New evidence of pharmacologic approaches to glycemic treatment: Which SGLT2i is better after metformin use?

臺北榮總內分泌新陳代謝科 主治醫師 林怡君

20180901

Outline

1. SGLT2i Clinical Data vs Major Medication
   - Efficacy of Glycemic Control
   - vs DPP4i / with DPP4i
   - Beyond Glycemic Control
2. Guidelines
3. Special consideration

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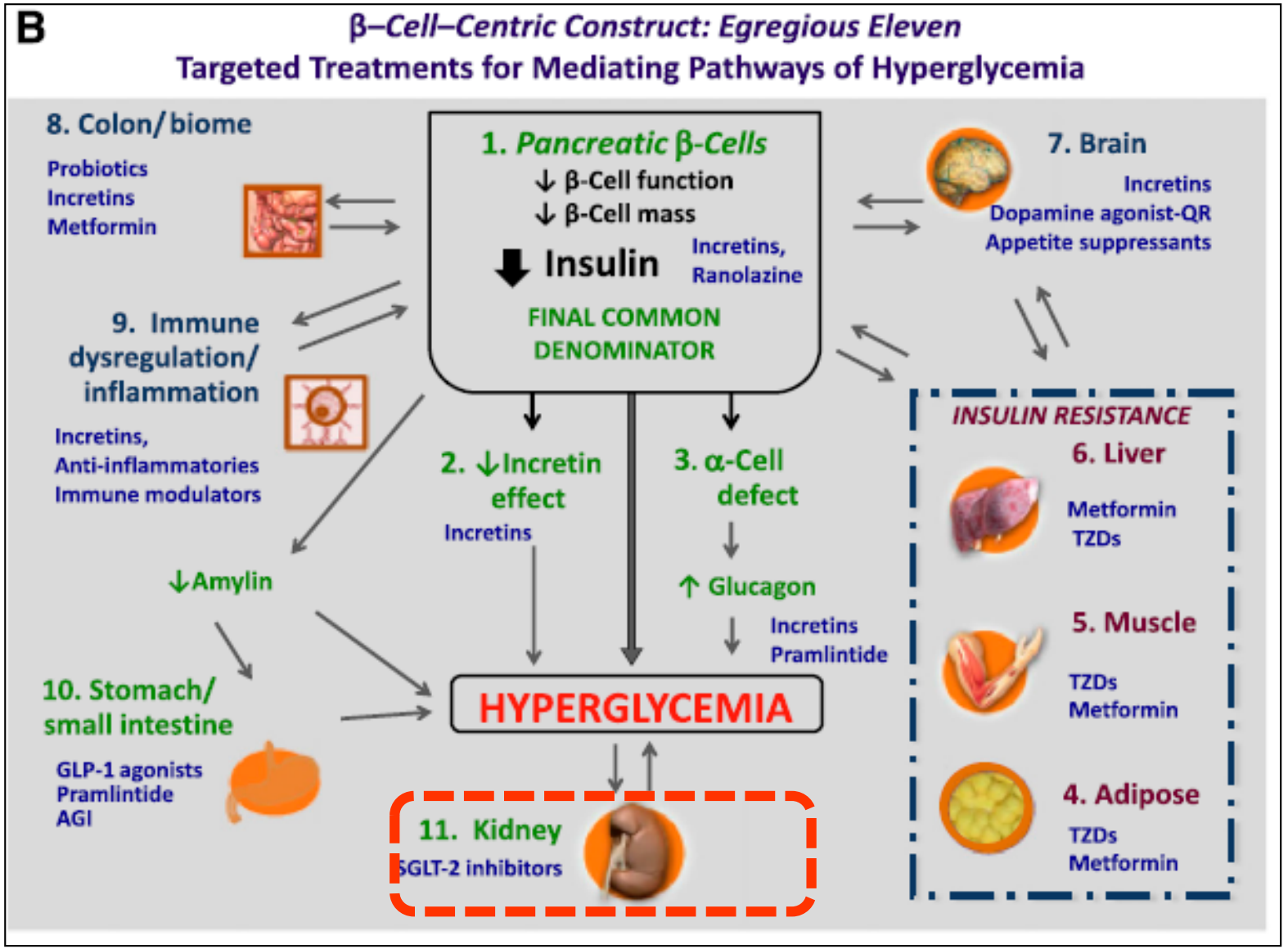
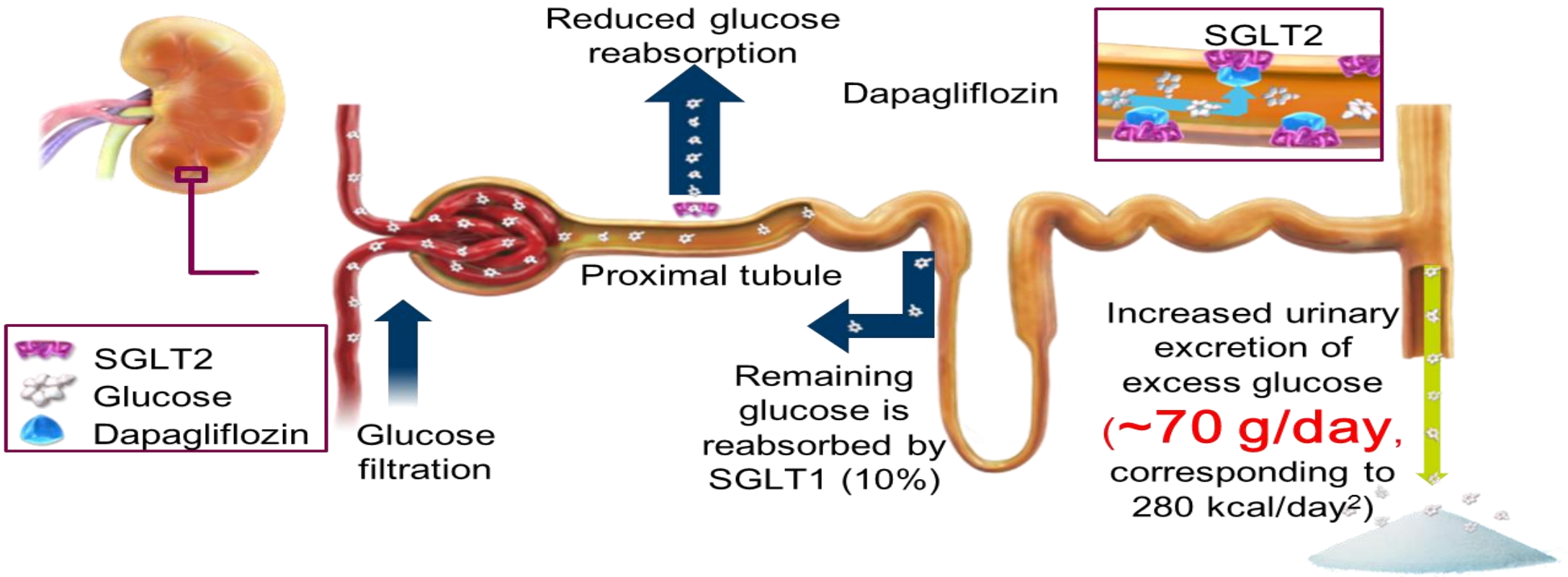
Unique Insulin Independent MOA to Control Glucose



Schwartz SS, Diabetes Care 2016;39:179–186

Forxiga Inhibits SGLT2 by an Insulin-independent Mechanism to Remove Excess Glucose in the Urine

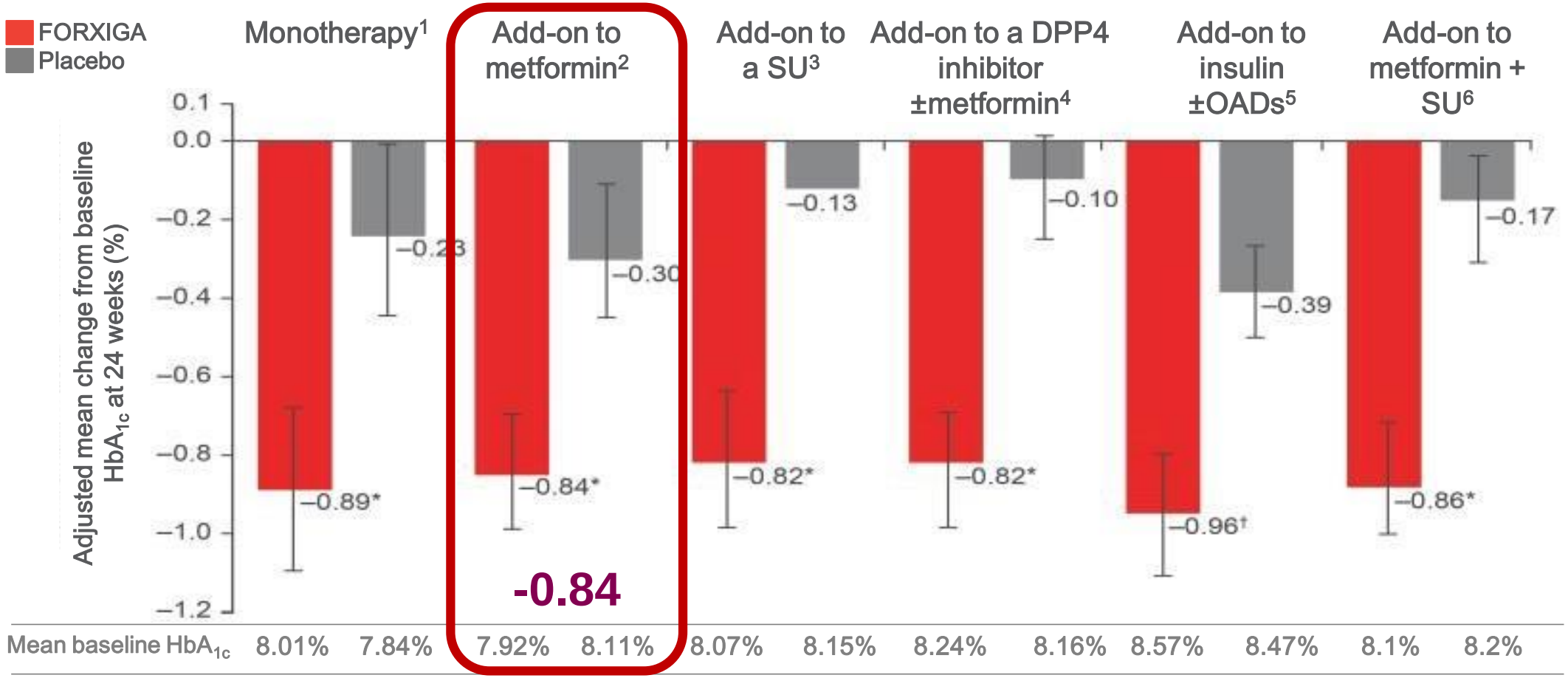


- By inhibiting SGLT2, dapagliflozin removes excess glucose in the urine and lowers HbA_{1c}[1]
- Dapagliflozin is >1400-times more selective for SGLT2 versus SGLT1[1]

SGLT2 and SGLT1—their relative roles in glucose reabsorption[1,2]

	SGLT2	SGLT1
Site	Almost exclusively kidney	Primarily intestine with some in kidney
Sugar specificity	Glucose	Glucose and galactose
Affinity for glucose	Low (2 mM)	High (0.4 mM)
Capacity for glucose transport	High (10 nmol/mg/min)	Low (2 nmol/mg/min)
Role	Renal glucose reabsorption	Dietary glucose absorption Renal glucose reabsorption

Extensive Evidence for Using Across a Broad Range of Treatments



*Statistically significant versus placebo ($p<0.0001$); †Statistically significant versus placebo ($p<0.001$).
DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; OAD, oral antidiabetic drug; SU, sulphonylurea.
1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. Mathieu C, *et al.* Presented at the Annual Scientific Sessions of the American Diabetes Association, Boston, USA. 5–9 June 2015. Abstract 105-OR;
5. Wilding JPH, *et al. Ann Intern Med* 2012;**156**:405–15; 6. Matthaei S, *et al.* Poster presented at the 49th European Association for the Study of Diabetes, Barcelona, Spain. 23–27 September 2013; Abstract 937-P.

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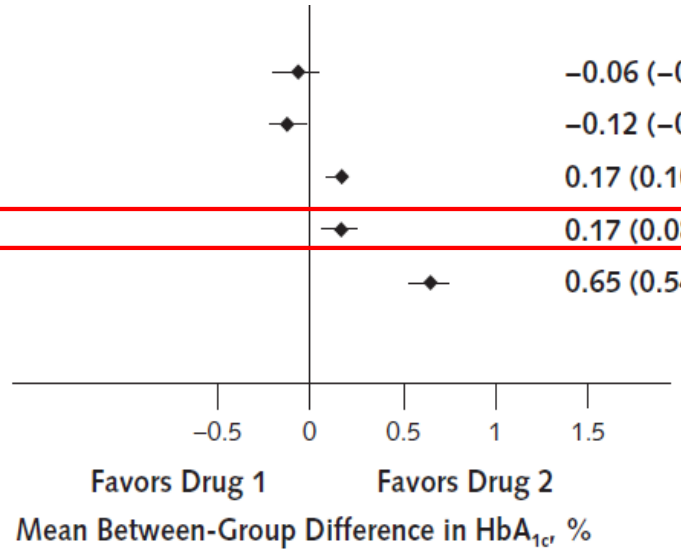
Pooled Between-group Differences in the change in HbA1c for Comparisons of Metformin-based Combination Therapies

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Participants, *n*	Study Characteristics	Effect Size (95% CI)	Strength of Evidence
Metformin-based combinations					
Met + TZD vs. Met + SU	8	3063	≤52 wk	−0.06 (−0.19 to 0.06)	Moderate
Met + TZD vs. Met + DPP-4	5	926	≤52 wk	−0.12 (−0.21 to −0.02)	Moderate
Met + SU vs. Met + SGLT-2	3	2933	104 wk	0.17 (0.10 to 0.20)	Moderate
Met + DPP4 vs. Met + SGLT-2	4	1278	≤52 wk	0.17 (0.08 to 0.26)	Moderate
Met + DPP4 vs. Met + GLP-1	3	1385	≤52 wk	0.65 (0.54 to 0.75)	Moderate

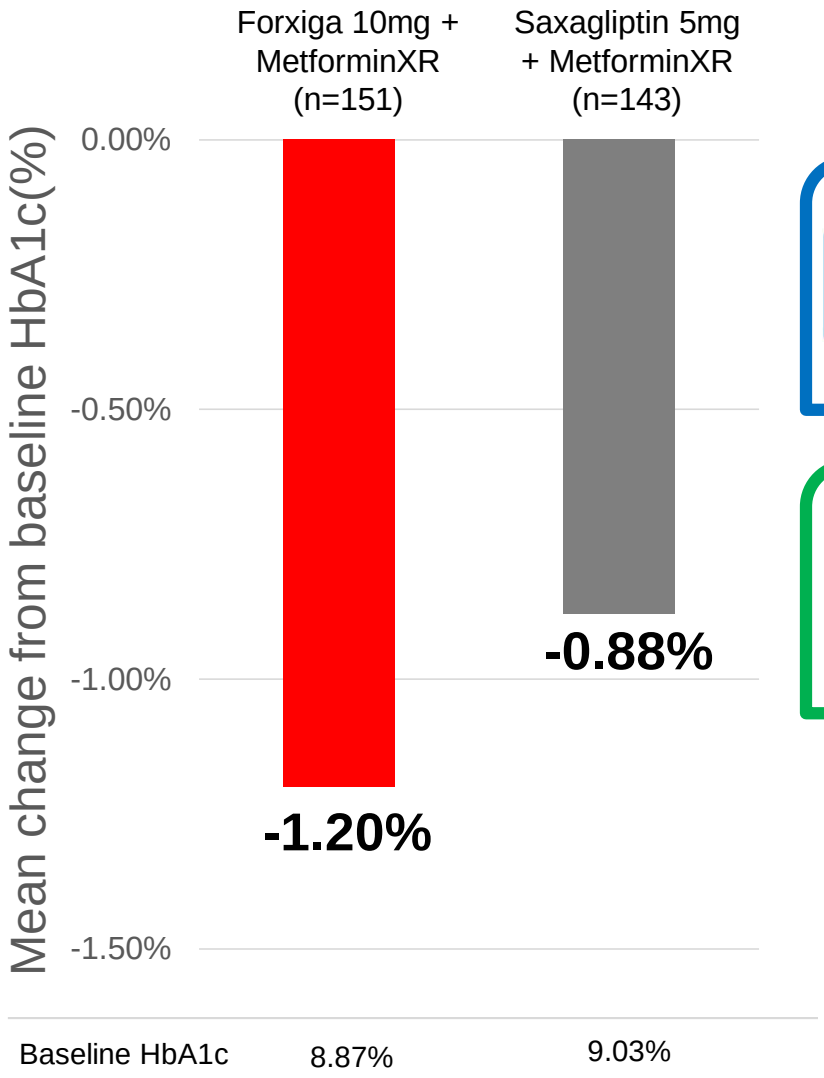


Nisa M. Maruthur et al. Ann Intern Med. 2016;164:740-751.

The Efficacy of HbA1c Reduction - SGLT2i vs DPP4i

Post-hoc Analysis of HbA1c Reductions with Forxiga vs DPP4i at 24 weeks

		DAPA+ MET	SAXA+ MET
HbA1c (%)	Baseline	8.87	9.03
	Change	-1.20	-0.88
PPG (mg/dL)	Baseline	247	256
	Change	-70	-36
FPG (mg/dL)	Baseline	185	192
	Change	-32	-14



Weight loss
-2.4 kg
vs saxagliptin

SBP reductions
-3.8 mmHg
vs saxagliptin

Rosenstock J, et al. Diabetes Care 2015;38:376-83

More than 56% T2DM Patients are Overweight in Taiwan

Table 1 – Clinical characteristics (mean ± SD) of, and percentage of goals attained by, diabetic subjects who participated in the 2011 survey.

	Total	Type 1 diabetes	Type 2 diabetes
Number	5599	82	5511
Men (%)	49.8	45.1	49.9
Age (years)	62.8 ± 12.4	38.1 ± 14.0	63.2 ± 12.0
Duration of diabetes (years)	10.6 ± 7.6	13.5 ± 8.1	10.5 ± 7.6
Height (cm)	160 ± 9	163 ± 9	160 ± 9
Weight (kg)	67 ± 13	62 ± 12	67 ± 13
BMI (kg/m^2)	26.0 ± 4.2	23.3 ± 3.9	26.1 ± 4.2
% of <23 kg/m^2	22.8	50.6	22.4
% of 23–24.9 kg/m^2	21.4	28.4	21.3
% of 25–29.9 kg/m^2	40.2	12.3	40.6
% of ≥30 kg/m^2	15.6	8.6	15.7

56% T2DM patients are overweight*

*BNHP=Bureau of National Health Promotion 國民健康局; WHO definition: Overweight (BMI≥25), Obese(BMI≥30)

Yu Neng-Chun, et al., diabetes research and clinical practice 99 (2013) 112 – 119

Prevalence of Hypertension in T2DM Patients is over 60% in Taiwan

Table 1 Prevalence of hypertension and dyslipidemia in individuals with diabetes stratified by gender and age in Taiwan, 2000–2009.

Gender	Age	N or %	Hypertension				Dyslipidemia				Hypertension + Dyslipidemia			
			2000	2004	2008	p*	2000	2004	2008	p*	2000	2004	2008	p*
F	<40	Number	2847	3465	4872	—	1584	3891	5499	—	609	1368	2106	—
		Prevalence	15.03%	18.76%	22.95%	<0.001	8.36%	21.06%	25.91%	<0.001	3.22%	7.41%	9.92%	<0.001
	40–65	Number	92,310	124,149	160,098	—	36,468	89,253	126,765	—	23,490	55,800	81,300	—
		Prevalence	51.55%	54.95%	58.28%	<0.001	20.37%	39.50%	46.15%	<0.001	13.12%	24.70%	29.60%	<0.001
	>65	Number	118,140	169,116	230,166	—	31,731	82,587	127,146	—	25,020	65,028	101,175	—
		Prevalence	71.41%	74.28%	76.91%	<0.001	19.18%	36.27%	42.49%	<0.001	15.12%	28.56%	33.81%	<0.001
	Total (F)	Number	213,297	296,730	395,136	—	69,783	175,731	259,410	—	49,119	122,196	184,581	—
		Prevalence	58.69%	62.85%	66.39%	<0.001	19.20%	37.22%	43.58%	<0.001	13.52%	25.88%	31.01%	<0.001
M	<40	Number	4419	6627	9897	—	3507	8277	11,937	—	1215	3066	5010	—
		Prevalence	20.02%	24.72%	30.81%	<0.001	15.89%	30.88%	37.16%	<0.001	5.50%	11.44%	15.60%	<0.001
	40–65	Number	80,652	124,929	182,427	—	34,683	92,295	146,253	—	20,139	52,659	88,890	—
		Prevalence	45.11%	48.69%	54.25%	<0.001	19.40%	35.97%	43.49%	<0.001	11.26%	20.52%	26.44%	<0.001
	>65	Number	95,337	130,467	173,787	—	19,248	52,044	82,314	—	14,502	38,946	62,472	—
		Prevalence	67.29%	69.38%	72.03%	<0.001	13.58%	27.68%	34.12%	<0.001	10.24%	20.71%	25.89%	<0.001
	Total (M)	Number	180,408	262,023	366,111	—	57,438	152,616	240,504	—	35,856	94,671	156,372	—
		Prevalence	52.66%	55.58%	60.05%	<0.001	16.77%	32.37%	39.45%	<0.001	10.47%	20.08%	25.65%	<0.001

* p for Kendall tau-c coefficient.

Journal of the Formosan Medical Association (2012) 111, 625e636

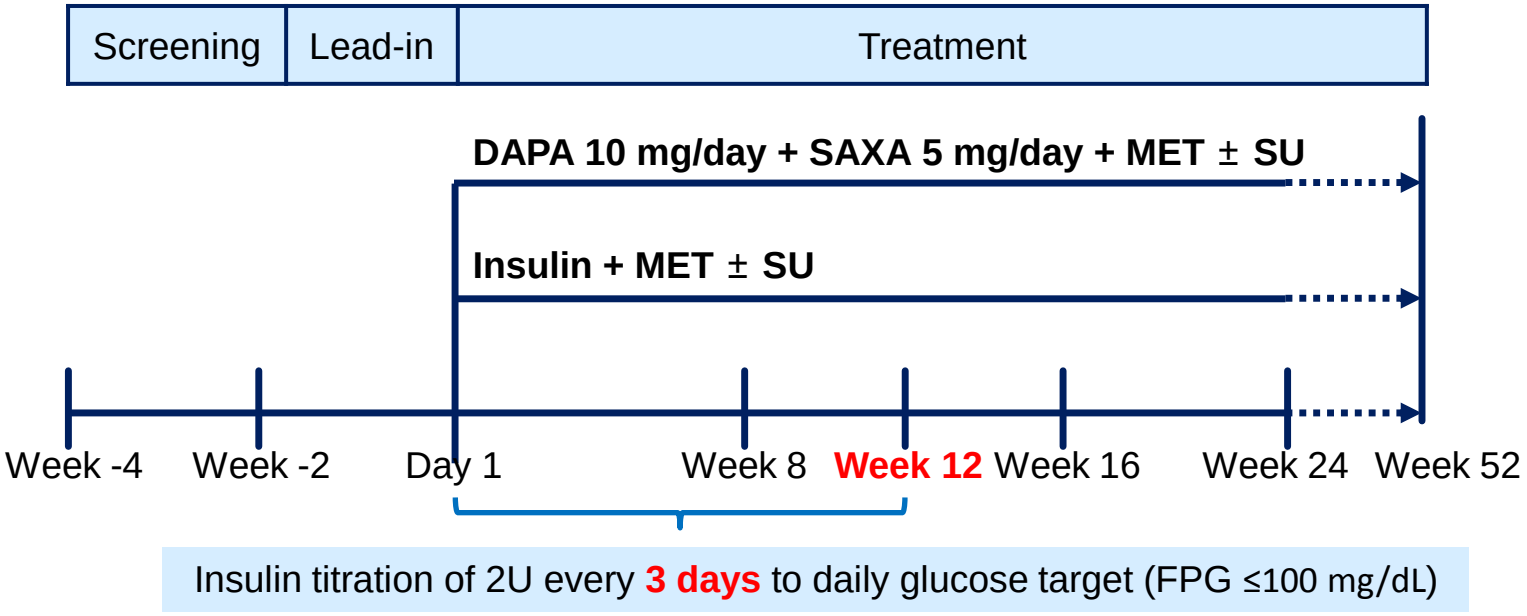
Dapagliflozin plus Saxagliptin Shows Noninferior A1C Reduction vs. Insulin Glargine in Patients with Type 2 Diabetes Inadequately Controlled by Metformin With or Without Sulfonylurea

TINA VILSBØLL, ELLA EKHOLM, EVA K. JOHNSSON, NALINA DRONAMRAJU, SERGE JABBOUR, MARCUS LIND, Copenhagen, Denmark, Mölndal, Sweden, Gaithersburg, MD, Philadelphia, PA, Gothenburg, Sweden

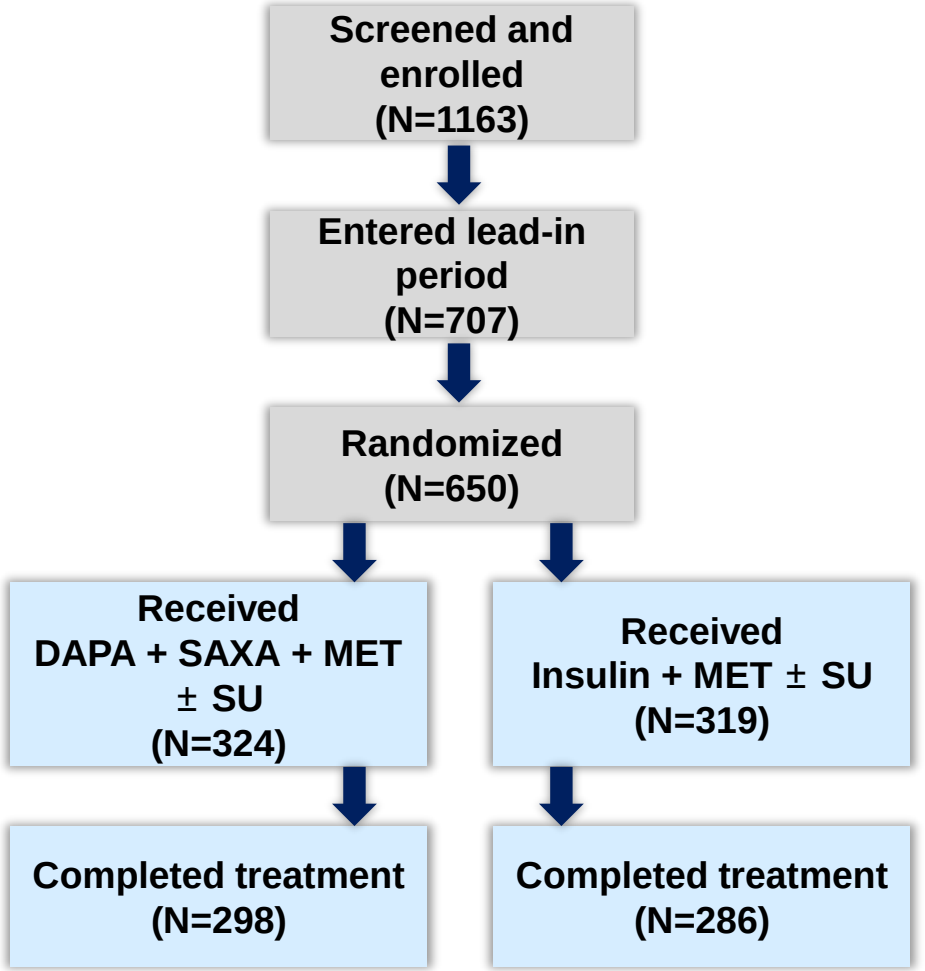
Serge Jabbour Presented at American Diabetes Association 78th Scientific Sessions (ADA); June 22–26, 2018; Orlando, Florida. 260-OR

Study design

- Multinational, randomized, open-label, active-controlled, parallel-group, **24-week**, phase 3b trial
- **Inclusion criteria:**
  - Age ≥18 years
  - BMI ≤45.0 kg/m^2
  - Stable-dose MET (≥1500 mg/day for >8 weeks) or MET with SU (≥50% maximum dose)
  - Baseline HbA1c 8.0-12.0%



Insulin titration of 2U every **3 days** to daily glucose target (FPG ≤100 mg/dL)



DAPA, dapagliflozin. MET, metformin. SAXA, saxagliptin. SU, Sulfonylurea

Serge Jabbour Presented at American Diabetes Association 78th Scientific Sessions (ADA); June 22–26, 2018; Orlando, Florida. 260-OR

Baseline characteristics

Characteristic	DAPA + SAXA + MET± SU (n=324)	Insulin + MET± SU (n=319)
Age, years	55.7 (9.5)	55.3 (9.6)
Women, n (%)	148 (45.7)	148 (46.6)
BMI, kg/m^2	32.5 (5.3)	32.0 (5.4)
Body weight, kg	89.8 (17.7)	89.4 (18.4)
Duration of T2D, years	9.6 (6.5)	9.3 (6.2)
HbA1c, %	9.0 (1.0)	9.1 (1.1)
eGFR, mL/min/1.73 m^2	92.2 (20.2)	92.9 (22.5)
FPG, mg/dL	189.5 (55.5)	188.6 (52.8)
Proportion of patients receiving SU, n (%)	166 (51.2)	165 (51.7)

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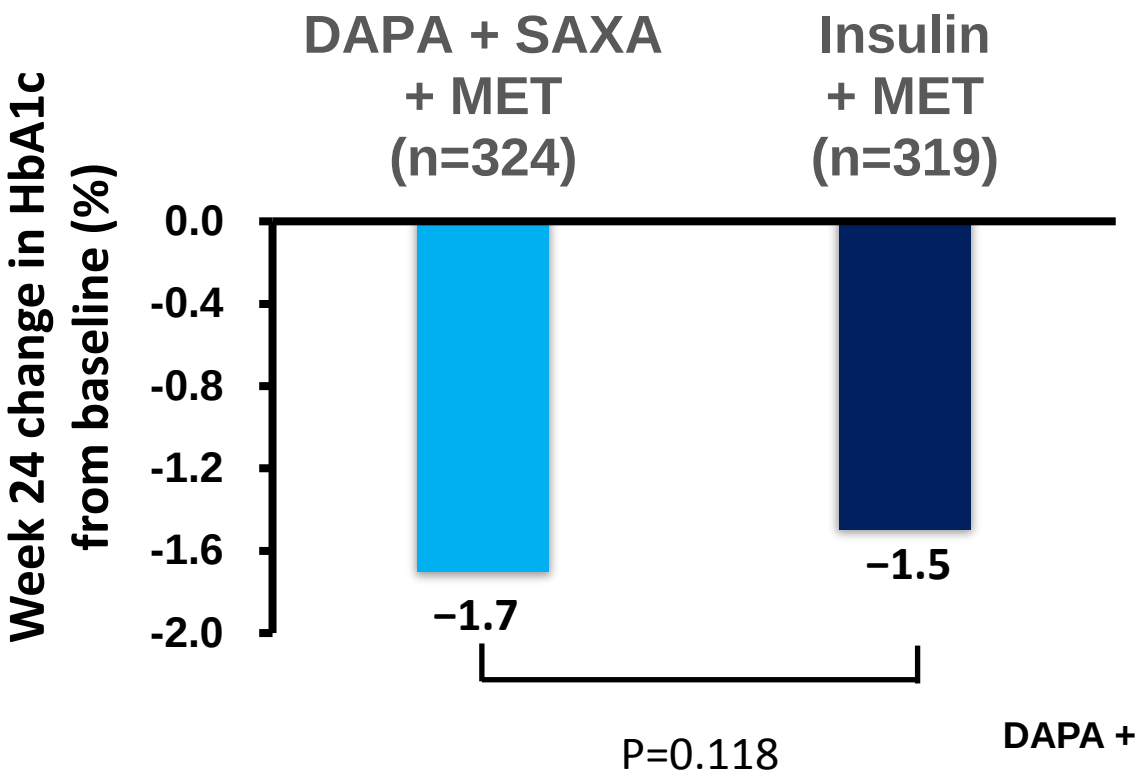
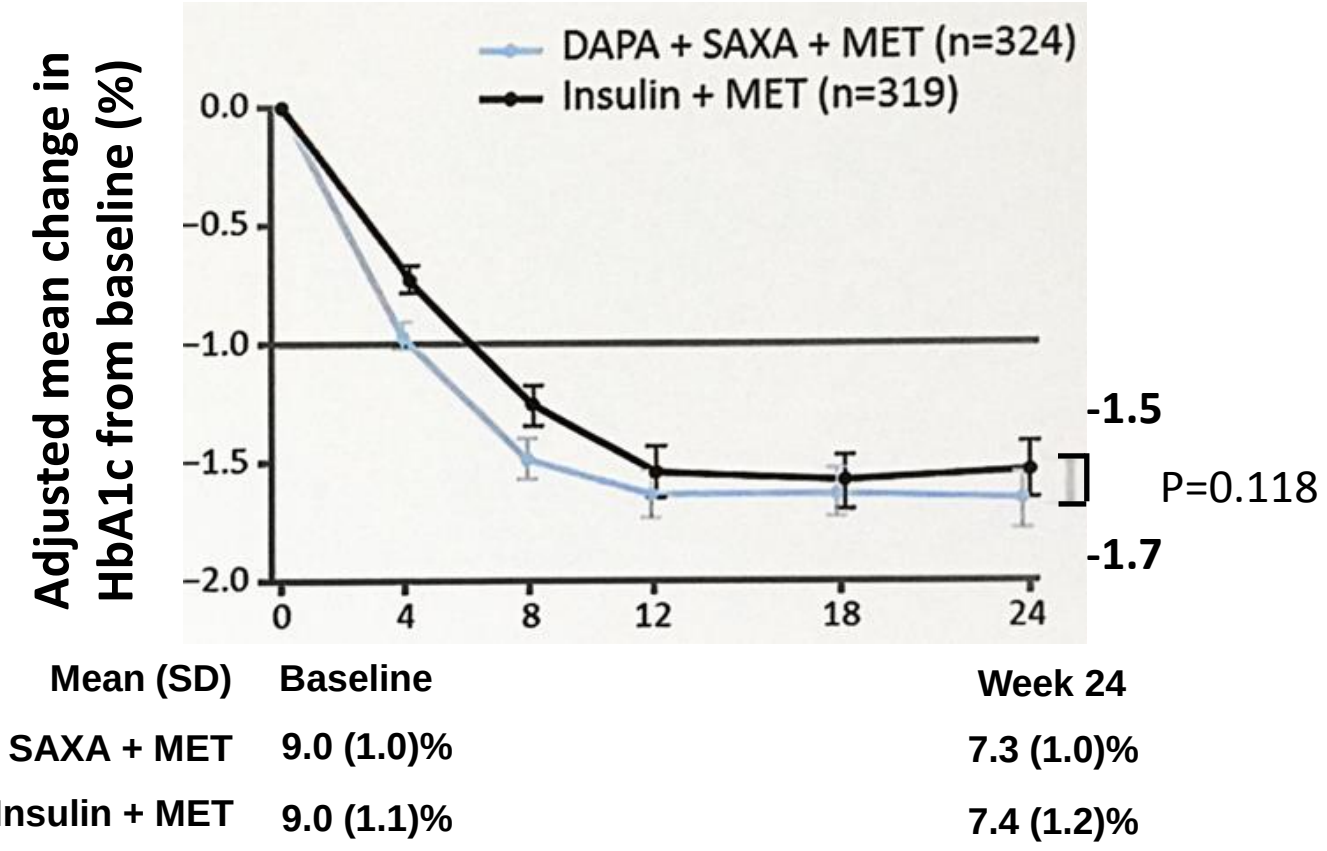
Non-inferior reductions in HbA1c with DAPA + SAXA compared with insulin add-on to MET





Mean (SD)	Baseline	Week 24
DAPA + SAXA + MET	9.0 (1.0)%	7.3 (1.0)%
Insulin + MET	9.0 (1.1)%	7.4 (1.2)%

A mixed statistical model was used to analyze between group differences.
Mean (SD) insulin glargine dose at week 24 was 36.6 (17.0) U.
DAPA, dapagliflozin. MET, metformin. SAXA, saxagliptin. SD, standard deviation.

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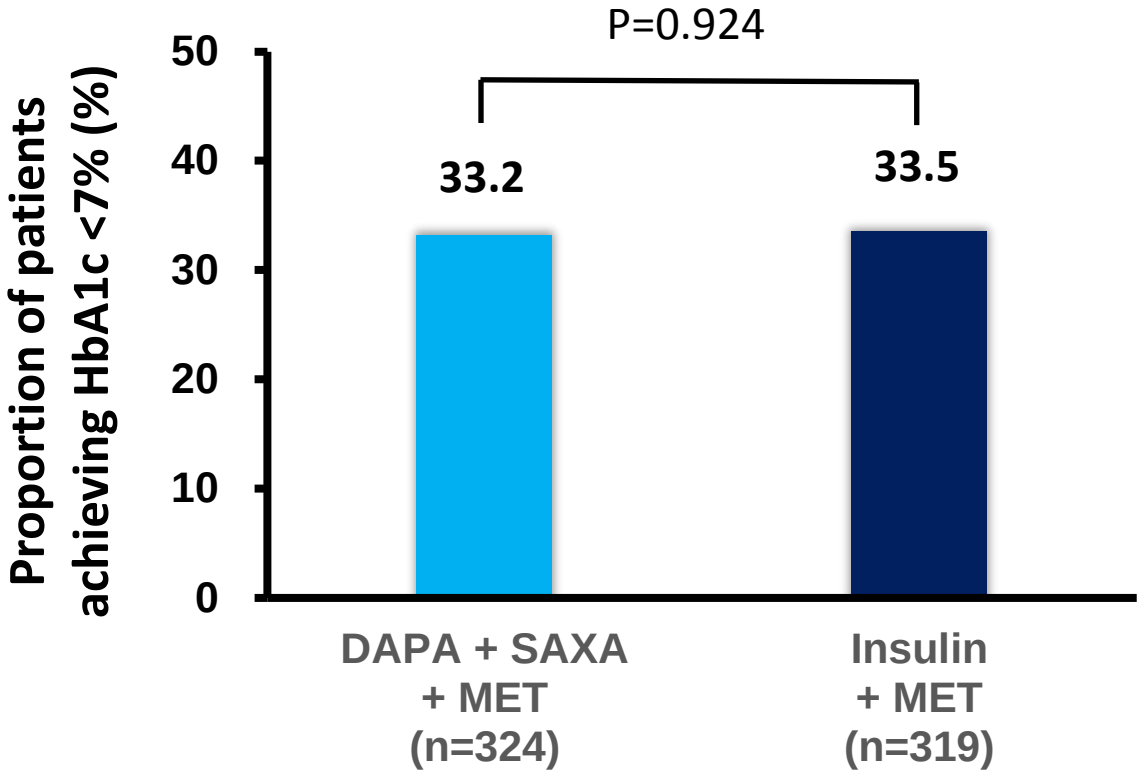
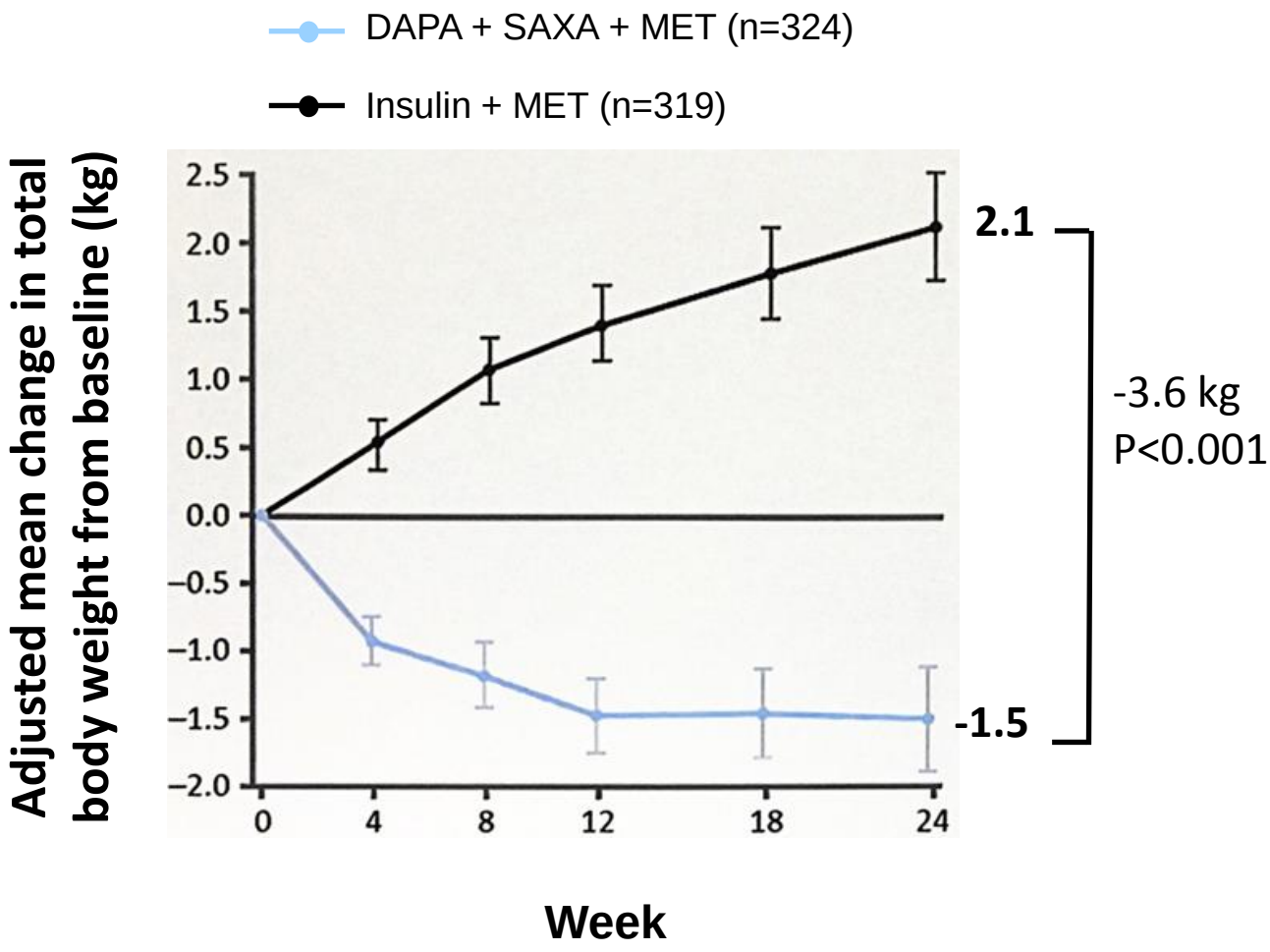
Proportion of patients achieving HbA1c <7%



Body weight



A mixed statistical model was used to analyze between group differences
DAPA, dapagliflozin. MET, metformin. SAXA, saxagliptin.

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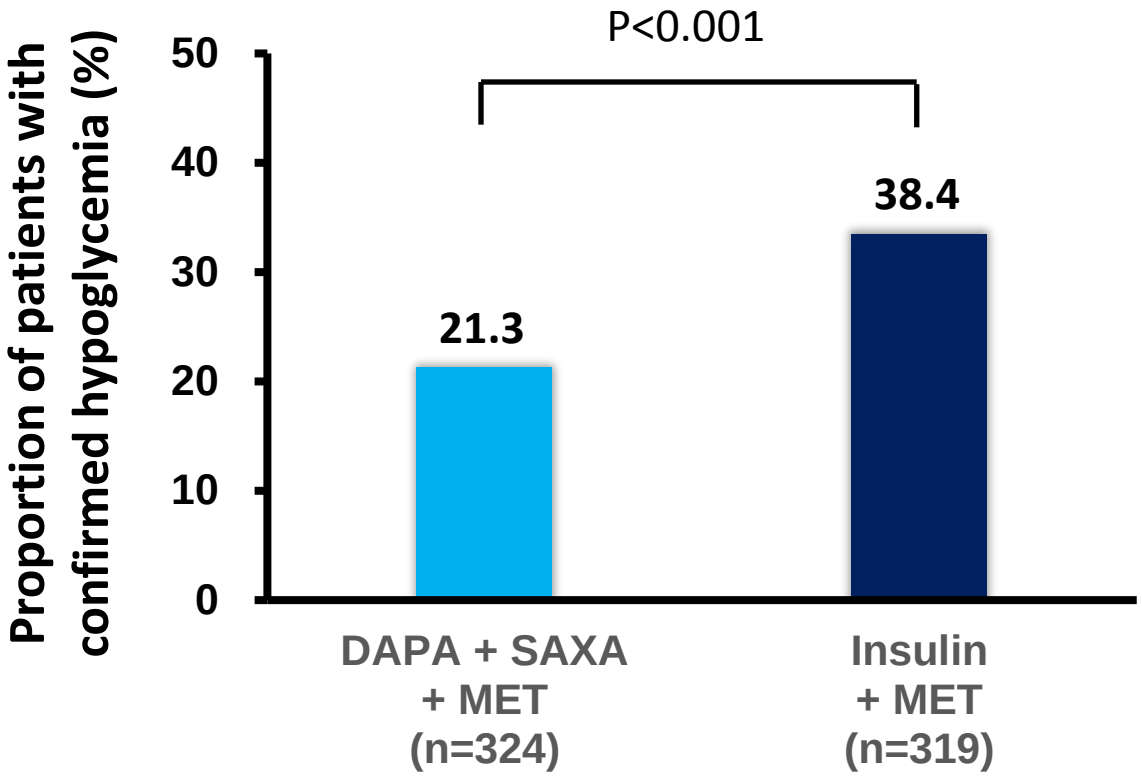
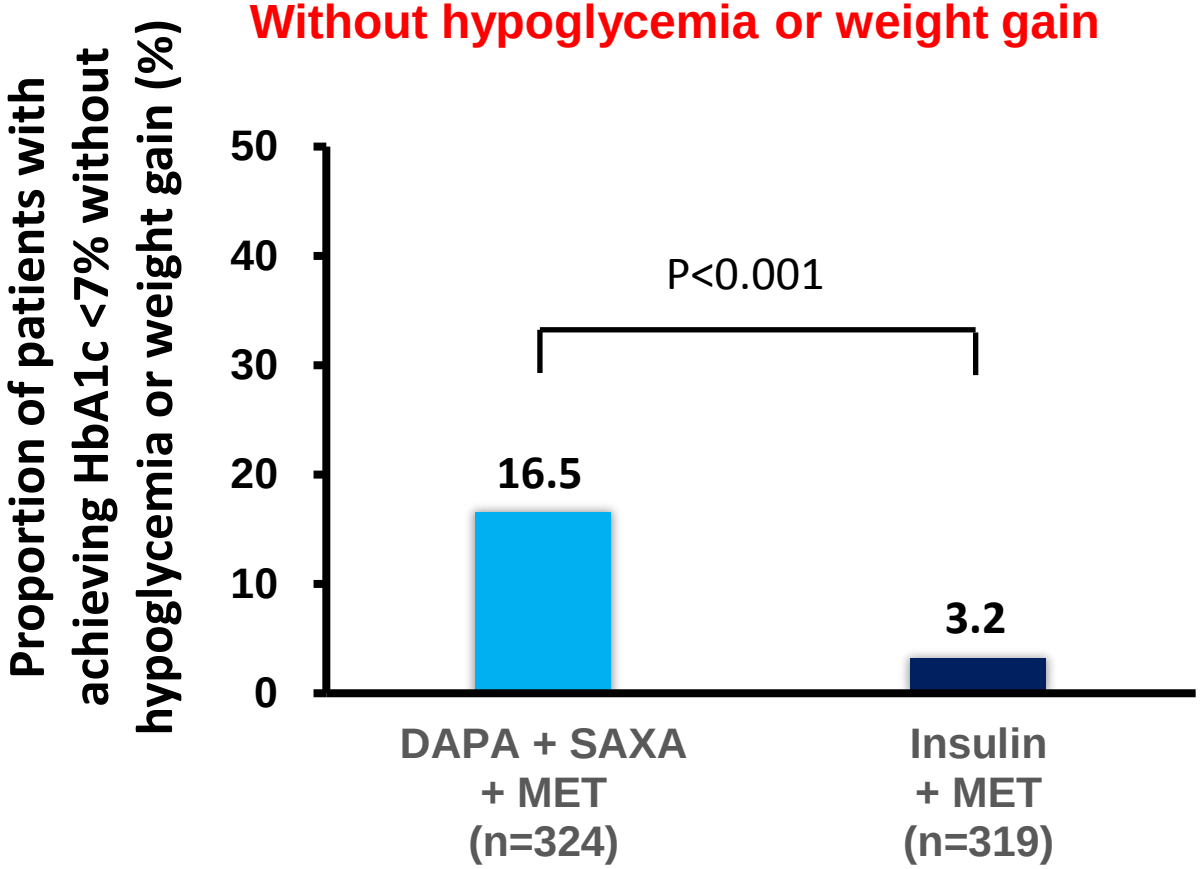
Hypoglycemia*



Achieved HbA1c <7%

Without hypoglycemia or weight gain



A mixed statistical model was used to analyze between group differences.

*Confirmed hypoglycemia= plasma glucose ≤70 mg/dL or signs/symptoms of hypoglycemia with self-monitored blood glucose ≤70 mg/dL

DAPA, dapagliflozin. MET, metformin. SAXA, saxagliptin.

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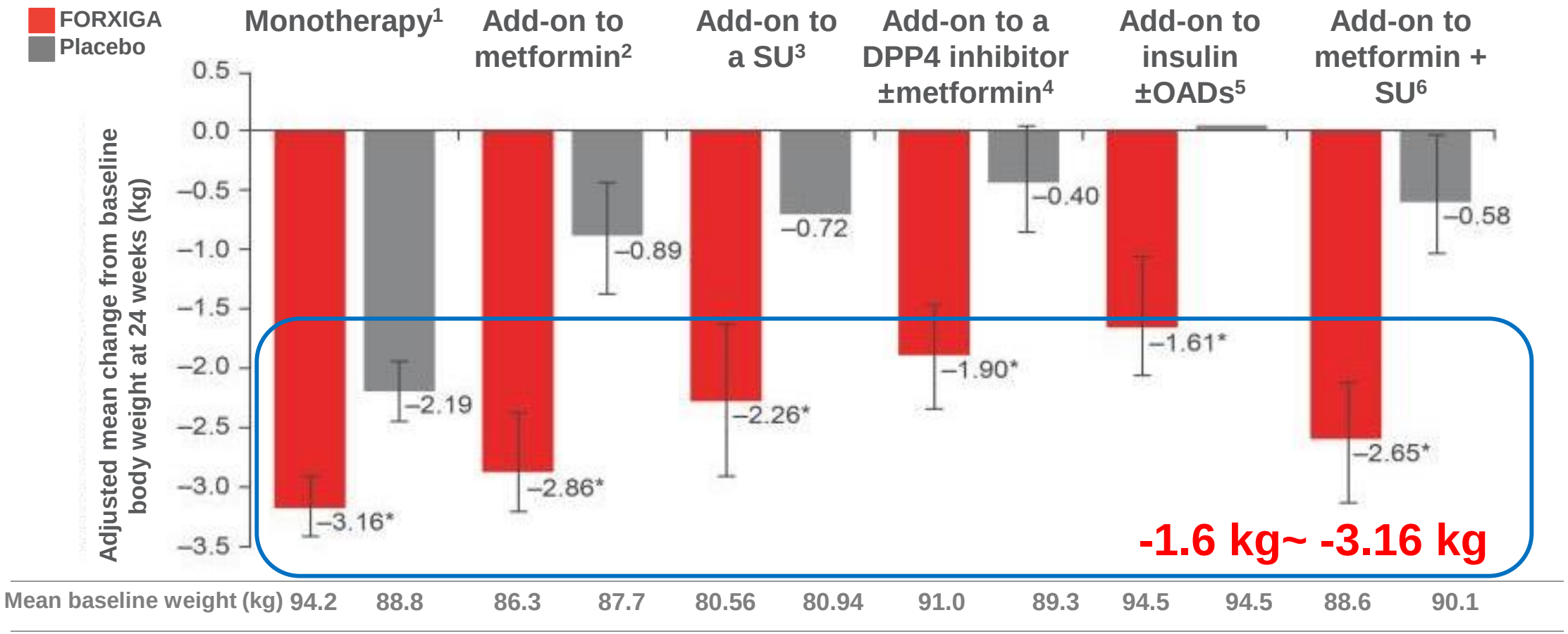
Additional Benefit of Body Weight Reduction Across a Broad Range of Treatments



FORXIGA is not indicated for the management of weight loss. Weight change was a secondary endpoint in clinical trials.
*Statistically significant versus placebo (p<0.0001).

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; OAD, oral antidiabetic drug; SU, sulphonylurea.

1. Ferrannini E, *et al. Diabetes Care* 2010;**33**:2217–24; 2. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33; 3. Strojek K, *et al. Diabetes Obes Metab* 2011;**13**:928–38; 4. Mathieu C, *et al.* Presented at the Annual Scientific Sessions of the American Diabetes Association, Boston, USA. 5–9 June 2015. Abstract 105-OR;
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Weight Loss Provides Multiple Benefits in T2DM patients

Odds ratio meaningful changes in CVD risk factors at 1 year after a weight loss of ≥5% to <10% (n=1000/5145)

Clinical criteria	Odds ratio	95% CI
0.5% ↓ in HbA_{1c}	3.52	2.81, 4.40
5 mmHg ↓ in SBP	1.56	1.27, 1.91
5 mmHg ↓ in DBP	1.48	1.20, 1.82
5 mg/dL ↑ in HDL cholesterol	1.69	1.37, 2.07
40 mg/dL ↓ in triglycerides	2.20	1.71, 2.83

This study was an observational analysis of participants in the Look AHEAD study conducted at 16 US sites in 5,145 participants (40.5% male, 37% from ethnic/racial minorities).

AHEAD, Action for Health Diabetes; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein, SBP, systolic blood pressure.

Wing RG, et al. Diabetes Care 2011;34:1481–6.

Look AHEAD Action for Health in Diabetes

Look AHEAD: Incidence of Cardiovascular Disease Varied by Changes in Weight (overall study population)

	Weight-change categories (percentage weight loss in first year; n=4834)				
	Gain or stable (<2% loss)	Small loss (≥2–<5%)	Medium loss (≥5–<10%)	Large loss (≥10%)	p value
Primary outcome					
Events per person-years	289/17 075	141/7870	154/8570	128/8942	..
Crude rate per 100 person-years	1·69	1·79	1·80	1·43	..
Adjusted hazard ratio†(95% CI)	1·00	1·08 (0·88–1·33)	1·16 (0·95–1·42)	0·79 (0·64–0·98), p=0·034*	0·17
Secondary outcome					
Events per person-years	422/16 699	206/7657	203/8411	186/8792	..
Crude rate per 100 person-years	2·53	2·69	2·41	2·12	..
Adjusted hazard ratio† (95% CI)	1·00	1·05 (0·88–1·25)	0·97 (0·82–1·16)	0·76 (0·63–0·91), p=0·003*	0·006

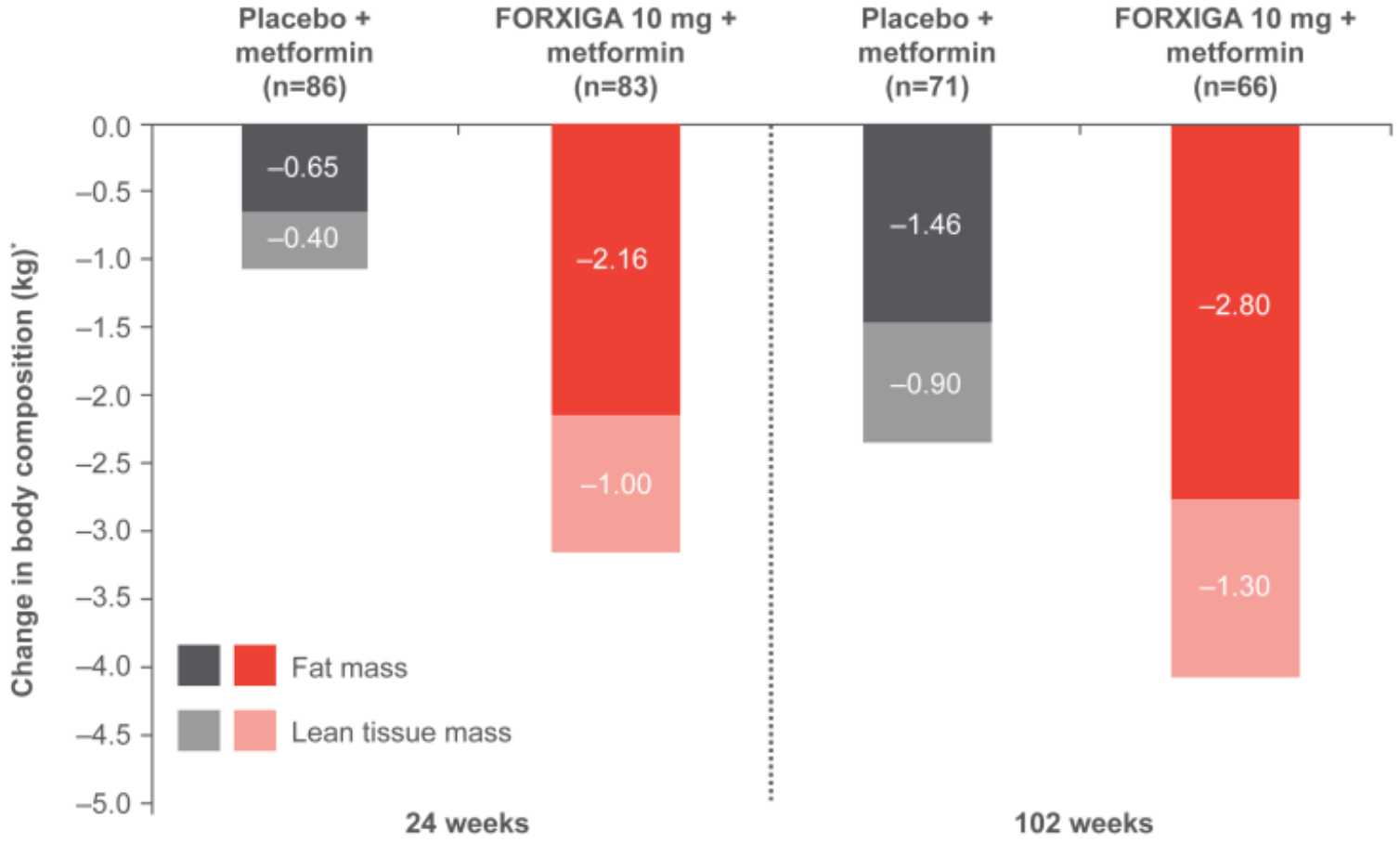
- Lost at least **10%** of their body weight in the first year of the study
- **21%** lower risk of the primary outcome
- **24%** reduced risk of the secondary outcome.

Look AHEAD Action for Health in Diabetes

Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921.

Weight Loss Mainly Associated with Body Fat Mass Reduction

Dapagliflozin demonstrated a significant reduction in fat mass rather than lean tissue or fluid loss sustained up to 102 weeks



FORXIGA is not indicated for the management of obesity.[2] Weight change was a secondary endpoint in clinical trials.[2,3]

*Data are adjusted mean change from baseline derived from a longitudinal repeated-measure mixed model and include data after rescue therapy.

Bolinder J, *et al. Diabetes Obes Metab* 2014;**16**:159–69

FORXIGA®. Summary of product characteristics, 2014

Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

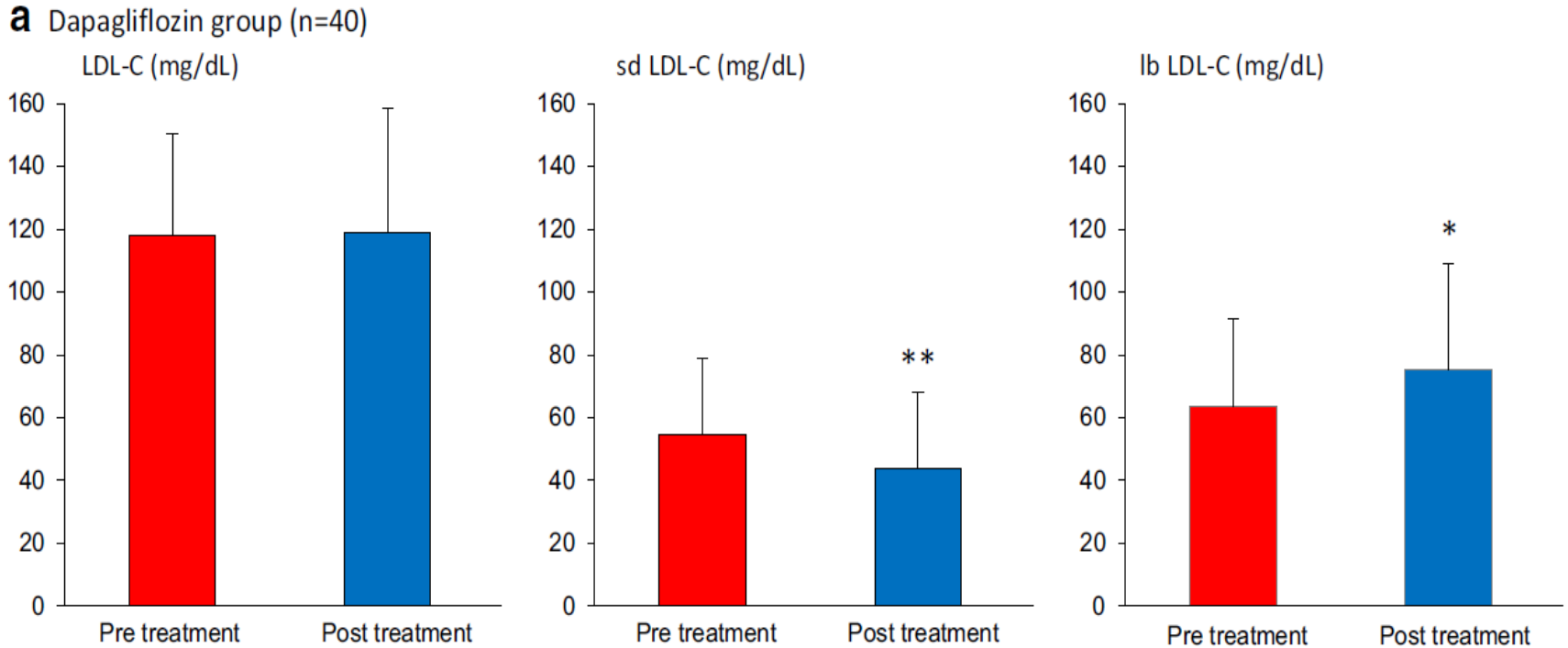
Hayashi *et al. Cardiovasc Diabetol (2017) 16:8*
DOI 10.1186/s12933-016-0491-5

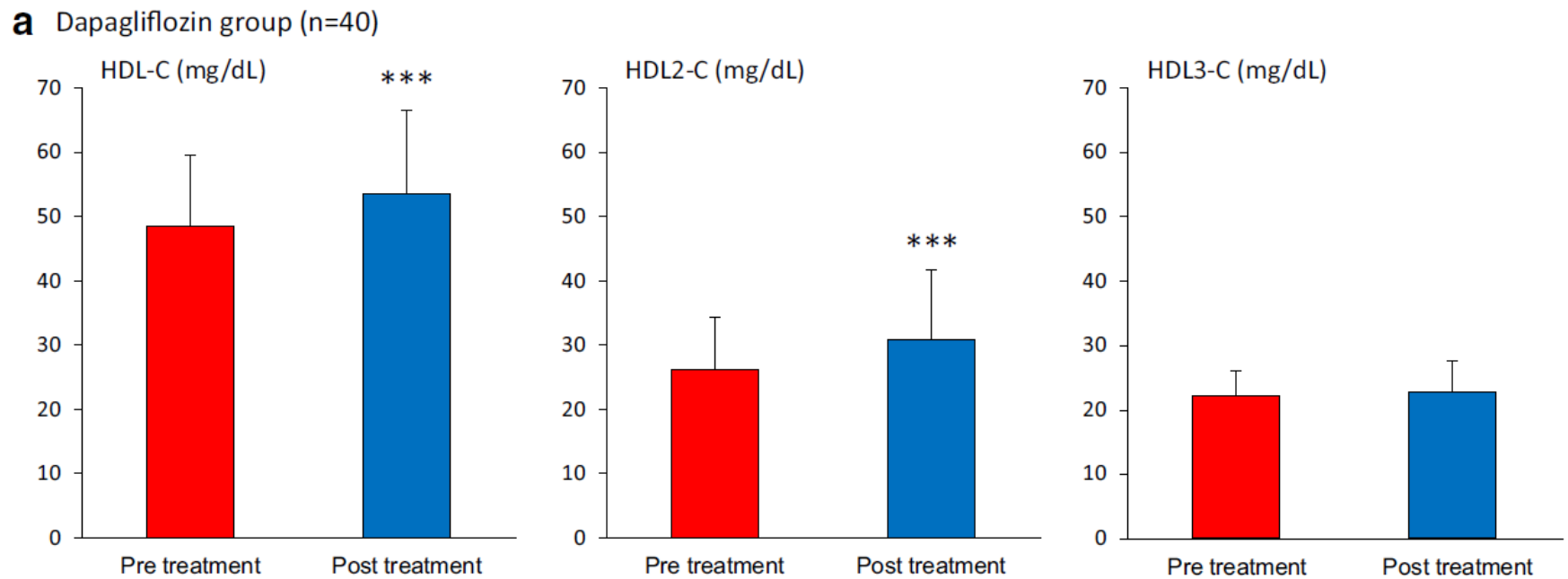
Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin

Backgrounds: Several clinical studies have revealed that **SGLT-2i decrease TG and increase HDL-C and LDL-C level.**


a Dapagliflozin group (n=40)
LDL-C (mg/dL)
sd LDL-C (mg/dL)
lb LDL-C (mg/dL)
160
140
120
100
80
60
40
20
0
**
*
Pre treatment
Post treatment


a Dapagliflozin group (n=40)
HDL-C (mg/dL)
HDL2-C (mg/dL)
HDL3-C (mg/dL)
70
60
50
40
30
20
10
0
***
***
Pre treatment
Post treatment

2018年 Dapagliflozin預計的重要發表

CVDREAL 2

47萬人, 87%
亞洲病患

3月10-12日
ACC (美國心臟學院)年會

ACC.18
67th Annual Scientific Session & Expo

DELIGHT

eGFR 25-75 + 蛋白尿[2]
+/- Saxagliptin

10月1-5日
EASD (歐洲糖尿病學會)年會

(TBC)

3月17-20日
ENDO (美國內分泌學會)
100th年會

eGFR 45-60[1]

DERIVE[1]

ENDO 2018
THE ENDOCRINE SOCIETY'S 100TH ANNUAL MEETING & EXPO

6月22-26日
ADA (美國糖尿病學會) 年會

DEPICT 1

T1DM, 52 weeks[5]

(TBC)

(TBC)

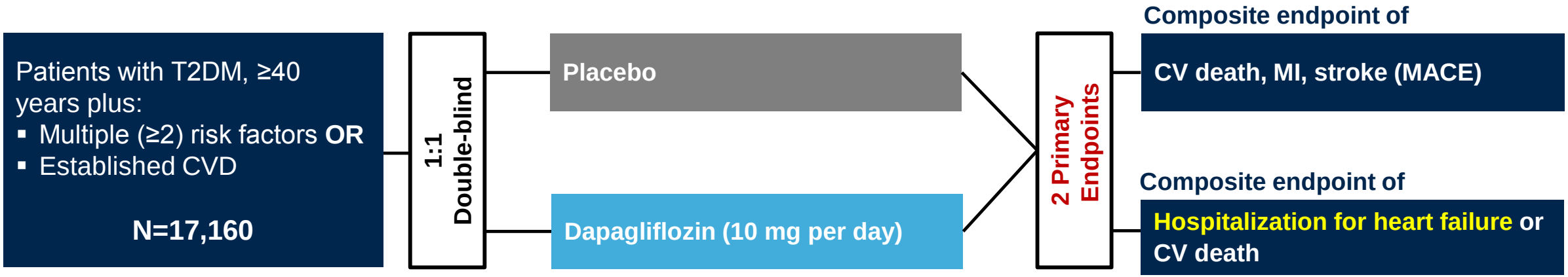
17,000人, ~6年
60% non-CVD病患[3]
預計7月18完成試驗[4]

11月10-14日
AHA (美國心臟學會年會)

DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG

參考資料：1. https://clinicaltrials.gov/ct2/show/NCT02413398 2. https://clinicaltrials.gov/ct2/show/study/NCT02547935 3. Itamar Raz et al. The 77th Scientific Sessions of the American Diabetes Association, San Diego, California, June 9-13, 2017; 1245-P 4. https://clinicaltrials.gov/ct2/show/NCT01730534 5. https://clinicaltrials.gov/ct2/show/NCT02460978

DECLARE-TIMI 58: Broad CV risk population & 2 clinically important CV co-primary endpoints in Type 2 Diabetes



- **Add on to background CV and GLD per treating physician**
- **Event-driven duration: 1,390 events**
- **Planned ~6 years follow-up with median ~4.5 years**

Estimated Study Completion Date:
April 2019 → July 18, 2018

Secondary Endpoints

- **All-cause mortality**
- **Renal composite: sustained ≥40% decrease in eGFR to eGFR<60, ESRD, renal or CV death**

CV, cardiovascular; CVD, cardiovascular disease; 2; T2DM, type 2 diabetes mellitus; NF, non-fatal; MACE, major adverse cardiac event; hHF, hospitalization for heart failure. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217; Wiviott SD, et al. *Am Heart J* 2018. http://dx.doi.org/10.1016/j.ahj.2018.01.012; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01730534

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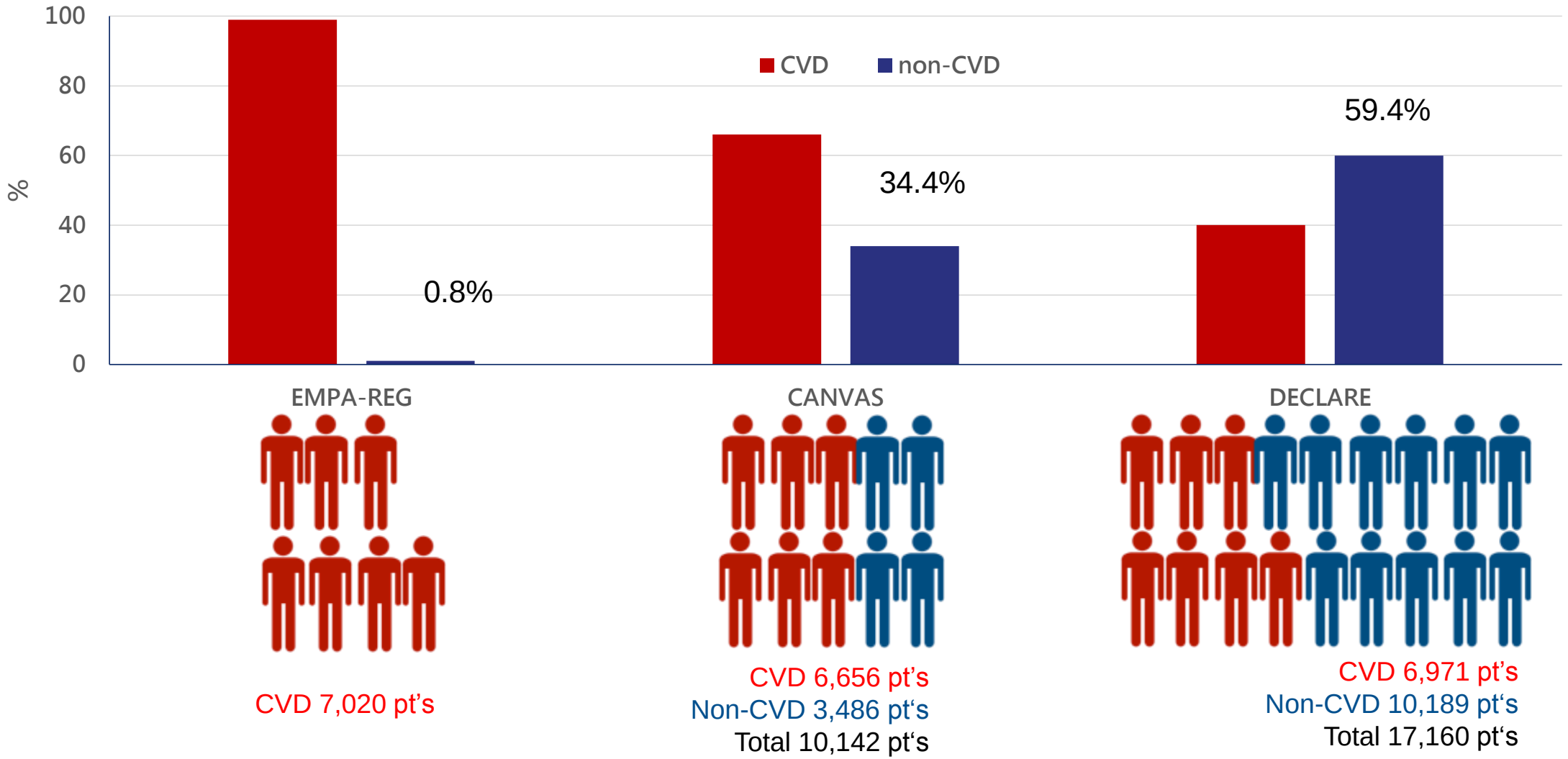
CVD and Non-CVD proportion in 3 CVOTs of SGLT2i



CVD, cardiovascular disease; CVOT, cardiovascular outcome trials; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Zinman B, et al. Cardiovasc Diabetol. 2014 Jun 19;13:102.; 2. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7):644-657;
3. Raz I, et al. Diabetes Obes Metab. 2018 Jan 11. doi: 10.1111/dom.13217.

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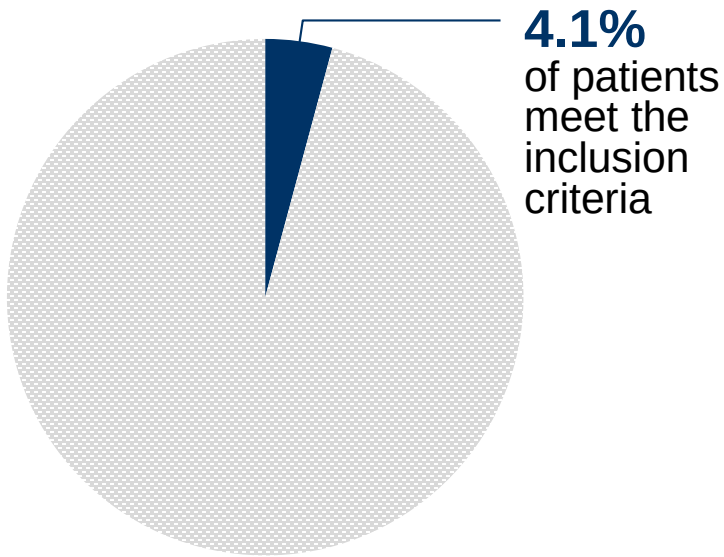
DECLARE is the most inclusive SGLT2i CV outcomes trial to date[1,2]

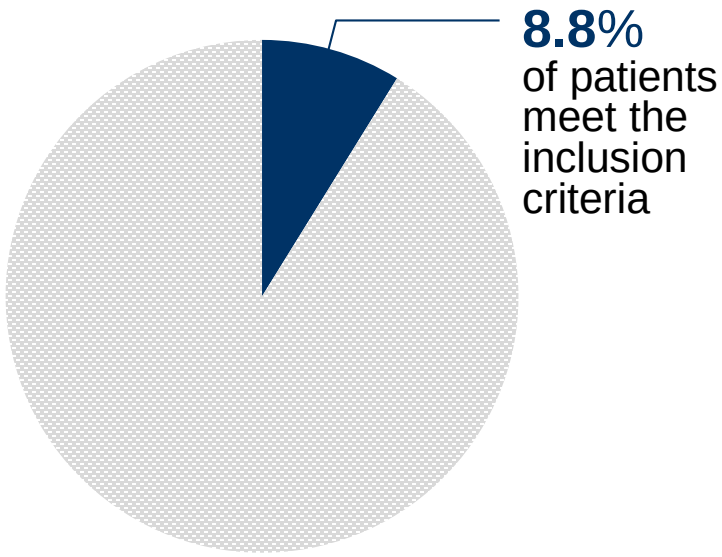
The generalizability of the eligibility criteria of the 3 SGLT2 inhibitor CV outcome studies was assessed in the 2009−2010 and 2011−2012 National Health and Nutrition Examination Survey (NHANES) databases

EMPA-REG OUTCOME



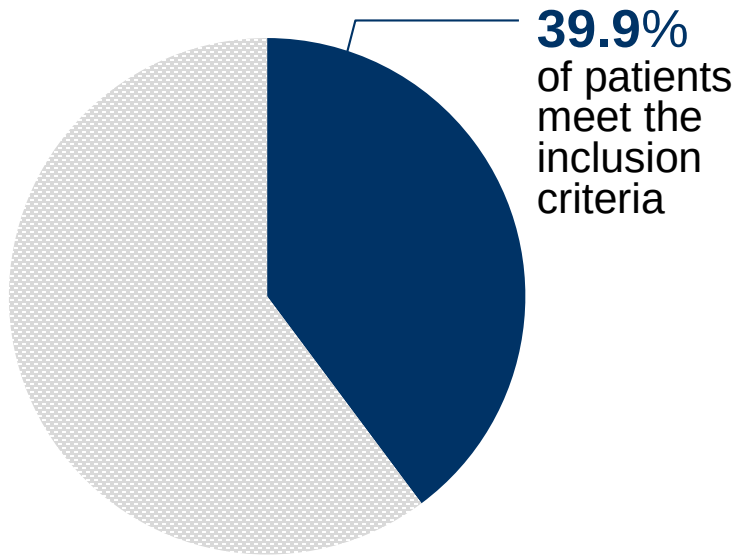
4.1% of patients meet the inclusion criteria

CANVAS



8.8% of patients meet the inclusion criteria

DECLARE



39.9% of patients meet the inclusion criteria

As the most inclusive study, DECLARE is poised to provide guidance on how to reduce risk in a population of patients with type 2 diabetes and a broader CV risk profile

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

1. Wittbrodt. Presented at the 15th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease 2017;
2. Am J Manag Care. 2018;24:S138-S145

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Demographics and Disease History

	EMPA-REG	CANVAS	DECLARE
Mean age, y	63.1	63.3	63.8
Female, %	28	35	37
Mean duration of diabetes, y	57% >10 y	14	50% >10 y
Hypertension, %	94	90	89
Cardiovascular disease, %	**99**	**66**	**40**
Myocardial Infarction, %	47	CAD: 56	20
Multi-vessel CAD, %	47	-	12
CABG, %	25	-	10
Stroke, %	23	19	6
PAOD, %	21	21	6
Heart failure, %	Cardiac failure: 10	14	10

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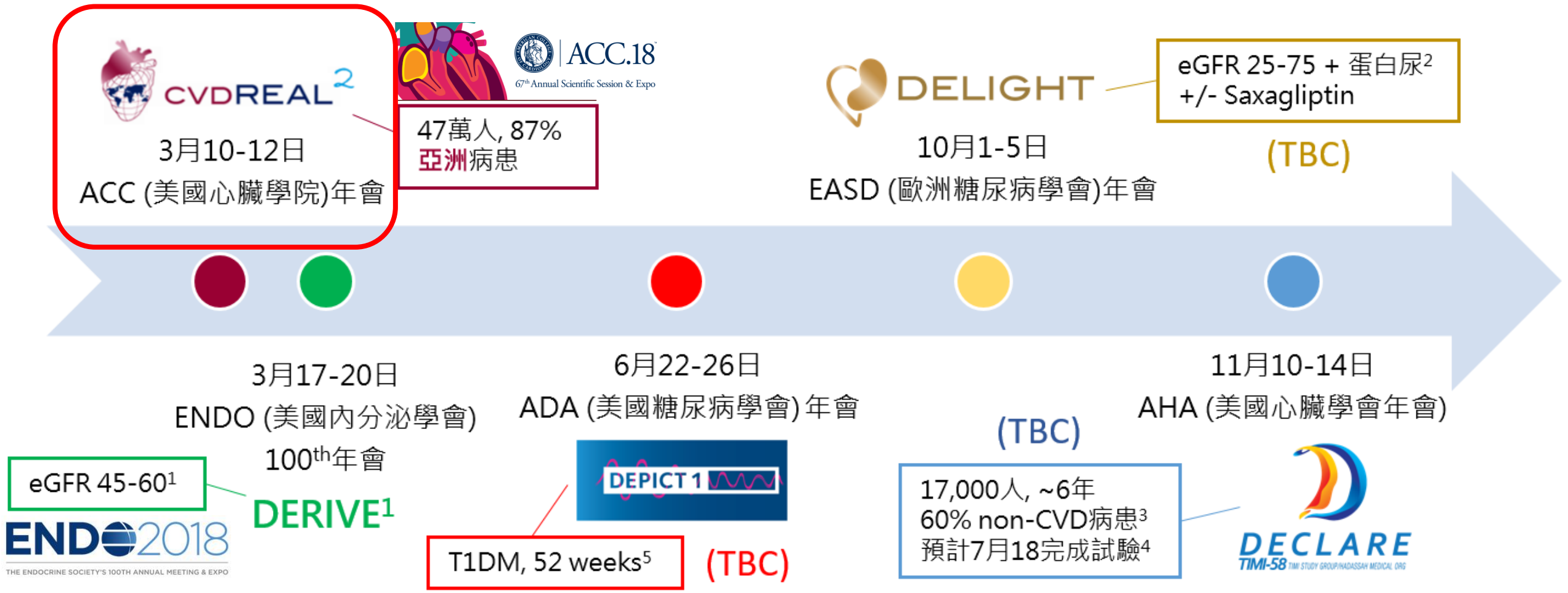
2018年 Dapagliflozin預計的重要發表



參考資料：1. https://clinicaltrials.gov/ct2/show/NCT02413398 2. https://clinicaltrials.gov/ct2/show/study/NCT02547935 3. Itamar Raz et al. The 77th Scientific Sessions of the American Diabetes Association, San Diego, California, June 9-13, 2017; 1245-P 4. https://clinicaltrials.gov/ct2/show/NCT01730534 5. https://clinicaltrials.gov/ct2/show/NCT02460978

RWE complements data from RCTs

	RCT	RWE study
Objective	Can it work?	Does it work?
Purpose	To gain regulatory approval	To influence clinical practice
Setting/design	Ideal conditions	Real world conditions
Intervention	Fixed regimen	Flexible regimen
Compliance	High	Low to high
External validity	Low to medium: homogeneous populations	High: heterogeneous populations
Internal validity	High	Variable

Circulation. 2017 Jul 18;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190. Epub 2017 May 18.

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors).

Kosiborod M[1], Cavender MA[2], Fu AZ[2], Wilding JP[2], Khunti K[2], Holl RW[2], Norhammar A[2], Birkeland KI[2], Jørgensen ME[2], Thuresson M[2], Arya N[2], Bodegård J[2], Hammar N[2], Fenici P[2]; CVD-REAL Investigators and Study Group*.

Author information

Abstract

BACKGROUND: Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i) empagliflozin in patients with type 2 diabetes mellitus who have atherosclerotic cardiovascular disease. We compared HHF and death in patients newly initiated on any SGLT-2i versus other glucose-lowering drugs in 6 countries to determine if these benefits are seen in real-world practice and across SGLT-2i class.

METHODS: Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

RESULTS: After propensity matching, there were 309 056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154 528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the 2 groups. There were 961 HHF cases during 190 164 person-years follow-up (incidence rate, 0.51/100 person-years). Of 215 622 patients in the United States, Norway, Denmark, Sweden, and the United Kingdom, death occurred in 1334 (incidence rate, 0.87/100 person-years), and HHF or death in 1983 (incidence rate, 1.38/100 person-years). Use of SGLT-2i, versus other glucose-lowering drugs, was associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51-0.73; $P<0.001$); death (hazard ratio, 0.49; 95% confidence interval, 0.41-0.57; $P<0.001$); and HHF or death (hazard ratio, 0.54; 95% confidence interval, 0.48-0.60; $P<0.001$) with no significant heterogeneity by country.

CONCLUSIONS: In this large multinational study, treatment with SGLT-2i versus other glucose-lowering drugs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with type 2 diabetes mellitus in real-world practice.

J Am Coll Cardiol. 2018 Mar 7. pii: S0735-1097(18)33528-9. doi: 10.1016/j.jacc.2018.03.009. [Epub ahead of print]

Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study.

Kosiborod M[1], Lam CSP[2], Kohsaka S[3], Kim DJ[4], Karasik A[5], Shaw J[6], Tangri N[7], Goh SY[8], Thuresson M[9], Chen H[10], Surmont F[11], Hammar N[12], Fenici P[13]; CVD-REAL Investigators and Study Group.

Author information

Abstract

BACKGROUND: Randomized trials demonstrated lower risk of cardiovascular (CV) events with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in patients with type 2 diabetes (T2D) at high CV risk. Prior real-world data suggested similar SGLT-2i effects in T2D patients with broader risk profile, but focused on heart failure and death, and were limited to US and Europe.

OBJECTIVES: To examine a broad range of CV outcomes in patients initiated on SGLT-2i vs. other glucose lowering drugs (oGLD) across six countries in Asia Pacific, Middle East and North America (NCT02993614).

METHODS: New users of SGLT-2i and oGLD were identified via claims, medical records and national registries in South Korea, Japan, Singapore, Israel, Australia and Canada. Propensity scores for SGLT-2i initiation were developed in each country, with 1:1 matching. Hazard ratios (HRs) for death, hospitalization for heart failure (HHF), death or HHF, MI and stroke were assessed by country and pooled using weighted meta-analysis.

RESULTS: After propensity-matching, there were 235,064 episodes of treatment initiation in each group; ~27% had established CVD. Patient characteristics were well-balanced between groups. Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3% and 1% of exposure time in the SGLT-2i group, respectively. Use of SGLT-2i vs. oGLDs was associated with lower risk of death (HR 0.51, 95%CI 0.37-0.70; P<0.001), HHF (HR 0.64, 95%CI 0.50-0.82; P=0.001), death or HHF (HR 0.60; 95%CI 0.47-0.76; P<0.001), MI (HR 0.81, 95%CI 0.74-0.88; P<0.001) and stroke (HR 0.68, 95%CI 0.55-0.84; P<0.001). Results were directionally consistent both across countries, and patient subgroups, including those with and without CVD.

CONCLUSIONS: In this large, international study of patients with T2D from the Asia-Pacific, Middle East and North America, initiation of SGLT-2i was associated with a lower risk of CV events, across a broad range of outcomes and patient characteristics.

Lower Risk of Cardiovascular Events and Death Associated with Initiation of SGLT-2 vs DPP-4 inhibitors – Analysis from the CVD-REAL 2 study

Shun Kohsaka[1], Carolyn S. P. Lam[2], Dae Jung Kim[3], Matthew A. Cavender[4], Alex Z. Fu[5], Anna Norhammar[6], Marit E. Jørgensen[7], Kåre I Birkeland[8], Reinhard Holl[9], Josep Franch-Nadal[10], Avraham Karasik[11], Jonathan Shaw[12], Navdeep Tangri[13], Su-Yen Goh[14], Marcus Thuresson[15], Hungta Chen[16], Eric Wittbrodt[17], Johan Bodegård[18], Filip Surmont[19], Niklas Hammar[6,20], Peter Fenici[21], Mikhail Kosiborod[22] on behalf of the CVD-REAL Investigators and Study Group

1 Keio University School of Medicine, Tokyo, Japan; 2 National Heart Centre, Singapore and SingHealth Duke-NUS, Singapore; 3 Ajou University School of Medicine, Suwon, Republic of Korea; 4 University of North Carolina, Chapel Hill, NC, USA; 5 Bristol-Myers Squibb and Georgetown University Medical Center, Washington DC, USA; 6 Karolinska Institutet, Stockholm, Sweden; 7 Steno Diabetes Center, Copenhagen, Gentofte, Denmark and National Institute of Public Health, Southern Denmark University, Denmark; 8 University of Oslo and Oslo University Hospital, Oslo, Norway; 9 University of Ulm, Ulm, Germany; 10 Institut Universitari d'investigació en Atenció Primaria (IDIAP Jordi Gol), Barcelona, Spain; 11 Tel Aviv University, Ramat Aviv, and Maccabi Healthcare, Israel; 12 Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia; 13 University of Manitoba, Winnipeg MB, Canada; 14 Singapore General Hospital, Singapore; 15 Statisticon AB, Uppsala, Sweden; 16 AstraZeneca, Gaithersburg, MD, USA; 17 AstraZeneca, Wilmington, Delaware, USA; 18 AstraZeneca, Oslo, Norway; 19 AstraZeneca, Luton, UK; 20 AstraZeneca, Gothenburg, Sweden; 21 AstraZeneca, Cambridge, UK; 22 Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, USA

Shun Kohsaka et al. Published at American Diabetes Association 78th Scientific Sessions (ADA); June 22–26, 2018; Orlando, Florida. 124-LB

Data Sources

Data Sources

- Deidentified health records from 12 countries, South Korea, Japan, Singapore, Australia, USA, Canada, Denmark, Sweden, Norway, Spain, Israel and Germany, were analyzed

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Study Objectives

- CV outcome trials showed SGLT-2i significantly reduce the risk of major adverse cardiovascular events (MACE) and hospitalizations for heart failure (HHF)[1,2]; while DPP-4i are largely neutral [3-5]

- This study compared the risk of all-cause death, HFF, MI, and stroke in patients newly initiated on SGLT-2i vs DPP-4i, using real world data from clinical practice from 12 countries.

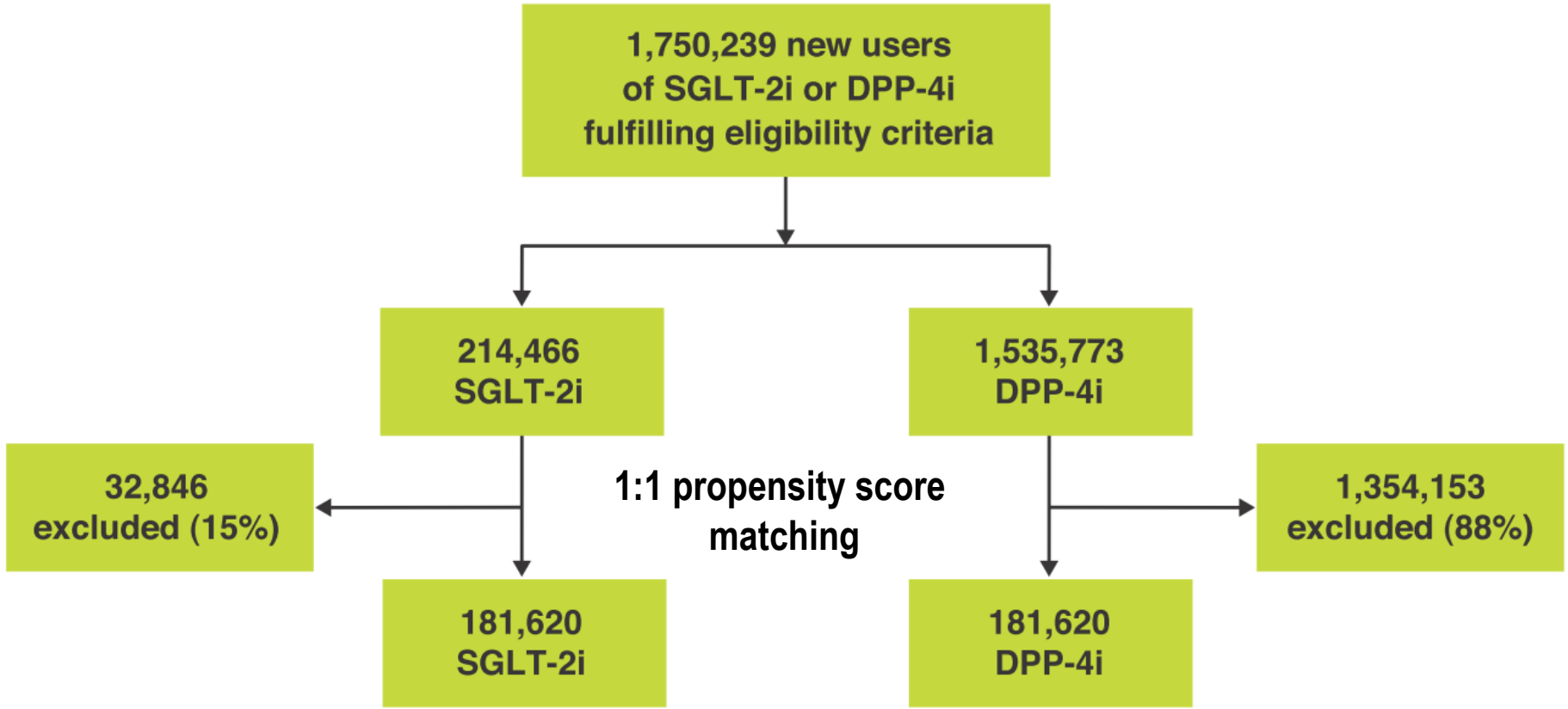
CV outcome trials: cardiovascular outcome trials; MI: myocardial infarction

1. Zinman B, et al. N Engl J Med 2015;373:2117–28; 2. Neal B, et al. N Engl J Med 2017;377:644–57; 3. Zannad F, et al. Lancet 2015;385:2067–76; 4. Scirica BM, et al. N Engl J Med 2013;369:1317–26;
5. White WB, et al. N Engl J Med 2013;369:1327–35; 6. Persson F, et al. Diabetes Obes Metab 2018;20:344–51

Patient Cohort

- Patients with T2D newly initiated on either SGLT-2i or DPP-4i were selected from each data source between December 2012 and November 2017

Figure 1. Study flow diagram



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Baseline Characteristics (1)

Table 1. Baseline characteristics after propensity-score matching

	SGLT-2i (N=181,620)	DPP-4i (N=181,620)	Standardized difference*
Age, years (SD)	57.6 (11.9)	57.5 (12.7)	1.1%
Women	79,898 (44.0)	79,959 (44.0)	0.1%
Established CVD	52,087 (29.8)	50,221 (28.8)	2.3%
Metformin	140,971 (77.6)	142,342 (78.4)	1.8%
Sulphonylurea	66,007 (36.3)	65,960 (36.3)	0.1%
Thiazolidinedione	14,784 (8.1)	14,480 (8.0)	0.6%
GLP-1 receptor agonist	12,523 (6.9)	11,096 (6.1)	3.2%
Insulin	44,963 (24.8)	43,781 (24.1)	1.5%

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Baseline Characteristics (2)

	SGLT-2i (N=181,620)	DPP-4i (N=181,620)	Standardized difference*
Anti-hypertensive therapy	124,772 (68.7)	123,543 (68.0)	1.5%
Loop diuretics	16,102 (8.9)	15,729 (8.7)	0.7%
Thiazide diuretics	26,049 (14.3)	25,780 (14.2)	0.4%
ACE inhibitors	44,745 (24.6)	44,487 (24.5)	0.3%
ARBs	67,816 (37.3)	67,629 (37.2)	0.2%
Statin therapy	114,121 (62.8)	113,272 (62.4)	1.0%

Data are n (%) unless otherwise stated. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; GLP-1, glucose-like peptidase-1. *Standardized differences >10% represent a non-negligible difference

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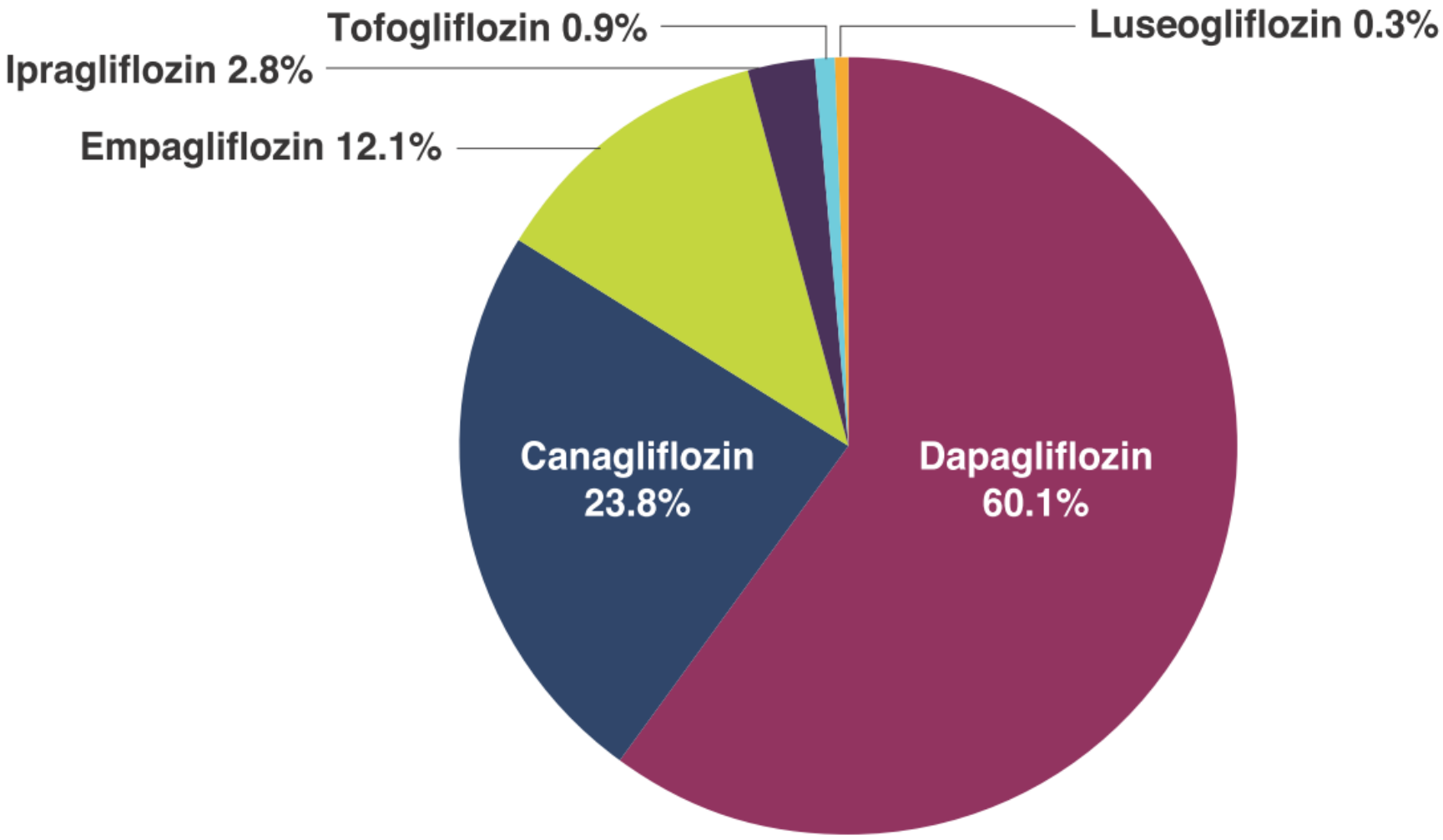
Proportion of exposure time in the SGLT-2i class



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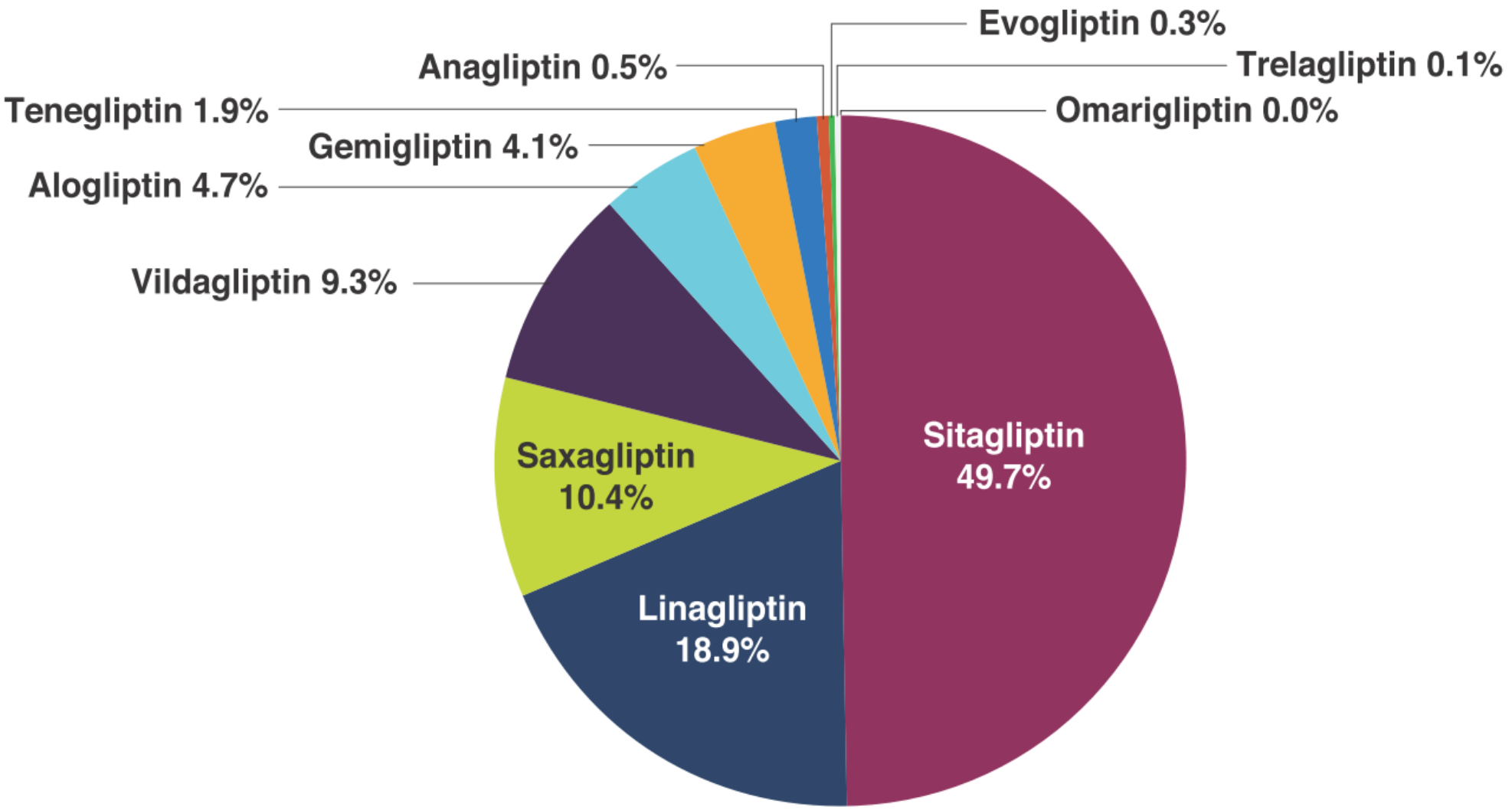
Proportion of exposure time in the DPP-4i class



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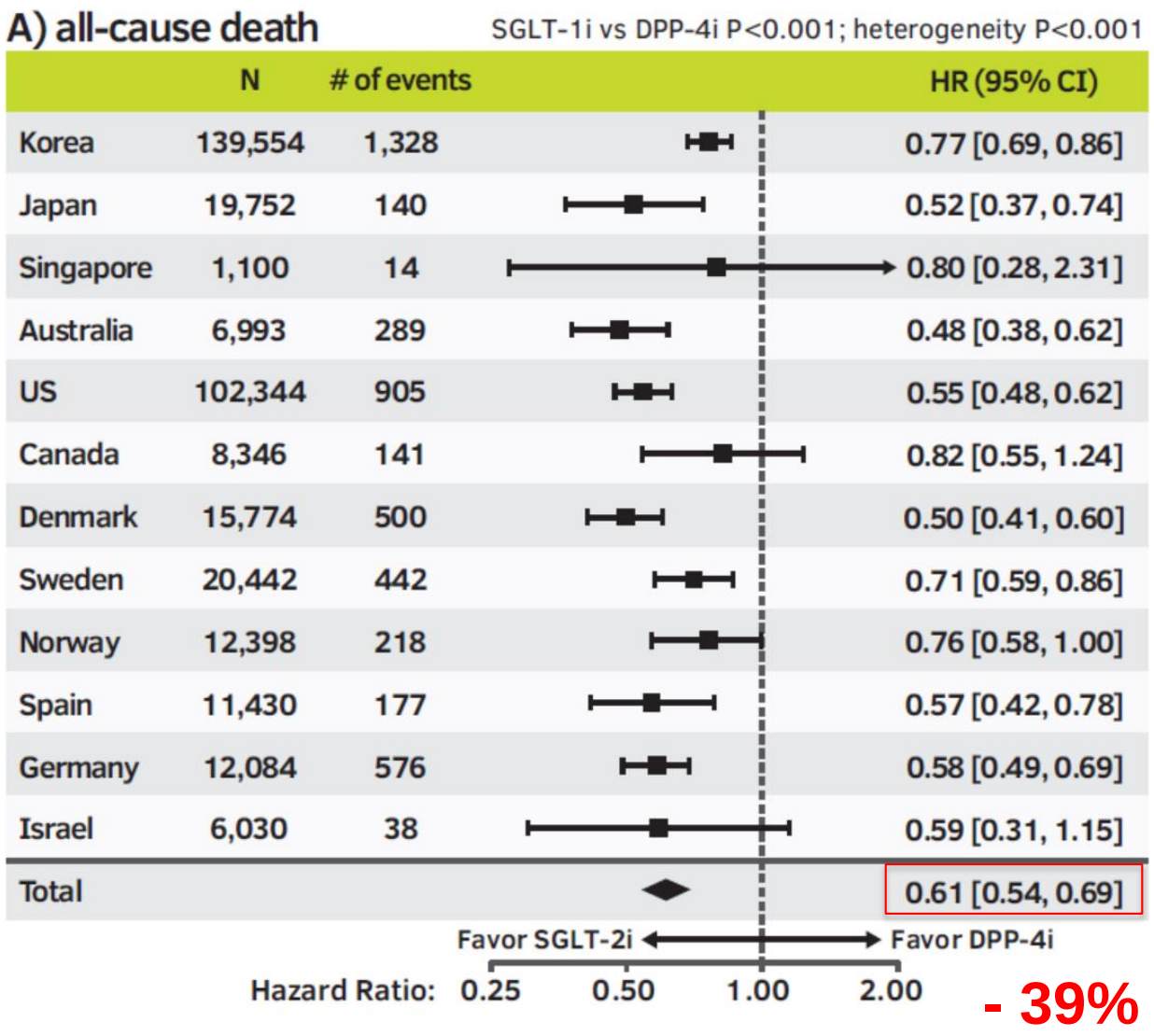
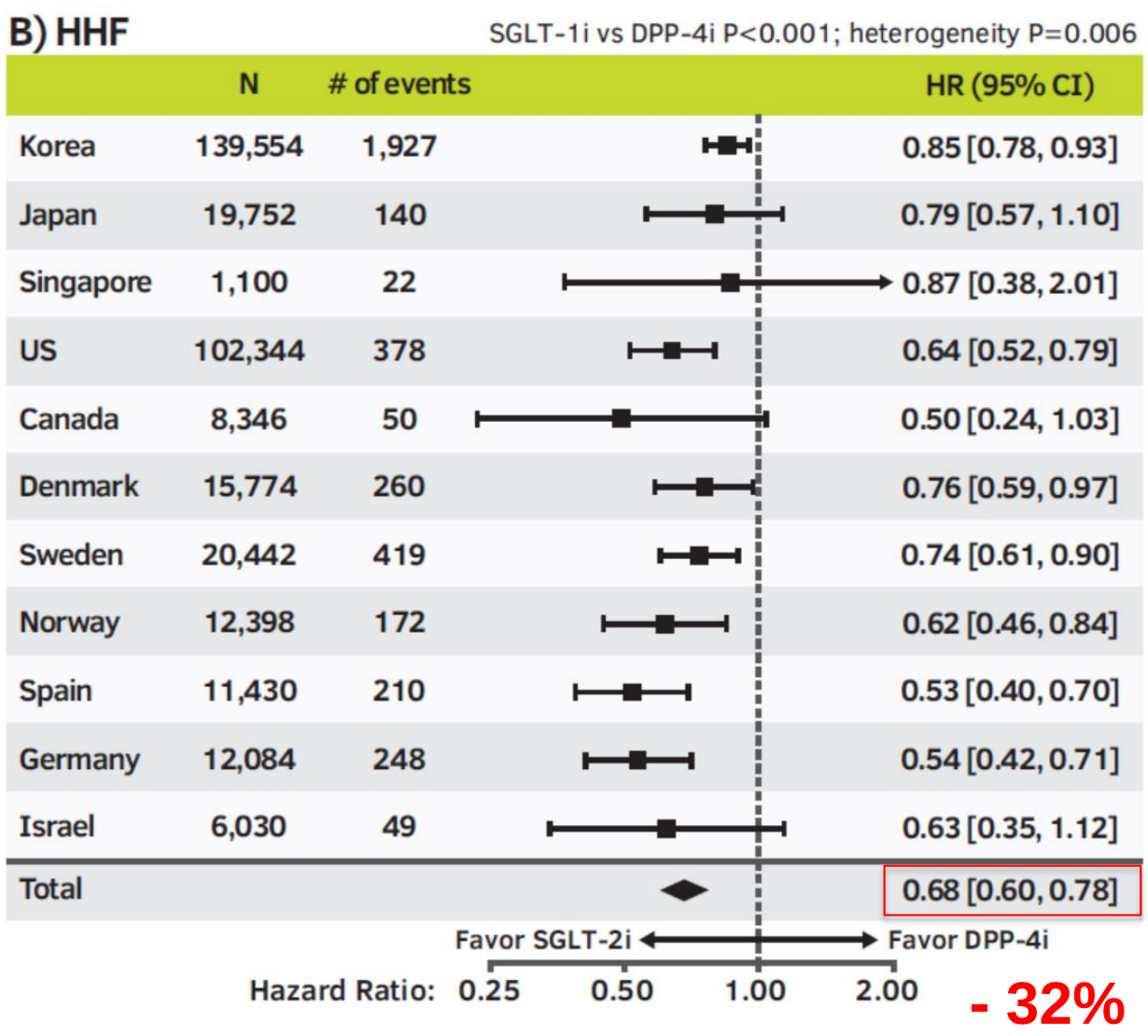
All cause death, hospitalization for heart failure (HHF)



- 39%



- 32%

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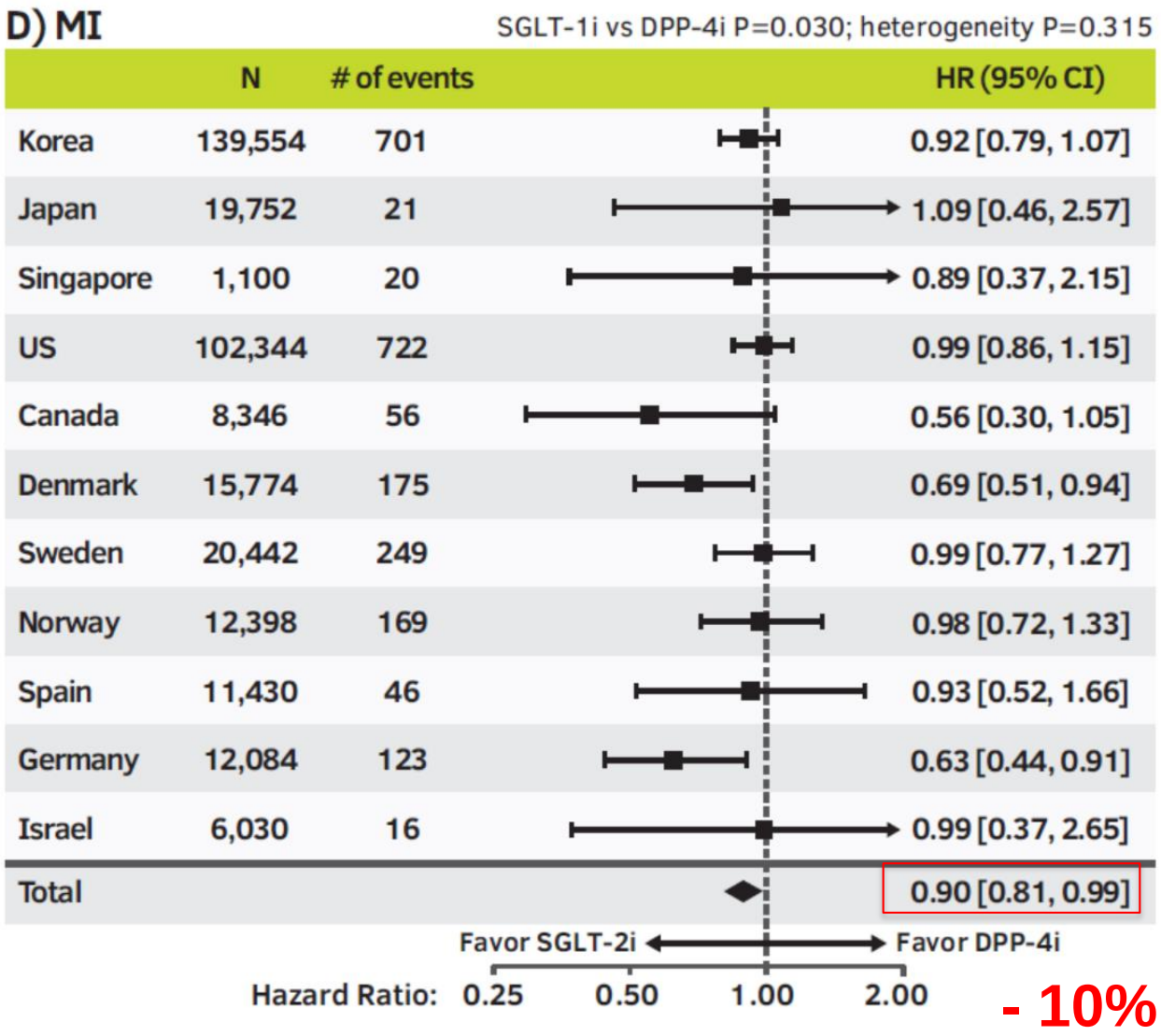
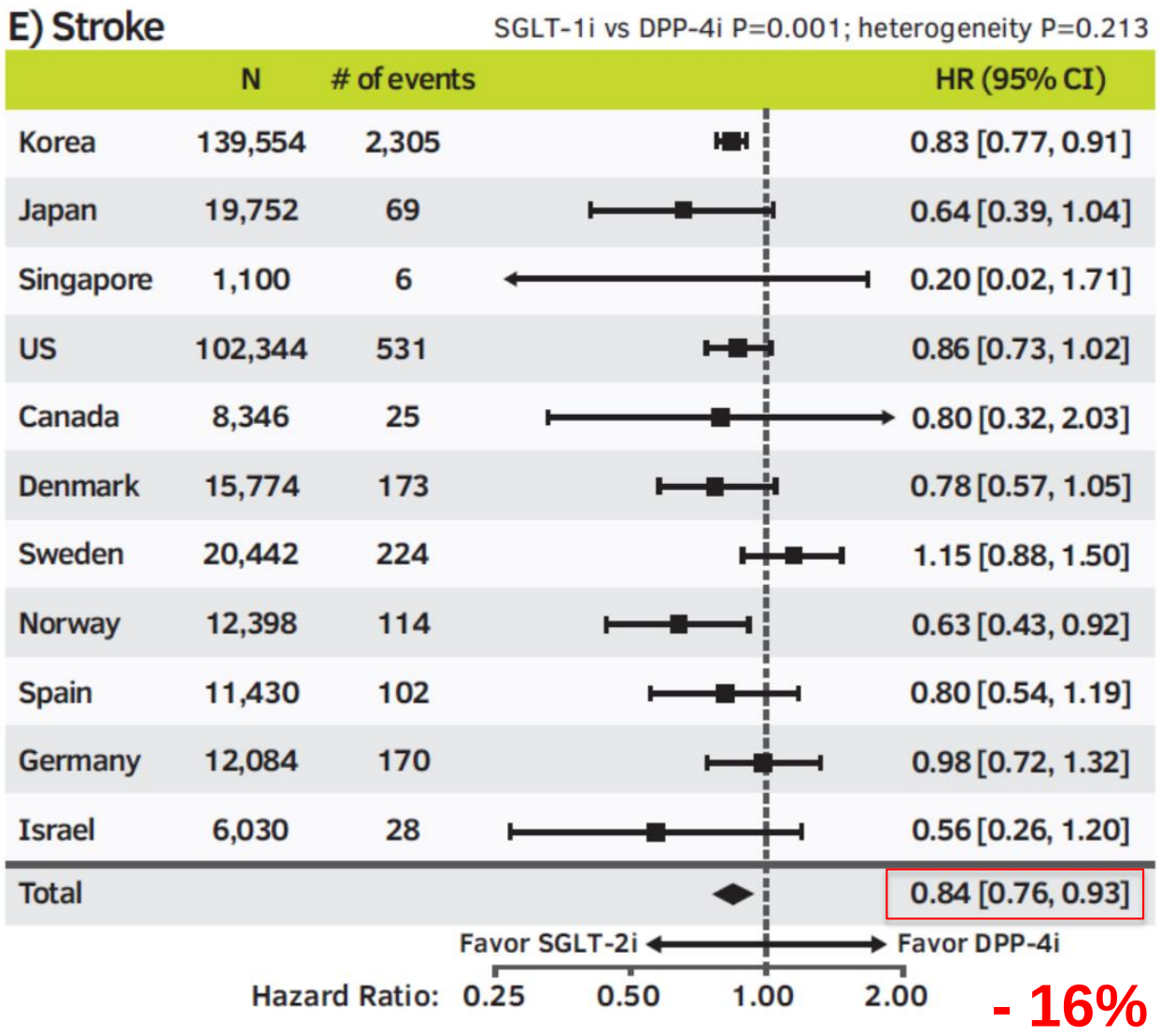
Myocardial infarction (MI), stroke



- 10%



- 16%

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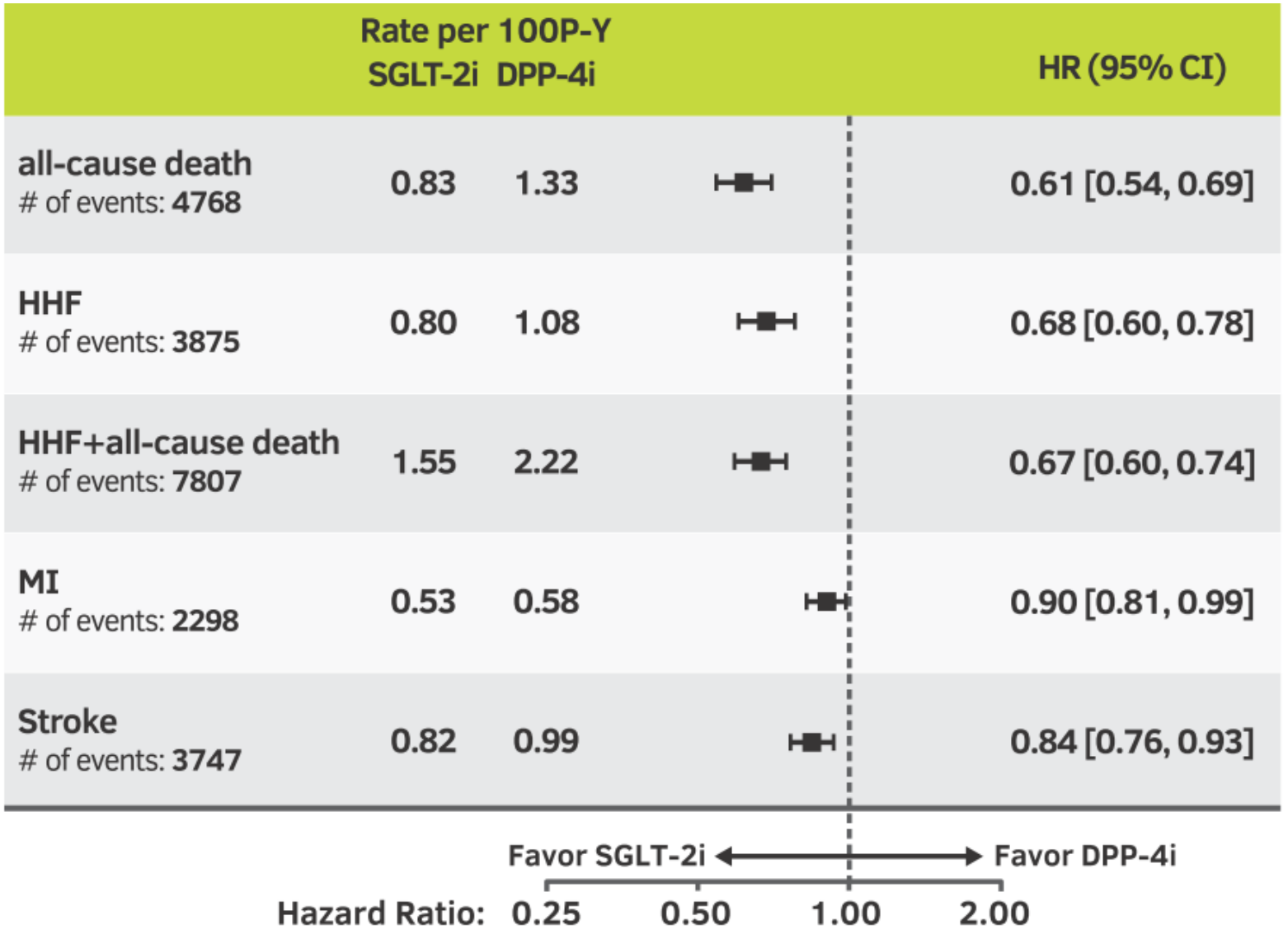
All five outcomes



- 39%

- 32%

- 33%

- 10%

- 16%

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Conclusions

- This was a large contemporary analysis of real-world administrative data across 12 countries, with over 360,000 patients
- Initiation of SGLT-2i was associated with a significantly lower risk of all-cause death and HHF compared with initiation of DPP-4i, and a modestly lower risk of MI and stroke
- These findings are complementary to previous observational study results (CVD-REAL Nordic)[1], and clinical trials[2-6] which did not include head-to-head comparisons of SGLT-2i with specific glucose-lowering drug classes

1. Persson F, et al. Diabetes Obes Metab 2018;20:344–51; 2. Zinman B, et al. N Engl J Med 2015;373:2117–28; 3. Neal B, et al. N Engl J Med 2017;377:644–57; 4. Zannad F, et al. Lancet 2015;385:2067–76; 5. Scirica BM, et al. N Engl J Med 2013;369:1317–26; 6. White WB, et al. N Engl J Med 2013;369:1327–35; 6. Persson F, et al. Diabetes Obes Metab 2018;20:344–51

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Outline

1. Forxiga Clinical Data vs Major Medication
   - Efficacy of Glycemic Control
   - vs DPP4i / with DPP4i
   - Beyond Glycemic Control
2. **Guidelines**
3. Special consideration

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Journal of the Chinese Medical Association xx (2018) 1–34

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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

中華民國糖尿病學會
The Diabetes Association of the Republic of China (Taiwan)

中華民國心臟學會
TAIWAN SOCETY OF CARDIOLOGY

J Chin Med Assoc. 2018 Feb 13. pii: S1726-4901(18)30018-2.

2018 Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC) consensus on T2DM patients with CVD

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			

Treatment algorithm in diabetic patients with **Coronary Heart Disease**

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		

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			

J Chin Med Assoc. 2018 Feb 13. pii: S1726-4901(18)30018-2.

2018 Taiwan Society of Cardiology (TSOC) and the Diabetes Association of Republic of China (DAROC) consensus on T2DM patients with CVD

Treatment algorithm in diabetic patients with **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		

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			

J Chin Med Assoc. 2018 Feb 13. pii: S1726-4901(18)30018-2.

2018 DAROC Clinical Practice Guidelines for Diabetes Care

中華民國糖尿病學會
The Diabetes Association of the Republic of China (Taiwan)

DAROC Clinical Practice Guidelines for Diabetes Care- 2018, Taiwan, Diabetes Association of the R.O.C., 2018

2018 DAROC Clinical Practice Guidelines for Diabetes Care

若單一治療未達控制目標時，加上以下不同機轉的抗糖尿病藥

SU/Glinide	AGI	TZD	DPP4i	SGLT2i	GLP1-RA	Basal insulin
效　果：佳 低血糖：中 體　重：增加 副作用：低血糖 心血管實證:缺	效　果：中等 低血糖：低 體　重：稍下降 副作用：腸胃道 心血管實證:中立	效　果：佳 低血糖：低 體　重：增加 副作用：水腫 心衰竭、骨折 心血管實證:有	效　果：中等 低血糖：低 體　重：無影響 副作用：少見 心血管實證:中立	效　果：中等 低血糖：低 體　重：下降 副作用：泌尿道 感染、脫水、骨折 心血管實證:有	效　果：佳 低血糖：低 體　重：下降 副作用：腸胃道 心血管實證:部分有	效　果：最佳 低血糖：高 體　重：增加 副作用：低血糖 心血管實證:中立

未達控制目標

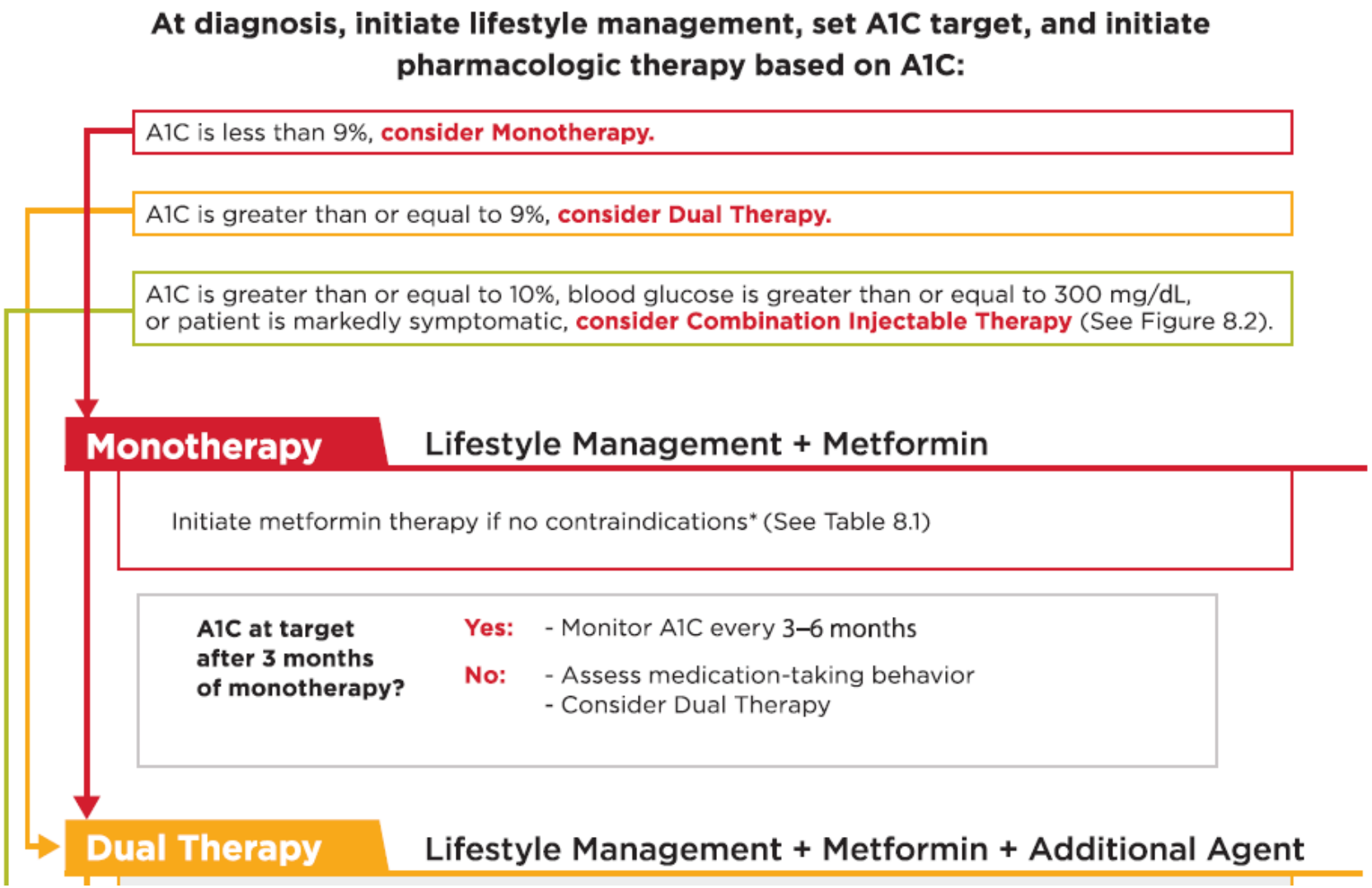
再加上另一種不同機轉的抗糖尿病藥
(SU和Glinide不建議合併，DPP4i和GLP1-RA不建議合併)

未達控制目標

建議照會專科或強化注射型藥物治療

DAROC Clinical Practice Guidelines for Diabetes Care- 2018, Taiwan, Diabetes Association of the R.O.C., 2018

Antihyperglycemic Therapy in Adults with T2DM



Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S73-S85

2018 ADA recommend agents with CV benefit for second-line therapy on patients with ASCVD

American Diabetes Association

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

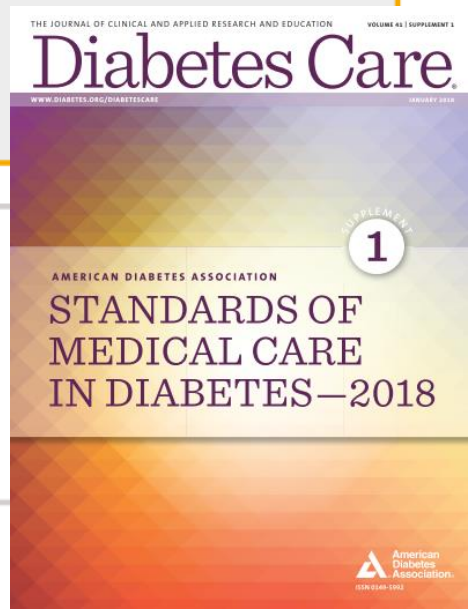
No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

ASCVD: atherosclerotic cardiovascular disease
Defined as：coronary heart disease, cerebrovascular disease, or peripheral arterial disease

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy



Diabetes Care 2018 Jan; 41 (Supplement 1): S73-S85.

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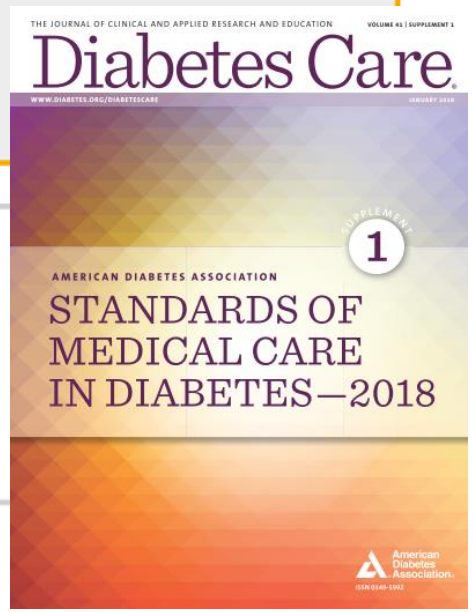


Diabetes Care 2018 Jan; 41 (Supplement 1): S73-S85.

Principles of the AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

1.	Lifestyle modification underlies all therapy (e.g. weight, exercise, 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

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

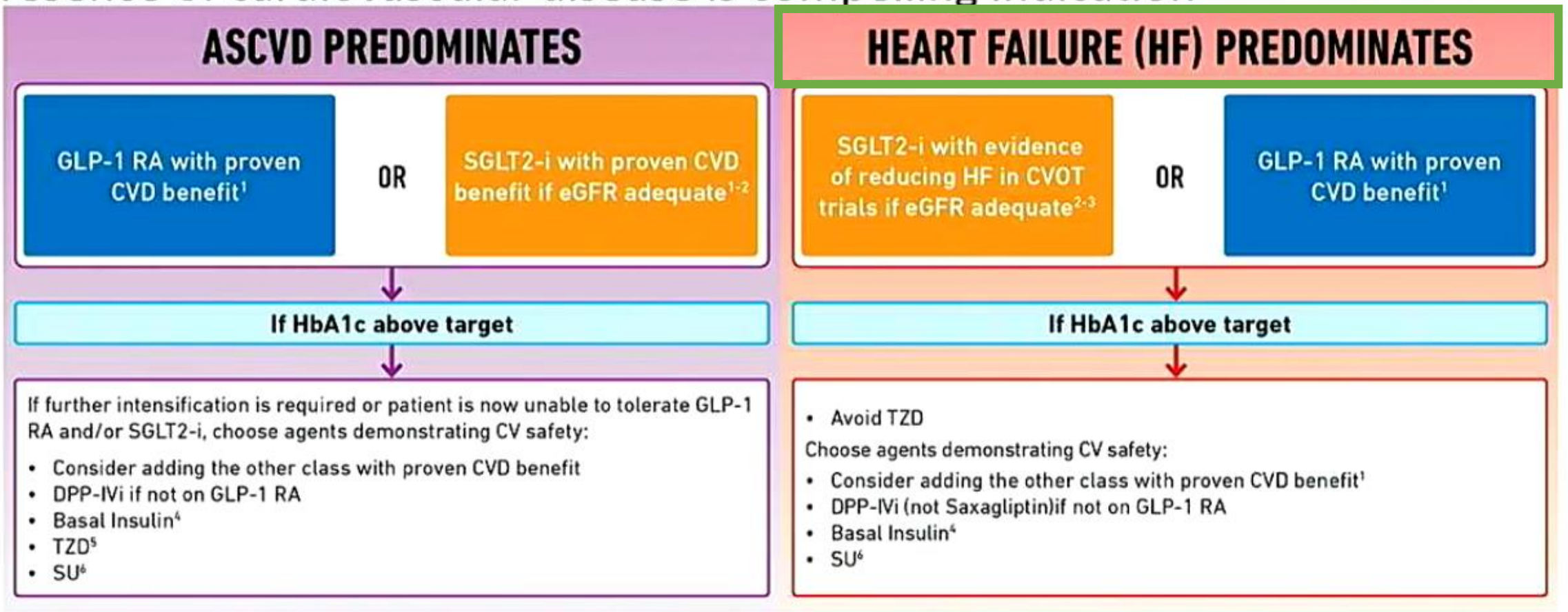
2018

2018 New add

2018 ADA/EASD consensus

Step 1: Assess cardiovascular disease

Presence of cardiovascular disease is compelling indication



1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see hierarchy of evidence in manuscript for CVD benefits for agents within the GLP-1 RA and SGLT2-i class, 2. Be aware that SGLT2-i 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 in CVOT trials, 4. Degludec or U100 Glargine have demonstrated CVD safety, 5. Low dos hypoglycaemia

American Diabetes Association, 78th Scientific Sessions, Orlando, FL, June 22-28, 2018. Session: Management of Hyperglycemia in Type 2 Diabetes—Draft ADA/EASD Consensus Report 2018. Access from: https://professional.diabetes.org/2018EASDconsensus

American Diabetes Association.

Copyright ADA 2018

EASD European Association for the Study of Diabetes

If heart failure predominates, consider SGLT2 inhibitor as part of treatment strategy

Rationale: Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2 inhibitor trials

Caveat: trials were not designed to adjudicate heart failure

Majority of patients did not have clinical heart failure at baseline

SGLT2-i with evidence of reducing HF in CVOT trials if eGFR adequate[4]

OR

GLP-1 RA with proven CVD benefit[1] if eGFR less than adequate[2,3]

If HbA1c above target

- Avoid TZD

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-IVi (not saxagliptin) if not on GLP-1 RA
- Basal Insulin[5]
- SU[7]

American Diabetes Association, 78th Scientific Sessions, Orlando, FL, June 22-28, 2018. Session: Management of Hyperglycemia in Type 2 Diabetes—Draft ADA/EASD Consensus Report 2018. Access from: https://professional.diabetes.org/2018EASDconsensus

1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class, 2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use, 3. Caution with GLP1-RA in End Stage Renal Disease, 4. Both empagliflozin and canagliflozin have shown reduction in HF in CVOT trials, 5. Degludec or U100 Glargine have demonstrated CVD safety, 7.Choose later generation SU to lower risk of hypoglycaemia

American Diabetes Association.

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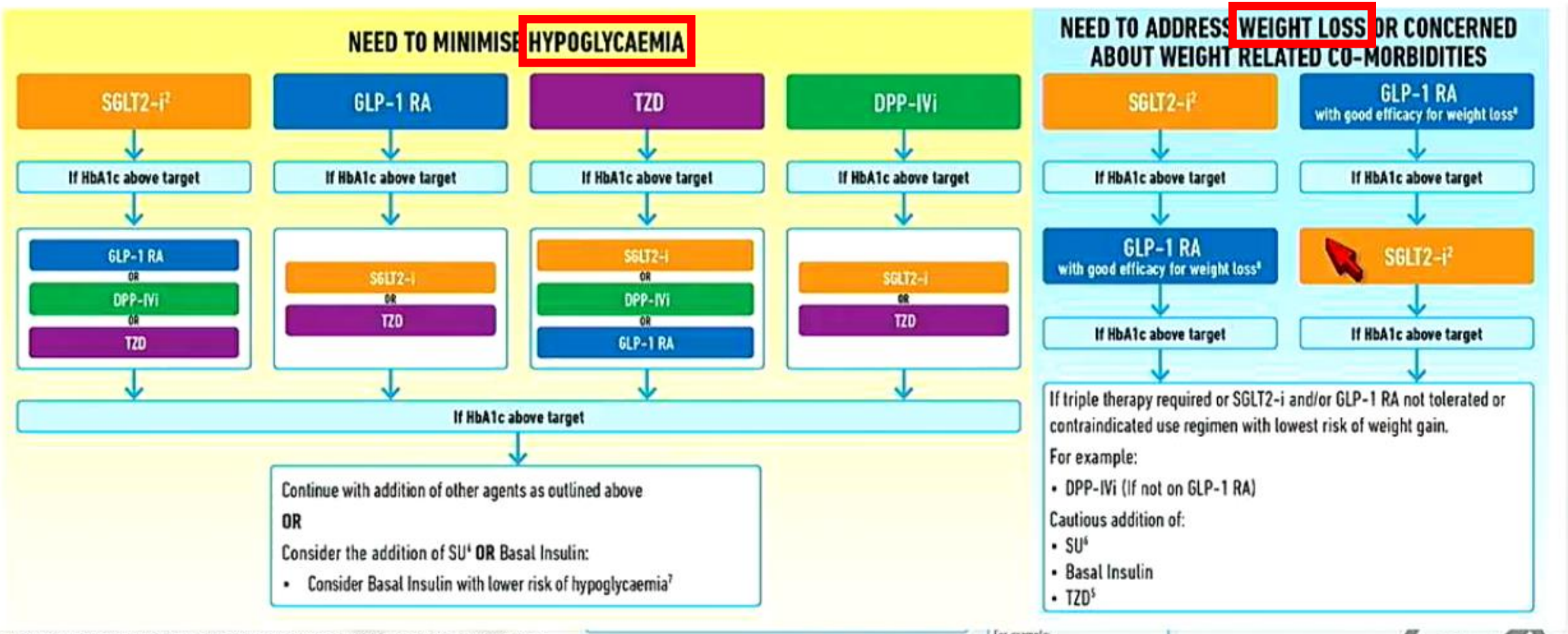
EASD European Association for the Study of Diabetes

ANTIHYPERGLYCEMIC MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class
2. Be aware that SGLT2-i 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 in CVOT trials
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 risk of hypoglycaemia
7. Degludec / Glargine U300 < Glargine U100 / Detemir < NPH insulin
8. GLP-1 RA with best efficacy for weight loss Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide
9. If no specific co-morbidities (i.e. established CVD), low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related co-morbidities: using the algorithm to minimise medication costs
10. Consider country and region specific cost of drugs. In some countries TZD relatively more expensive and DPP-IVi relatively cheaper

For example:
• DPP-IVi (If not on GLP-1 RA)
Cautious addition of:
• SU[6]
• Basal Insulin
• TZD[5]

American Diabetes Association, 78th Scientific Sessions, Orlando, FL, June 22-28, 2018. Session: Management of Hyperglycemia in Type 2 Diabetes—Draft ADA/EASD Consensus Report 2018. Access from: https://professional.diabetes.org/2018EASDconsensus

American Diabetes Association.
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EASD European Association for the Study of Diabetes

ANTIHYPERGLYCEMIC MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

IF NO SUCH NEEDS IDENTIFIED OR COST IS A MAJOR ISSUE[9-10]

SU[6]

↓

If HbA1c above target

↓

TZD[10]

↓

If HbA1c above target

↓

- **Insulin therapy** NPH Basal Insulin preferred.

OR

- Consider DPP-IVi **OR** SGLT2-i with lowest acquisition cost[10]

TZD[10]

↓

If HbA1c above target

↓

SU[6]

↓

If HbA1c above target

↓

- DPP-IVi (If not on GLP-1 RA)

Cautious addition of:

- SU[6]
- Basal Insulin
- TZD[8]

1. SGLT2i = [illegible] preferred, GLP-1RA = [illegible] preferred. Proven CVD benefit implies that level indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class
2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
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EASD European Association for the Study of Diabetes

Draft Consensus Recommendation:

For patients with chronic kidney disease (CKD) and high cardiovascular risk, it is safe to use GLP-1 receptor agonists and SGLT2 inhibitors, albeit with dose reduction for some medications.

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment

American Diabetes Association, 78th Scientific Sessions, Orlando, FL, June 22-28, 2018. Session: Management of Hyperglycemia in Type 2 Diabetes—Draft ADA/EASD Consensus Report 2018. Access from: https://professional.diabetes.org/2018EASDconsensus

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Outline

1. Forxiga Clinical Data vs Major Medication
   - Efficacy of Glycemic Control
   - vs DPP4i / with DPP4i
   - Beyond Glycemic Control
2. Guidelines
3. **Special consideration**

Safety Profile from RCT Urinary Tract and Genital Infections

The safety of dapagliflozin 10 mg as assessed in a pooled analysis of 13 placebo-controlled studies (>2,300 patients)

	Placebo-controlled pool	
Events (%)	**Dapagliflozin 10 mg** (n=2360)	**Placebo** (n=2295)
UTIs	110 (4.7)	81 (3.5)
Genital infections*	130 (5.5)	14 (0.6)

*Genital infection includes the preferred terms: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial and vulval abscess.UTI: urinary tract infections; RCT: randomised clinical trial

Diabetic ketoacidosis (DKA)

Incidence of DKA with $SGLT_2$ inhibitors

AACE/ACE Position Statement

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Yehuda Handelsman, MD, FACP, FNLA, FACE, Co-Chair[1]; Robert R. Henry, MD, FACE, Co-Chair[2]; Zachary T. Bloomgarden, MD, MACE[3]; Sam Dagogo-Jack, MD, DM, FRCP, FACE[4]; Ralph A. DeFronzo, MD, BMS, MS, BS[5]; Daniel Einhorn, MD, FACP, FACE[6]; Ele Ferrannini, MD[7];

The incidence of DKA in clinical trials of $SGLT_2$ inhibitors with T2DM was 0.2-0.8 cases per 1,000 patient-years[1]

The estimated incidence of DKA with dapagliflozin was 0.02%[2]

Potential events of DKA	Placebo/comparator-controlled 21-study pool Dapagliflozin total (N = 5936; 6247.2 patient-years)
SAE of DKA, n	1
AE of ketonuria, n	2
AE of metabolic acidosis, n	1
Estimated incidence of DKA, % (95% CI)	0.02 (0.004, 0.059)
Estimated incidence of DKA/metabolic acidosis, % (95% CI)	0.03 (0.010, 0.089)

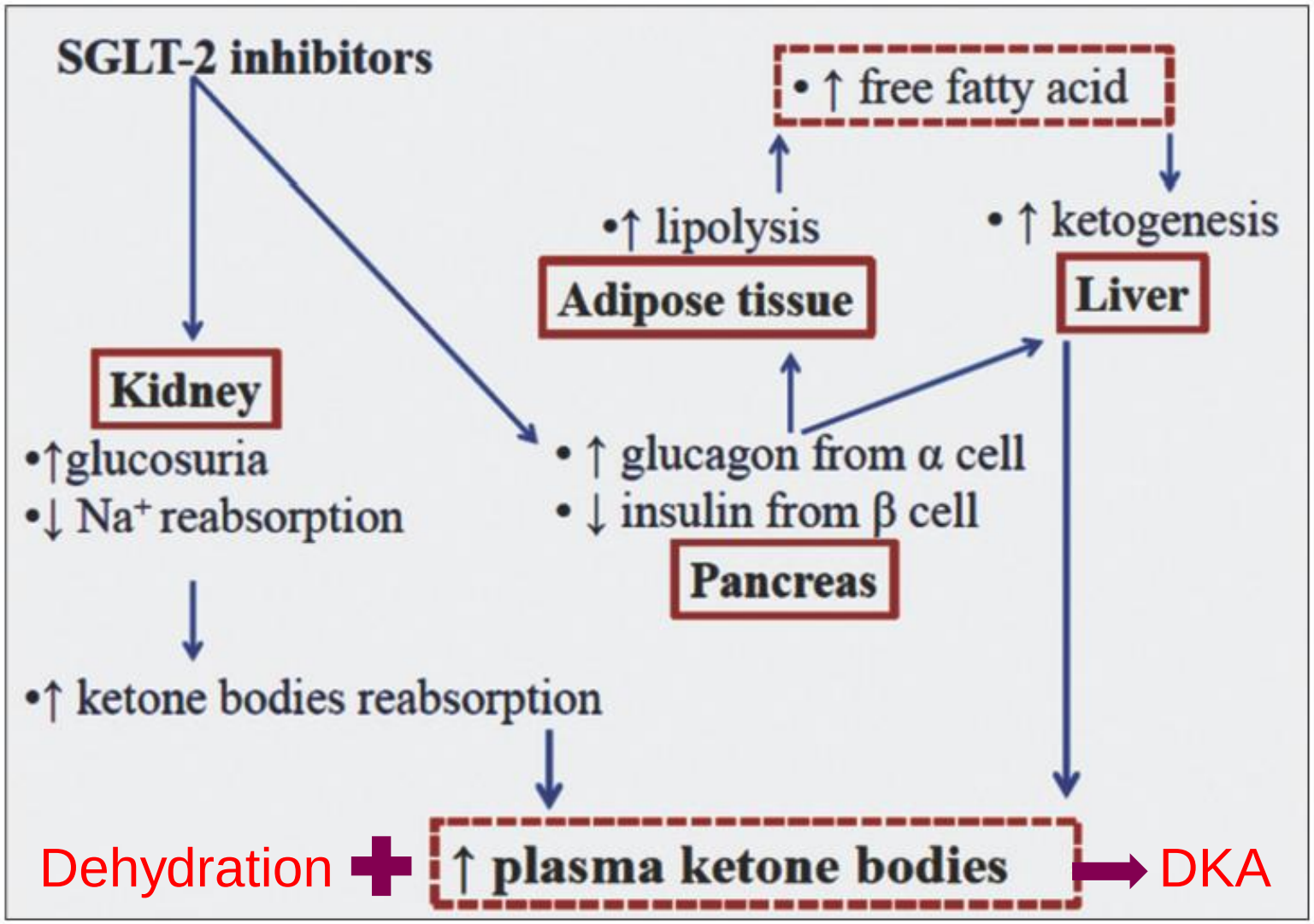
The incidence of acute pancreatitis:

- Sitagliptin is 1.1 cases per 1000 person-year[3]
- Linagliptin is 1.5 cases per 1000 patient-year[4]

DKA: diabetic ketoacidosis 1. Endocr Pract. 2016 Jun;22(6):753-62. 2. Diabetes Obes Metab. 2017 Sep 26. doi: 10.1111/dom.13124. 3. N Engl J Med. 2015 Jul 16;373(3):232-42. 4. Ther Adv Drug Saf. 2014 Jun; 5(3): 138–146.

AstraZeneca do not recommend the use of dapagliflozin/metformin XR in any manner other than T2DM

Mechanism of ketosis with $SGLT_2$ inhibitors[1]



2 week (10 mg)	placebo	DAPA[2]
Ketones (mmol/L)	0.09	0.20

4 week (25 mg)	baseline	EMPA[3]
Ketones (mmol/L)	0.25	0.56

< 0.6 = normal (in mmol/L)

0.6 – 1.0 = slightly elevated. Drink extra fluids.

1.0 – 3.0 = serious and call healthcare provider and state the call is urgent. Take extra rapid-acting insulin and drink extra fluids.

> 3.0 = **Go directly to the Emergency Room.**

DAPA: dapagliflozin, EMPA: empagliflozin

1. Singh AK et al. Indian J Endocrinol Metab. 2015 Nov-Dec;19(6):722-30. 2. Daniele G et al. Diabetes Care. 2016 Nov;39(11):2036-2041.
3. Ferrannini E et al. Diabetes. 2016 May;65(5):1190-5.

AstraZeneca do not recommend the use of dapagliflozin/metformin XR in any manner other than T2DM

How minimize the risk of DKA

- **To minimize the risk of DKA associated with SGLT-2 inhibitors, AACE recommends the following[1]:**
  1. Consider stopping the SGLT-2 inhibitor at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon
  2. **For emergency surgery or any extreme stress event, the drug should be stopped immediately**

     Almost all cases of SGLT-2 inhibitor–associated DKA occurred in patients challenged with metabolically stressful events: surgery, extensive exercise, myocardial infarction, stroke, severe infections, prolonged fasting
  3. **Avoid stopping insulin or decreasing the dose excessively**
  4. Patients taking SGLT-2 inhibitors **should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets**
  5. Routine measurement of urine ketones is not recommended during use of SGLT-2 inhibitors because this measurement can be misleading. Instead, measurement of blood ketones is preferred for diagnosis of DKA in symptomatic patients

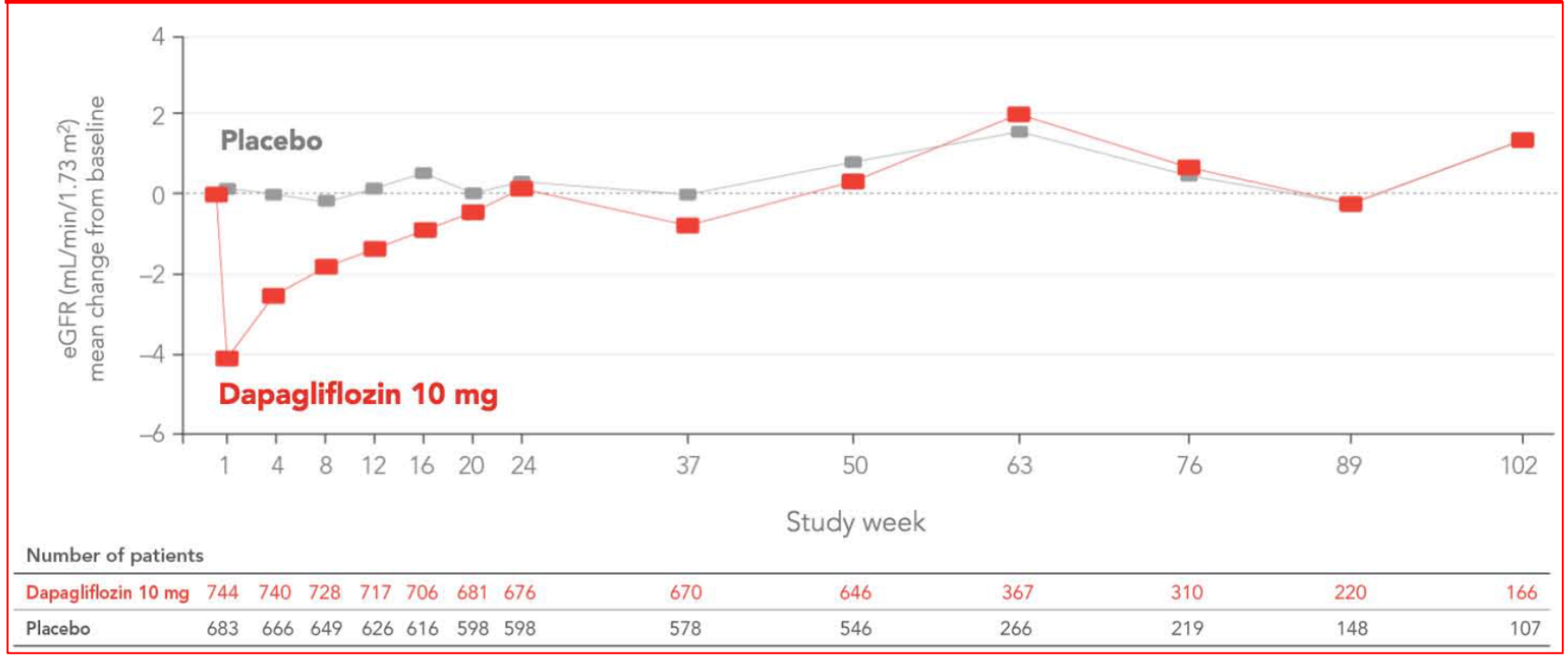
     DKA symptoms: abdominal pain, nausea, vomiting, fatigue, and dyspnea

1. Endocr Pract. 2016 Jun;22(6):753-62.

AstraZeneca do not recommend the use of dapagliflozin/metformin XR in any manner other than T2DM

Forxiga no Detrimental Effect on Renal Function over 102 Weeks

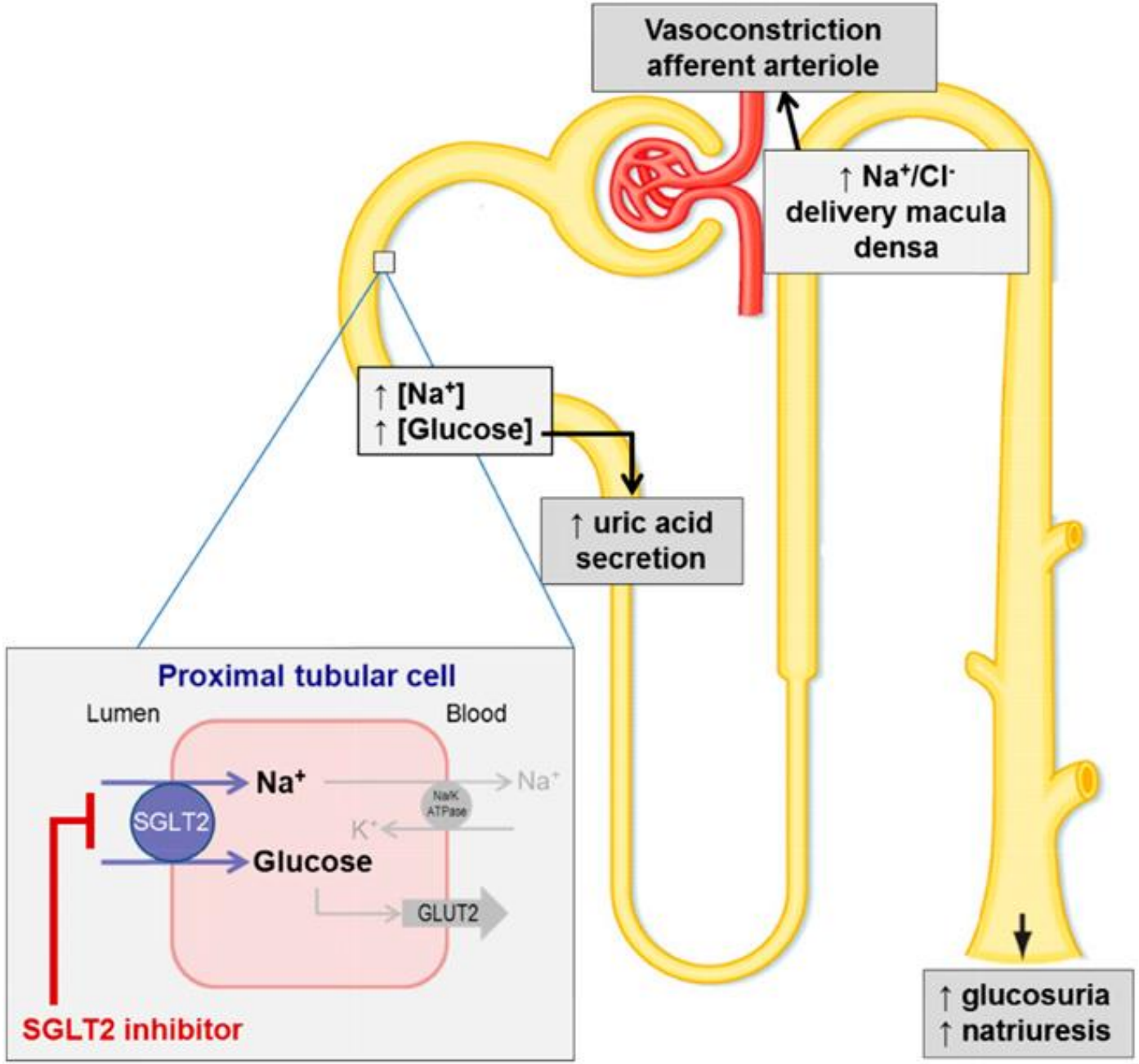
Stable eGFR over 102 weeks



Number of patients													
Dapagliflozin 10 mg	744	740	728	717	706	681	676	670	646	367	310	220	166
Placebo	683	666	649	626	616	598	598	578	546	266	219	148	107

- The efficacy of Forxiga is dependent on renal function
- Overall, patients taking Forxiga showed stable eGFR over 2 years
- Forxiga does not appear to be associated with deterioration in renal function over time up to 4 years
- All SGLT2i show a reduction in efficacy in patients with reduced renal function

Kohan DE, et al. J Nephrol 2016. DOI 10.1007/s40620-016-0261-1
FORXIGA. Summary of product characteristic, 2016.
Del Prato S, et al. Diabetes Obes Metab 2015;17:581-90
Del Prato S, et al. Diabetes Obes Metab 2015;17:581-90 (Supplementary data)
Inzucchi SE, et al. Diabetes Care 2015;38:140-9



Clinical findings

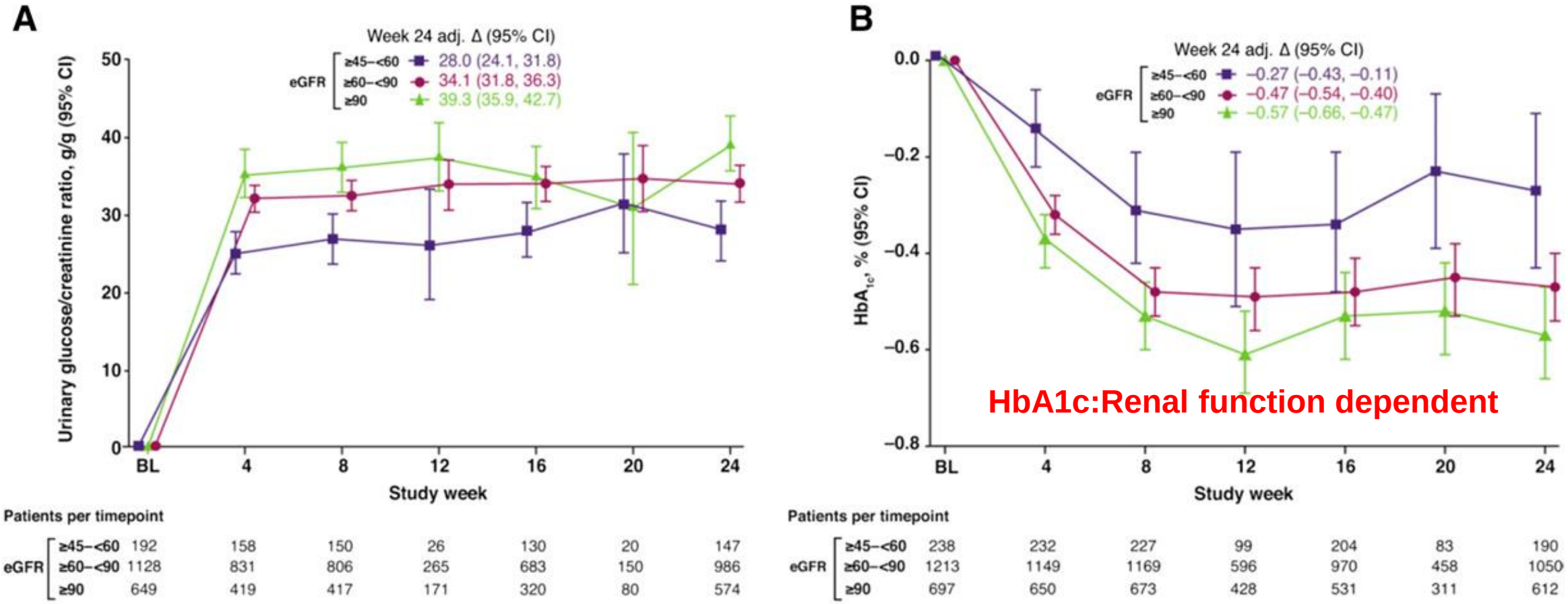
- ↓ Plasma glucose
- ↓ Body weight
- ↓ Blood pressure
- ↓ Plasma uric acid
- ↓ Glomerular hyperfiltration

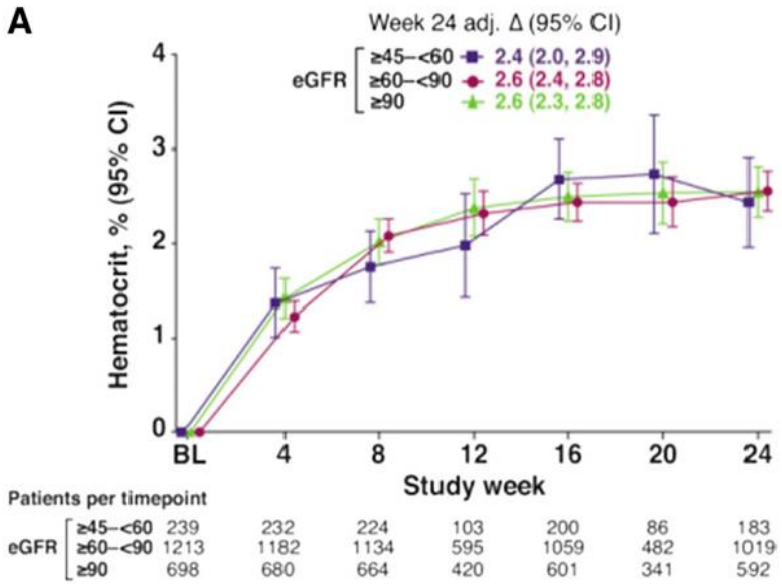
CJASN ePress. Published on March 16, 2017 as doi: 10.2215/CJN.10180916

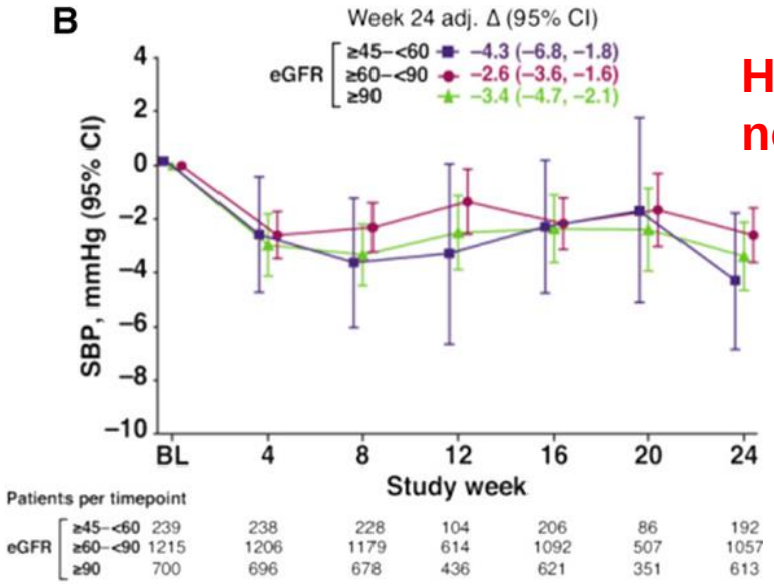
Article

Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function

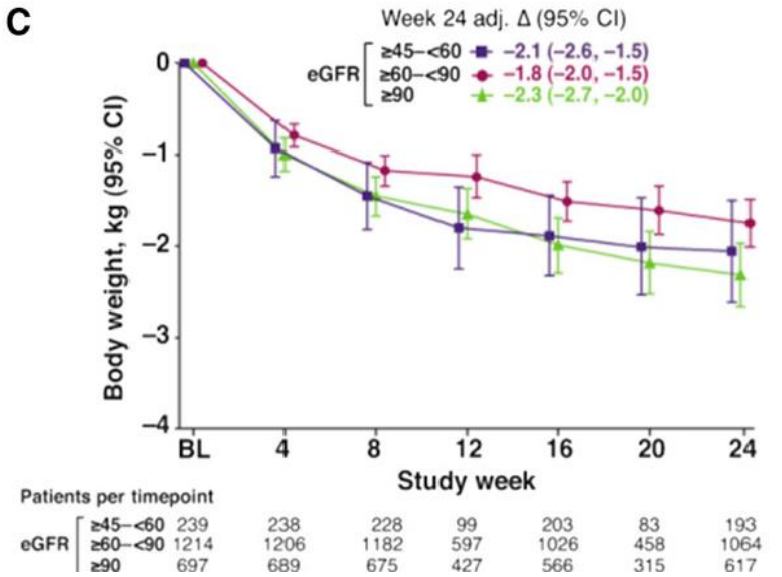
Sergei Petrykiv, C. David Sjöström,† Peter J. Greasley,† John Xu,‡ Frederik Persson,§ and Hiddo J.L. Heerspink**

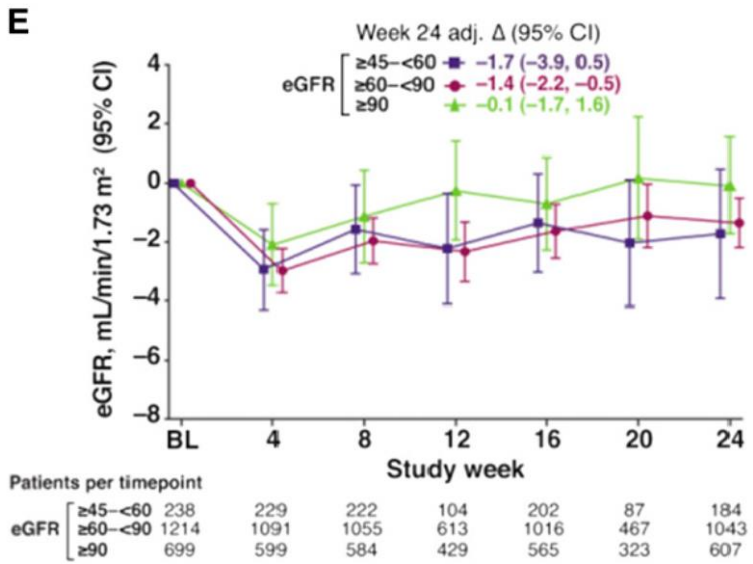


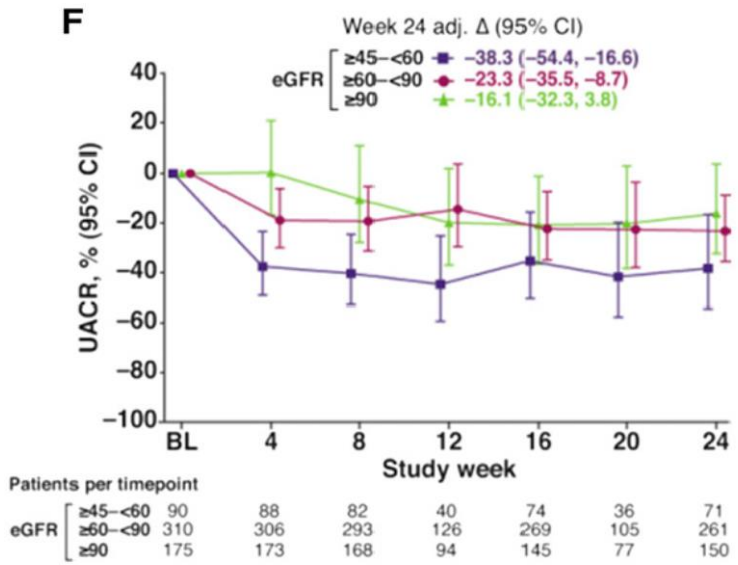




Hematocrit, BP, BW, MAU improvement: not renal function dependent







Case sharing

Patient 2 profile

- 楊oo
- Female
- 64 y/o
- T2DM: 8 years
- NDR, ACR 23 mg/gCr

[GLU累積報告內容(24)] Glucose 點選圖示查詢UpToDate/Micromedex]

日期	Glucose	Glu,1hrPC	Glu,2hrPC	Glu,3hrPC	HbA1c	C-PEPTIDE
2016-10-15 08.53	198	-	-	-	-	
2016-10-15 09.53	-	-	-	-	6.4	
2017-01-14 08.13	174	-	-	-	-	
2017-01-14 08.45	-	-	-	-	6.6	
2017-04-22 07.55	198	-	-	-	-	
2017-04-22 08.33	-	-	-	-	7.5	
2017-07-15 08.06	203	-	-	-	-	
2017-07-15 08.45	-	-	-	-	6.9	1J+1D+3M
2017-10-17 09.16	-	-	-	-	6.2	
2017-10-17 09.19	136	-	-	-	-	
2018-01-15 08.29	194	-	-	-	-	
2018-01-15 10.24	-	-	-	-	6.7	0.5F+1D+3M
2018-04-14 10.10	-	-	-	-	6.0	
2018-04-14 10.46	131	-	-	-	-	
2018-07-11 09.46	130	-	-	-	-	

[查詢條件]

其他時間範圍: 兩年內 累積報告類型 : (累積)SMAC

[CHEMN累積報告內容(24) TP 點選圖示查詢UpToDate/Micromedex]

日期	TP	ALB	CA	CHOL	BUN	UA	CREA	BILIT	ALKP	LDH	ALT	AST	NA	K	CL	GLU	IP	CK	GGT	HDLC	LDLC	RISKF	TG	CO2	DBILI	I
16-10-15 08.53	-	-	-	160	-	5.8	0.74	-	-	-	162	-	-	-	-	-	-	-	-	-	97	-	207	-	-	
16-11-10 15.10	-	-	-	-	-	-	-	1.02	95	-	208	121	-	-	-	-	-	-	-	-	-	-	-	-	-	
17-01-21 09.21	-	-	-	-	-	-	-	-	-	-	113	52	-						-	-	-	-	-	-	-	
17-07-15 08.06	-	-	-	-	-	-	-	-	-	-	170	77	-						-	-	-	-	-	-	-	
17-10-17 09.19	-	-	-	-	-	-	-	0.95	84	-	120	66	-						24	-	-	-	-	-	0.33	
18-01-15 08.29	-	-	-	176	-	-	0.71	-	-	-	124	-	-							-	104	-	253	-	-	
18-04-14 10.46	-	-	-	161	-	-	0.66	-	-	-	52	-	-	-	-	-	-	-	-	-	105	-	192	-	-	
18-04-17 11.11	-	-	9.3	-	-	-	-	-	-	-	-	-	138	4.4	-	-	-	-	-	-	-	-	-	-	-	
18-07-11 09.46	-	-	-	-	-	-	-	-	-	-	27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

1J+1D+3M

0.5F+1D+3M

BW decrease 4 kg

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Effects of Dapagliflozin on Body Composition and Liver Tests in Patients with Nonalcoholic Steatohepatitis Associated with Type 2 Diabetes Mellitus: A Prospective, Open-label, Uncontrolled Study.

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Author information

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Abstract

BACKGROUND: Nonalcoholic steatohepatitis (NASH) is an active form of nonalcoholic fatty liver disease. Risk factors for NASH include type 2 diabetes mellitus (T2DM) and obesity. Sodium-glucose cotransporter 2 (SGLT2) inhibitors used to treat T2DM prevent glucose reabsorption in the kidney and increase glucose urinary excretion. Dapagliflozin is a potent, selective SGLT2 inhibitor that reduces hyperglycemia in patients with T2DM and has been demonstrated to reduce some complications associated with NASH in rodent models.

OBJECTIVE: To assess the efficacy and safety profile of dapagliflozin for the treatment of NASH-associated with T2DM.

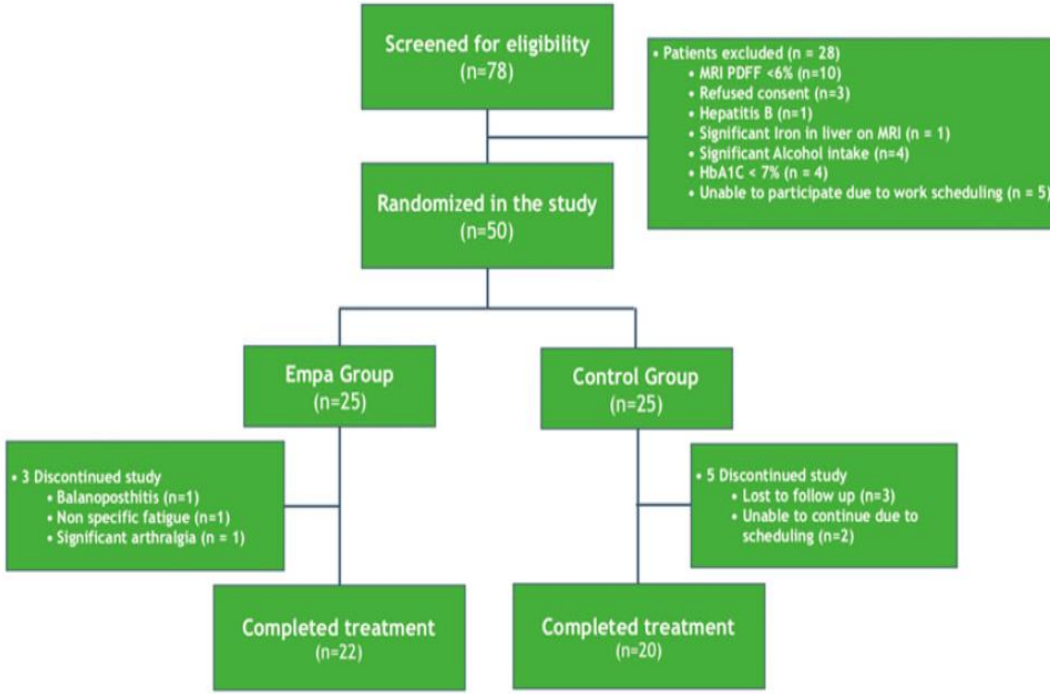
METHODS: In this single-arm, nonrandomized, open-label study, 16 patients with percutaneous liver biopsy-confirmed NASH and T2DM were enrolled to be prescribed dapagliflozin 5 mg/d for 24 weeks. Of these, 11 patients were evaluable. Patients with chronic liver disease other than NASH were excluded. Body composition, laboratory variables related to liver tests and metabolism, and glucose homeostasis were assessed at baseline and periodically during the study. Changes from baseline were evaluated with the Wilcoxon signed-rank test.

RESULTS: Administration of dapagliflozin for 24 weeks was associated with significant decreases in body mass index ($P < 0.01$), waist circumference ($P < 0.01$), and waist-to-hip ratio ($P < 0.01$). Changes in body composition were driven by reductions in body fat mass ($P < 0.01$) and percent body fat ($P < 0.01$), without changes in lean mass or total body water. Liver tests (ie, serum concentrations of aspartate aminotransferase, alanine aminotransferase, ferritin, and type IV collagen 7S) also significantly improved during the study. Insulin concentrations decreased ($P < 0.01$ by Week 24) in combination with significant reductions in fasting plasma glucose ($P < 0.01$) and glycated hemoglobin ($P < 0.01$) levels and increases in adiponectin ($P < 0.01$) levels from Week 4 onward.

CONCLUSIONS: Dapagliflozin was associated with improvements in body composition, most likely a reduction in visceral fat, which occurred together with improvements in liver tests and metabolic variables in patients with NASH-associated with T2DM. UMIN Clinical Trial Registry identifier: UMIN000023574.

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial)

N=50
Empa 10mg vs control
20 wks
MRI-PDFF



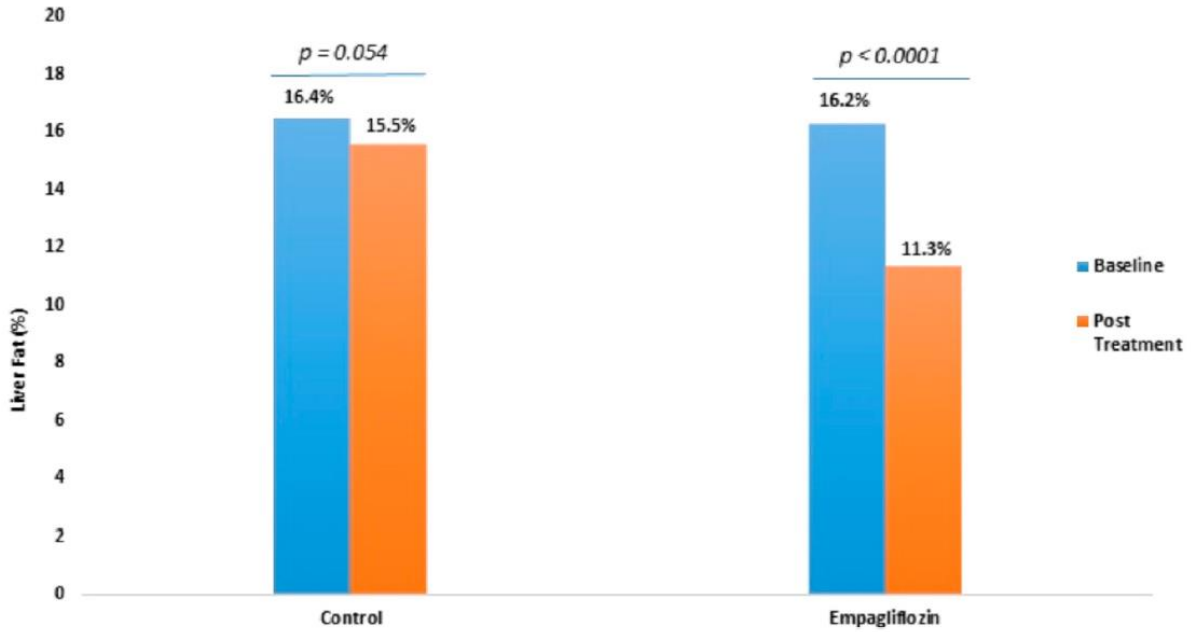


Figure 2—Baseline and posttreatment changes in liver fat in the empagliflozin and control groups as assessed by MRI-PDFF. Change in liver fat relative to baseline as assessed by MRI-PDFF. A significant difference was found in change in liver fat between the study groups ($P < 0.0001$).

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Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label, Active-Controlled Trial.

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Author information

Abstract

OBJECTIVE: To compare the efficacy of ipragliflozin versus pioglitazone in patients with type 2 diabetes complicated by nonalcoholic fatty liver disease (NAFLD).

RESEARCH DESIGN AND METHODS: In this open-label, randomized, active-controlled trial, we randomly assigned 66 patients with type 2 diabetes and NAFLD to receive ipragliflozin 50 mg (*n* = 32) or pioglitazone 15-30 mg (*n* = 34) orally once daily. The primary outcome was a change from baseline in the liver-to-spleen attenuation ratio (L/S ratio) on computed tomography at week 24.

RESULTS: At week 24, the mean ± SD L/S ratio had increased by 0.22 (from 0.80 ± 0.24 to 1.00 ± 0.18) in the ipragliflozin group and 0.21 (from 0.78 ± 0.26 to 0.98 ± 0.16) in the pioglitazone group (*P* = 0.90). Serum aspartate and alanine aminotransferase levels, HbA_{1c}, and fasting plasma glucose were similarly reduced in the two treatment groups. Nevertheless, body weight and visceral fat area showed significant reductions only in the ipragliflozin group compared with the pioglitazone group (*P* < 0.0001 and *P* = 0.0013, respectively). There were no serious adverse events in either group.

CONCLUSIONS: Compared with pioglitazone, ipragliflozin exerts equally beneficial effects on NAFLD and glycemic control during the treatment of patients with type 2 diabetes complicated by NAFLD. Furthermore, ipragliflozin significantly reduced body weight and abdominal fat area.

454.365.022_FOR_16/02/2017

Paradigm shift?

Perhaps the question should be: Which medicine is better before metformin use?