–69)**	38 (23–65)**	33 (24–67)**
Fibrosis-4 index	1.83 (1.35–2.49)	1.99 (1.13–2.52)	2.01 (1.25–2.90)	1.94 (1.13–2.34)	1.73 (1.12–1.95)**	1.59 (1.29–2.37)
Adiponectin (μg/mL)	5.40 (4.60–8.85)		5.90 (4.85–10.15)**			7.00 (5.60–11.80)**
hsCRP (mg/dL)	0.26 (0.11–0.53)		0.14 (0.08–0.26)**	0.13 (0.07–0.40)	0.12 (0.09–0.24)	0.12 (0.05–0.32)
FPG (mg/dL)	147 (132–176)	138 (121–153)*	126 (121–155)**	124 (115–153)**	120 (106–148)**	119 (107–150)**
HbA1c (%)	7.4 (6.9–8.3)		6.9 (6.5–7.95)**	7.0 (6.25–7.55)**	6.8 (6.15–7.4)**	6.7 (5.95–7.3)**
Glucagon (pg/mL)	184 (166–198)			168 (157–181)*	172 (158–181)	175 (181–198)
HDL-C (mg/dL)	52 (46–58)	52 (46–55)	51 (46–58)	52 (43–58)	55 (48–62)*	55 (49–64)*
LDL-C (mg/dL)	116 (106–124)	104 (97–123)	109 (91–127)	118 (94–129)	107 (96–119)	116 (106–126)
Triglycerides (mg/dL)	118 (111–162)	123 (97–157)	108 (80–145)	99 (90–141)*	97 (79–128)**	98 (84–154)

NASH: nonalcoholic steatohepatitis

HiroshiTobita et al. Curr Ther Res Clin Exp. 2017 Jul 8;87:13-19.

Effect of Dapagliflozin in patients with T2DM and NASH

- In this single-arm, nonrandomized, open-label study, 11 patients with percutaneous liver biopsy-confirmed NASH and T2DM were prescribed with dapagliflozin 5mg/day for 24 weeks.

Effects of dapagliflozin on body composition-related variables (n = 11).

	Week 0 (baseline)	Week 2	Week 4	Week 8	Week 16	Week 24
	Median (interquartile range)					
Body weight (kg)	79.6 (63.3–94.2)	78.3 (62.7–93.2)**	78.5 (62.8–92.8)*	78.8 (61.7–88.3)**	79.6 (59.8–82.9)**	75.8 (59.8–82.3)**
BMI	31.0 (27.0–32.5)	30.3 (26.9–32.2)**	29.9 (27.2–32.1)*	29.0 (26.8–31.7)**	27.4 (25.6–31.8)**	27.3 (24.8–31.3)**
Waist circumference (cm)	101.4 (97.6–108.5)	102.6 (96.2–108.0)	103.2 (97.9–107.7)	99.5 (96.6–106.6)**	94.8 (92.3–106.8)**	94.2 (89.9–104.5)**
Waist-to-hip ratio	1.02 (0.96–1.05)	1.02 (0.96–1.04)	1.01 (0.96–1.05)	1.00 (0.95–1.04)	1.00 (0.94–1.03)**	1.00 (0.92–1.04)**
Total body water (l)	32.7 (28.8–47.8)	32.7 (28.3–46.3)	33.0 (29.0–45.2)	32.9 (28.2–45.0)	34.1 (28.2–43.8)	33.9 (28.4–43.5)
Body fat mass (kg)	28.3 (25.7–35.4)	29.6 (24.9–34.5)	30.1 (25.9–34.4)	27.3 (24.9–33.0)*	25.0 (21.3–32.5)**	22.2 (18.8–31.4)**
Percent body fat (%)	42.4 (33.0–44.5)	40.0 (33.2–44.0)	41.2 (32.9–43.9)	39.5 (31.5–42.1)	38.2 (30.0–41.3)**	38.2 (27.2–41.0)**
Lean mass (kg)	45.0 (39.2–65.0)	44.3 (38.5–62.7)	44.6 (39.3–61.5)	44.5 (38.4–61.3)	46.1 (38.4–59.7)	45.8 (38.7–59.2)
Protein (kg)	8.7 (7.7–12.7)	8.6 (7.6–12.3)	8.7 (7.7–12.1)	8.6 (7.6–12.1)	8.9 (7.6–11.8)	8.8 (7.6–11.7)
Soft lean mass (kg)	41.9 (36.9–61.4)	41.9 (36.3–59.4)	42.2 (37.1–57.9)	42.1 (36.2–57.9)	43.6 (36.3–56.3)	43.3 (36.5–55.9)
Skeletal muscle mass (kg)	24.6 (21.1–36.3)	24.0 (20.7–34.9)	24.1 (21.1–34.4)	24.1 (20.9–34.6)	24.9 (20.9–33.6)	24.7 (20.9–33.3)
Percent skeletal muscle (%)	30.9 (30.2–37.2)	32.4 (30.2–37.3)	32.9 (30.4–37.3)	32.4 (31.4–37.3)	34.1 (31.7–38.2)*	34.1 (31.9–40.4)**
ASM (%)	23.3 (22.7–28.1)					25.5 (24.3–30.2)**
SMI (kg/m^2)	7.61 (6.36–9.12)					7.70 (6.19–8.56)

NASH: nonalcoholic steatohepatitis,
ASM: appendicular skeletal muscle,
SMI: skeletal muscle mass index
HiroshiTobita et al. Curr Ther Res Clin Exp. 2017 Jul 8;87:13-19.

SGLT2i can reduce AST and ALT level in Asia T2DM patients

AST and ALT were significantly (p<0.001) decreased by Dapagliflozin 5 mg QD, while the liver function remained unchanged by Sitagliptin 50 mg QD treatment for 12 weeks

	Dapagliflozin (n = 40)				Sitagliptin (n = 40)				p value[b]
	Pre treatment	Post treatment	% change	p value[a]	Pre treatment	Post treatment	% change	p value[a]	
BW (kg)	78.4 ± 14.3	76.2 ± 1.8	−2.8	<0.001*	77.6 ± 11.6	77.7 ± 11.6	0.1	0.089	0.042*
AST (IU/L)	34.5 ± 19.4	26.8 ± 12.8	−22.3	<0.001*	33.2 ± 9.8	35.4 ± 14.9	6.6	0.089	<0.001*
ALT (IU/L)	46.6 ± 37.0	33.5 ± 24.9	−28.1	<0.001*	42.8 ± 15.0	44.9 ± 18.4	4.9	0.202	<0.001*
Adiponectin (ng/mL)	6.0 ± 3.4	7.6 ± 4.2	26.7	<0.001*	6.2 ± 5.3	6.2 ± 3.8	0	0.899	0.002*

The single center, open-label, randomized trial included 80 patients with type 2 diabetes in Japan, whose blood glucose was inadequately controlled despite combined treatment with diet/exercise and an oral hypoglycemic drug for more than 12 weeks prior to screening (baseline A1c 7.6)

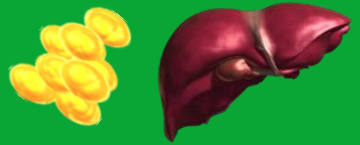
AST: aspartate aminotransferase, ALT: alanine aminotransferase
Hayashi T et al. Cardiovasc Diabetol. 2017 Jan 13;16(1):8.

4 Reasons to Use SGLT-2 Inhibitors Early in T2DM

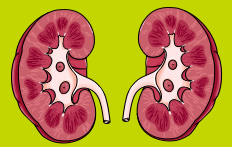
Effect on CVD & Death in non-CVD patients

β-cell function & Insulin resistance

HbA1c

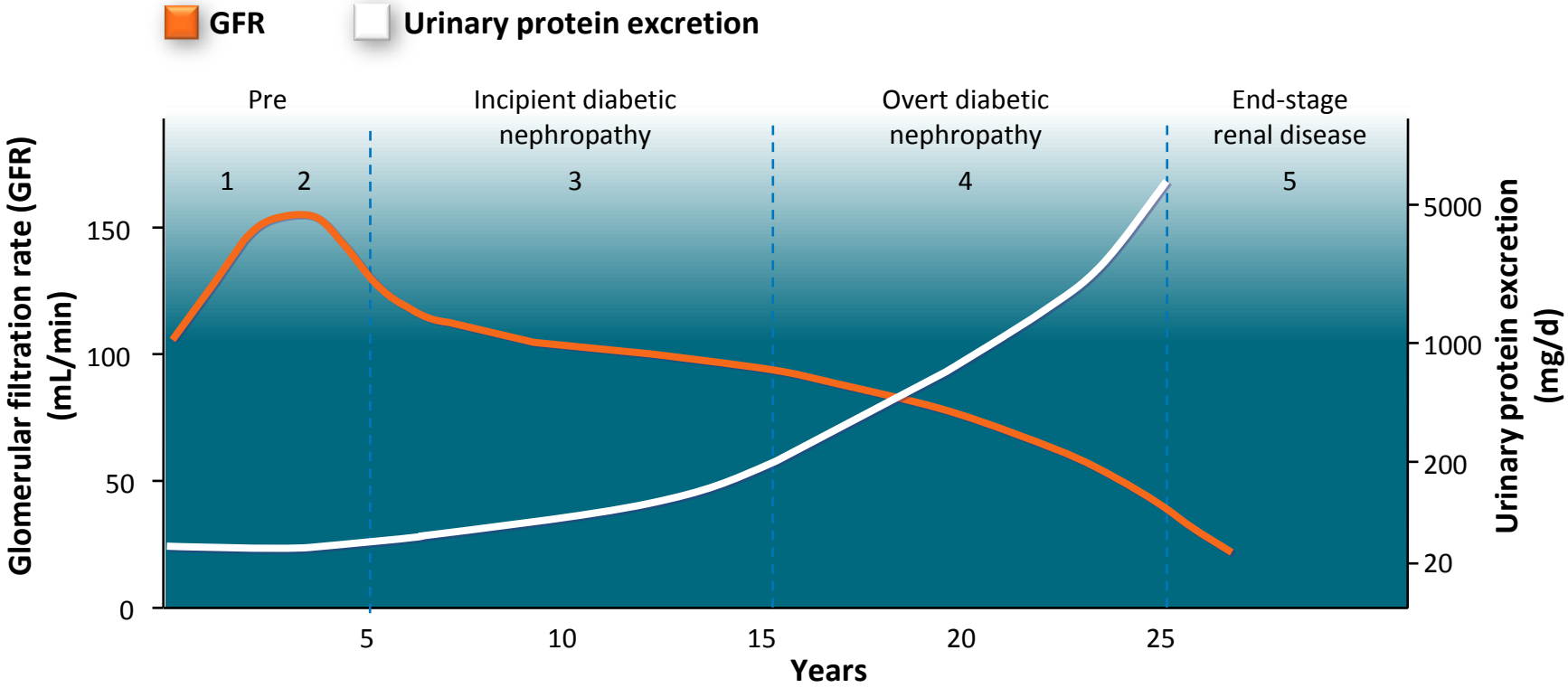


Fat mass & fatty liver



Renal function

Natural history of diabetic nephropathy

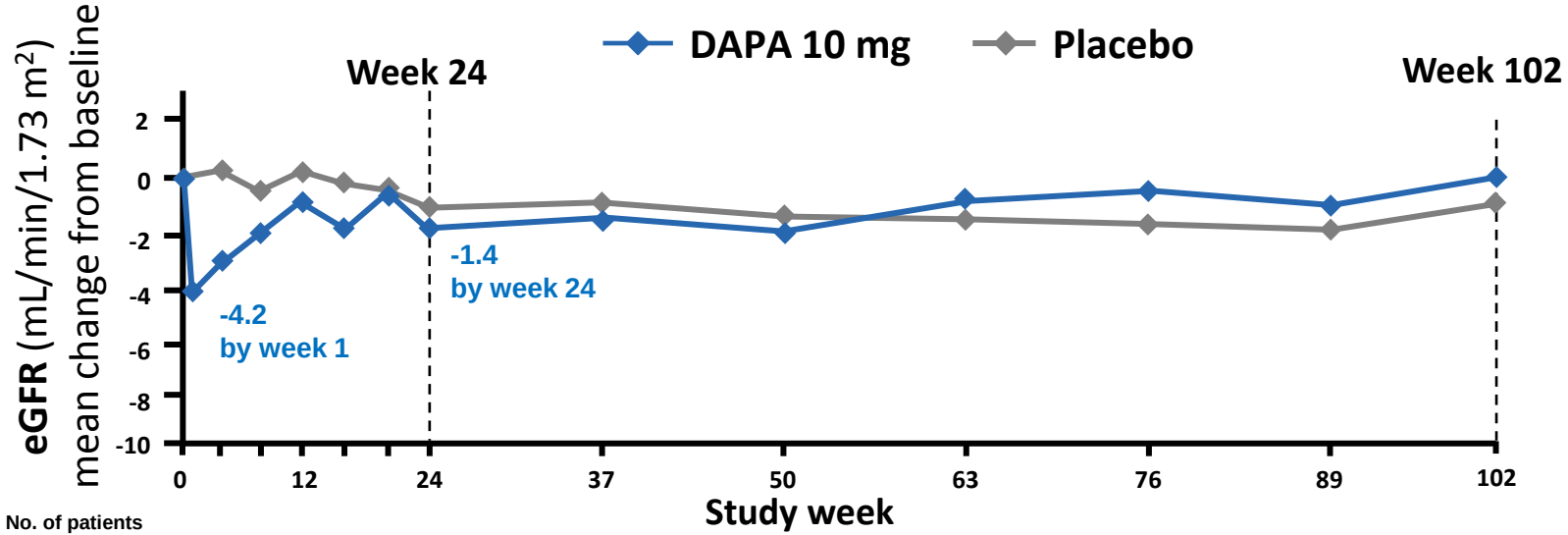


Functional	Hyperfiltration	Microalbuminuria, hypertension	Albuminuira, declining GFR

Vora JP, et al. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. New York: Mosby; 2000.

Initial, transient drop in eGFR followed by an increase towards baseline value over time

Pooled safety analysis of 9 short-term + long-term, Phase 3 placebo-controlled trials



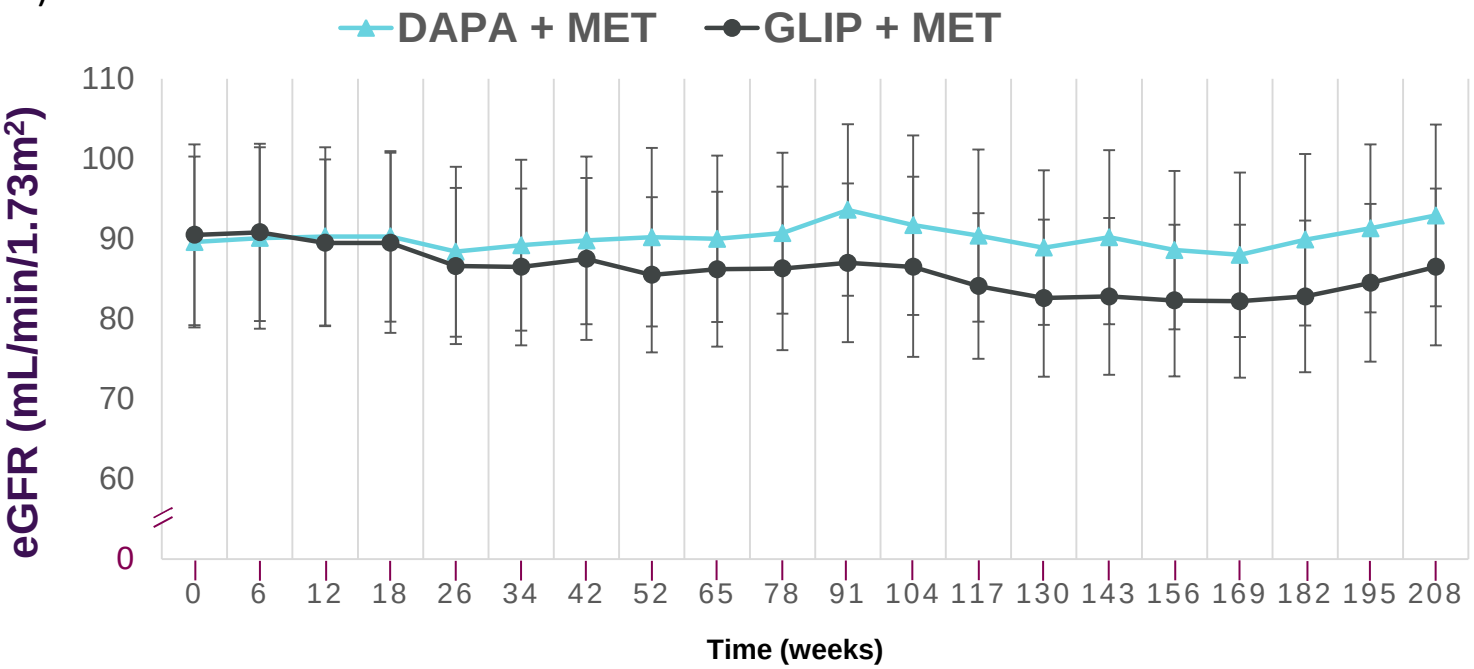
No. of patients									
DAPA 10 mg	2026	1655	1777	1600	1663	712	692	656	627
Placebo	1955	1570	1671	1513	1558	605	585	551	521

- Mean eGFR decreased initially by week 1 and then gradually increased towards eGFR baseline values over several weeks; mean eGFR values remained stable thereafter

eGFR, estimated glomerular filtration rate FDA, EMDAC: Dapagliflozin Background document 2013: www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf

Mean eGFR Remained Stable in Patients Receiving Dapagliflozin compared to SU for Up To 4 Years

- Randomized, double-blind, phase III study of dapagliflozin (n=406) vs glipizide (n=408) to 208 weeks (4 years)



Study's renal exclusion criteria included patients with calculated CrCl <60 mL/min, urine albumin:creatinine ratio >203.4 mg/mmol, or significant renal disorder. DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; SU: GLIP, glipizide; MET, metformin.

Del Prato S et al. Diabetes Obes Metab. 2015 Jun;17(6):581-90.

Dapagliflozin was not associated with higher renal impairment compared with SU for Up To 4 Years

	Dapagliflozin + metformin					Glipizide + metformin				
Time period	Entire study	Short-term (to 52 weeks)	First extension (to 104 weeks)	Second extension (to 156 weeks)	Second extension (to 208 weeks)	Entire study	Short-term (to 52 weeks)	First extension (to 104 weeks)	Second extension (to 156 weeks)	Second extension (to 208 weeks)
N	406	406	315	204	178	408	408	309	188	162
AEs, n (%)										
Hypoglycaemia	22 (5.4)	14 (3.4)	5 (1.6)	3 (1.5)	4 (2.2)	210 (51.5)	162 (39.7)	73 (23.6)	70 (37.2)	46 (28.4)
Major*	0	0	0	0	0	3 (0.7)	3 (0.7)	0	0	0
Minor†	15 (3.7)	7 (1.7)	5 (1.6)	3 (1.5)	4 (2.2)	200 (49.0)	147 (36.0)	69 (22.3)	68 (36.2)	45 (27.8)
Other‡	8 (2.0)	7 (1.7)	1 (0.3)	0	0	49 (12.0)	40 (9.8)	8 (2.6)	9 (4.8)	2 (1.2)
Confirmed genital infection	58 (14.3)	44 (10.8)	16 (5.1)	7 (3.4)	5 (2.8)	12 (2.9)	7 (1.7)	1 (0.3)	1 (0.5)	3 (1.9)
Males	17 (7.5)	NA	NA	NA	NA	1 (0.4)	NA	NA	NA	NA
Females	41 (22.8)	NA	NA	NA	NA	11 (5.9)	NA	NA	NA	NA
Confirmed UTI	55 (13.5)	35 (8.6)	15 (4.8)	6 (2.9)	12 (6.7)	38 (9.3)	22 (5.4)	13 (4.2)	6 (3.2)	7 (4.3)
Males	20 (8.8)	NA	NA	NA	NA	13 (5.8)	NA	NA	NA	NA
Females	35 (19.4)	NA	NA	NA	NA	25 (13.5)	NA	NA	NA	NA
Reduced renal creatinine clearance§	20 (4.9)	17 (4.2)	0	2 (1.0)	1 (0.6)	13 (3.2)	8 (2.0)	2 (0.6)	2 (1.1)	2 (1.2)
eGFR decreased§	2 (0.5)	1 (0.2)	0	1 (0.5)	0	4 (1.0)	3 (0.7)	0	1 (0.5)	0
Renal impairment§	10 (2.5)	4 (1.0)	1 (0.3)	5 (2.5)	1 (0.6)	11 (2.7)	2 (0.5)	4 (1.3)	3 (1.6)	2 (1.2)

eGFR, estimated glomerular filtration rate; SU: GLIP, glipizide; MET, metformin.

Del Prato S et al. Diabetes Obes Metab. 2015 Jun;17(6):581-90.

The pooled analyses indicated no renal toxic effects associated with dapagliflozin

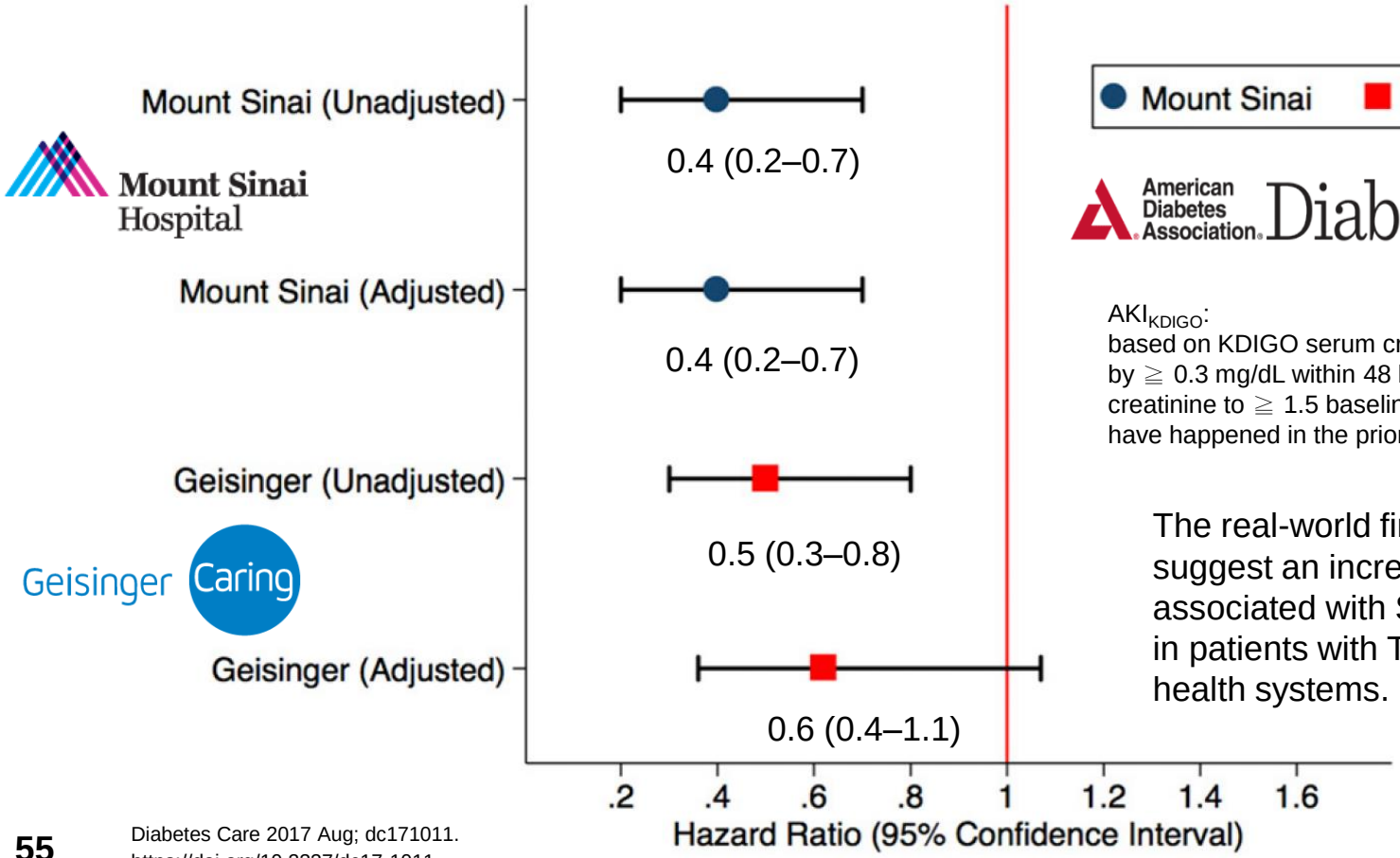
AEs of renal function: 12-study ST pool	DAPA (N=3291)	Placebo (N=1393)
Total renal AEs, %	1.2	0.9
≥1 serious renal AEs, %	0	0
AEs of renal function: Five of the 12-study pool with LT extension	**DAPA (N=2160)**	**Control (N=694)**
Total renal AEs, %	2	1.6
≥1 serious renal AEs, %	0.1	0.1
AEs of renal function: 21-study pool	**DAPA (N=5936)**	**Control (N=3403)**
Total renal SAEs, n (%)	9 (0.2)	5 (0.1)
Renal failure	4 (0.1)	1 (<0.1)
Renal failure (acute)	3 (0.1)	3 (0.1)
Creatinine renal clearance decreased	1 (<0.1)	0
Anuria	0	1 (<0.1)

AEs of bone fracture, renal function, and DKA were based on a pre-specified list of preferred terms. DAPA total includes DAPA 2.5, 5, 10, 20, and 50 mg; Control includes placebo with or without background medications or active control including benchmark treatments

AE, adverse event; DAPA, dapagliflozin; DKA, diabetic ketoacidosis; LT, long-term; NA, not assessed; SAE, serious adverse event; ST, short-term

Jabbour S, et al. 14th Annual World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease; December 1st–3rd, 2016; Los Angeles, CA; Poster 120

No increased risk of AKI with SGLT2i use in patients with T2DM in two large health systems



Mount Sinai Hospital

Geisinger Caring

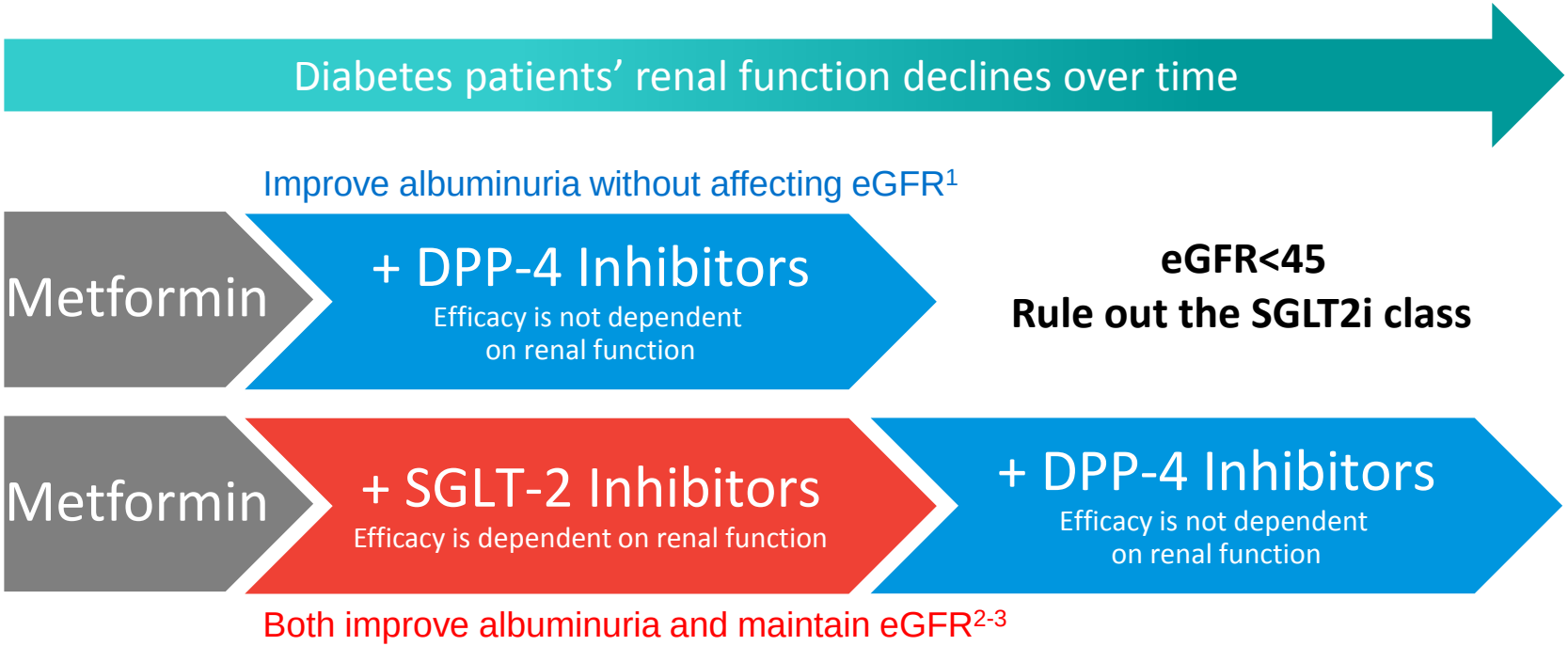
American Diabetes Association. Diabetes Care

AKI_{KDIGO}:
based on KDIGO serum creatinine criteria (increase by ≧ 0.3 mg/dL within 48 h or increase in serum creatinine to ≧ 1.5 baseline known or presumed to have happened in the prior 7 days)

The real-world findings do not suggest an increased risk of AKI associated with SGLT2 inhibitor use in patients with T2D in two large health systems.

Diabetes Care 2017 Aug; dc171011.
https://doi.org/10.2337/dc17-1011

A DPP4i would be a logical next step as add-on to metformin, but what if we change the order (SGLT2i ahead of DPP4i)?



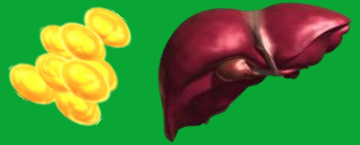
1. Diabetes Care 2017 Jan; 40(1): 69-76. 2. Diabetes Obes Metab. 2015 Jun;17(6):581-90. 3. N Engl J Med 2016;375:323-34.

Conclusions

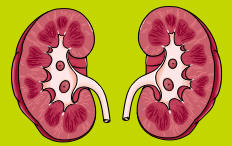
Effect on CVD & Death in non-CVD patients

β-cell function & Insulin resistance

HbA1c



Fat mass & fatty liver



Renal function