New Evidence of Pharmacology Approaches to Glycemic Treatment: Which SGLT-2i is Better After Metformin (I)

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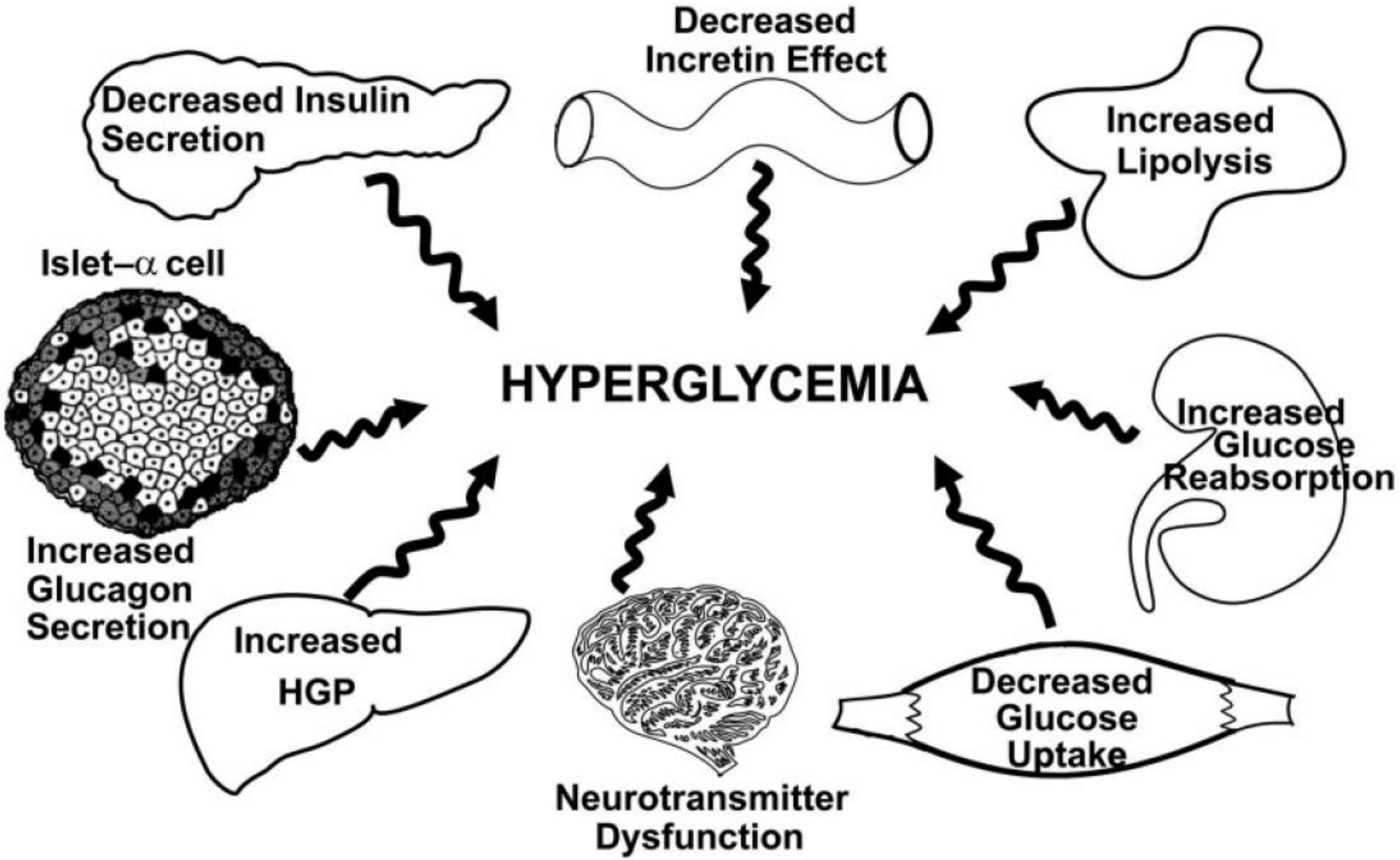
臺灣血脂衛教學會

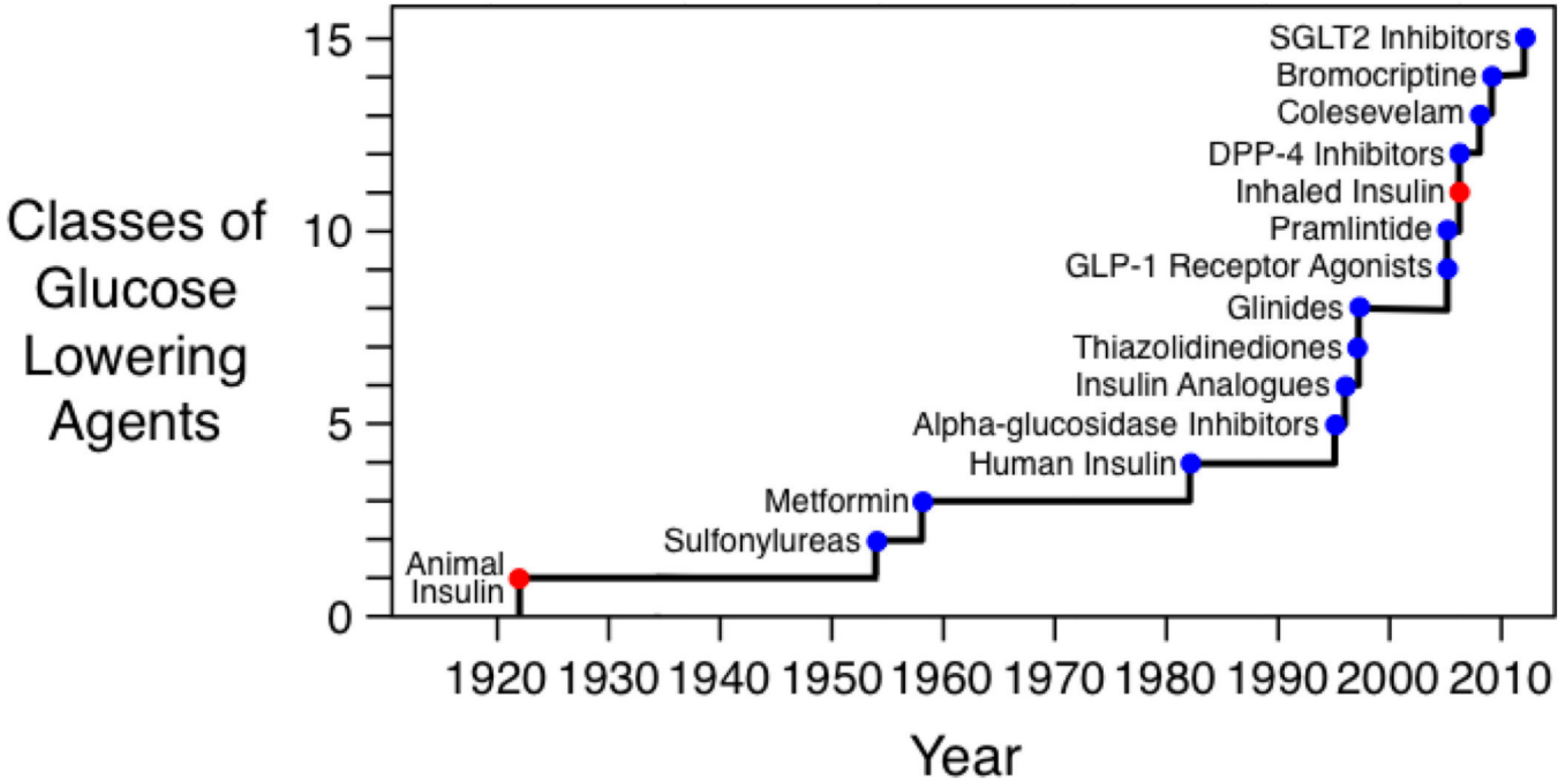
2018/09/09 15:30~16:00

The complex pathophysiology of T2DM



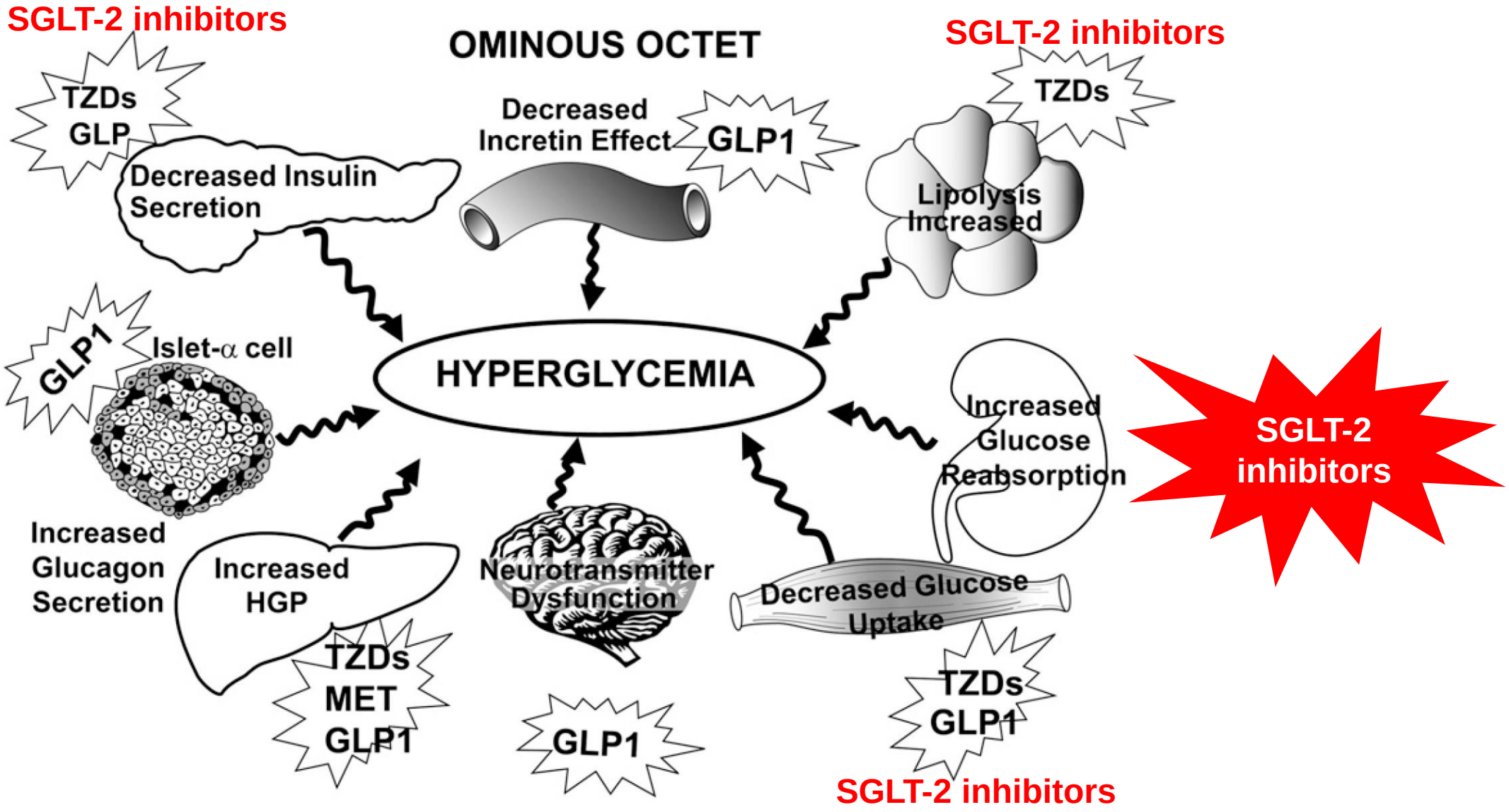
Ralph A. DeFronzo, Diabetes 2009 Apr; 58(4): 773-795.

Much more glucose lowering agents in the last decade



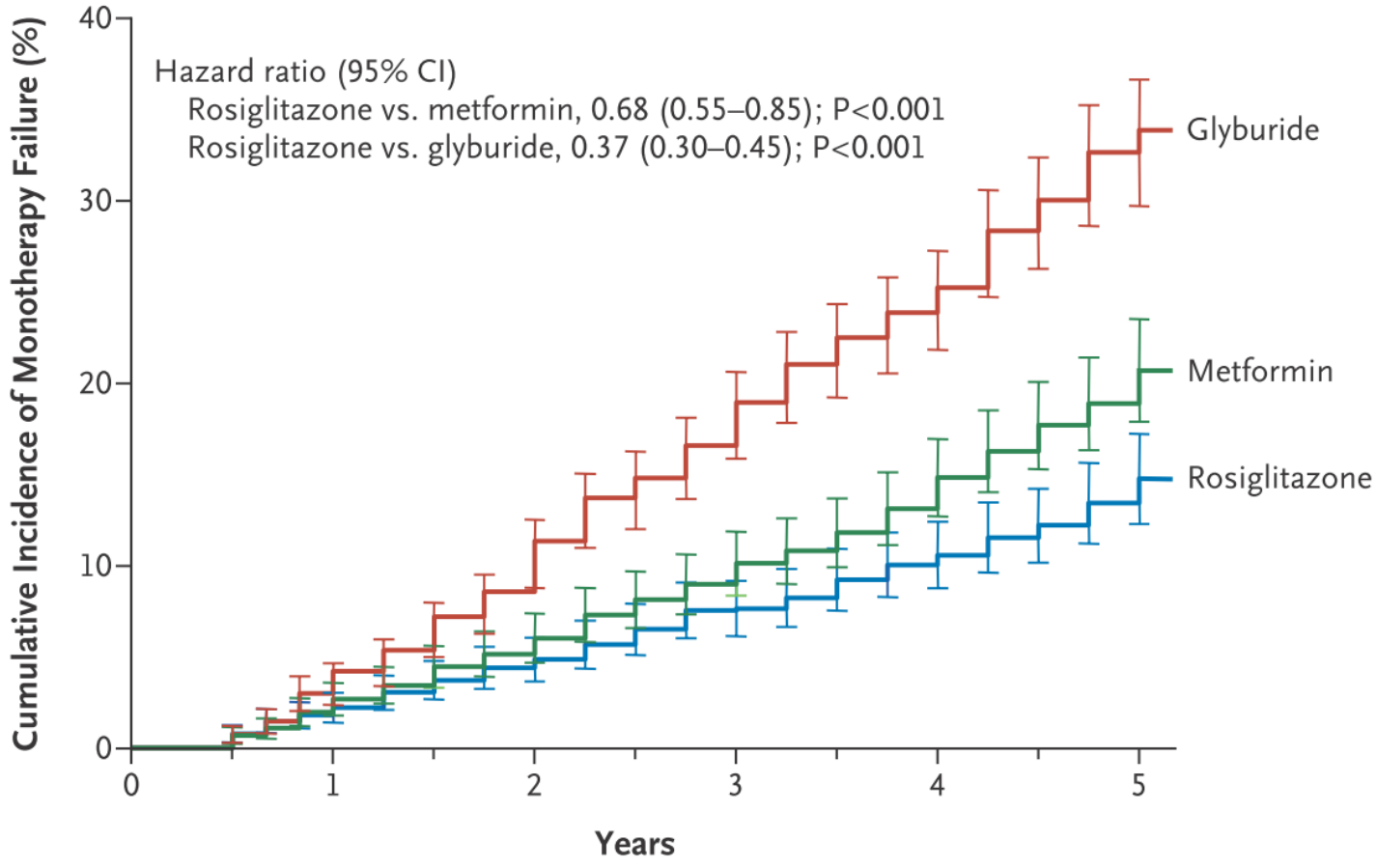
Lancet. 2014 March 22; 383(9922): 1068–1083.

The complex pathophysiology of T2DM



Ralph A. DeFronzo et al. Diabetes Care 2013 Aug; 36(Supplement 2): S127-S138.

Durability of oral glucose-lowering medications



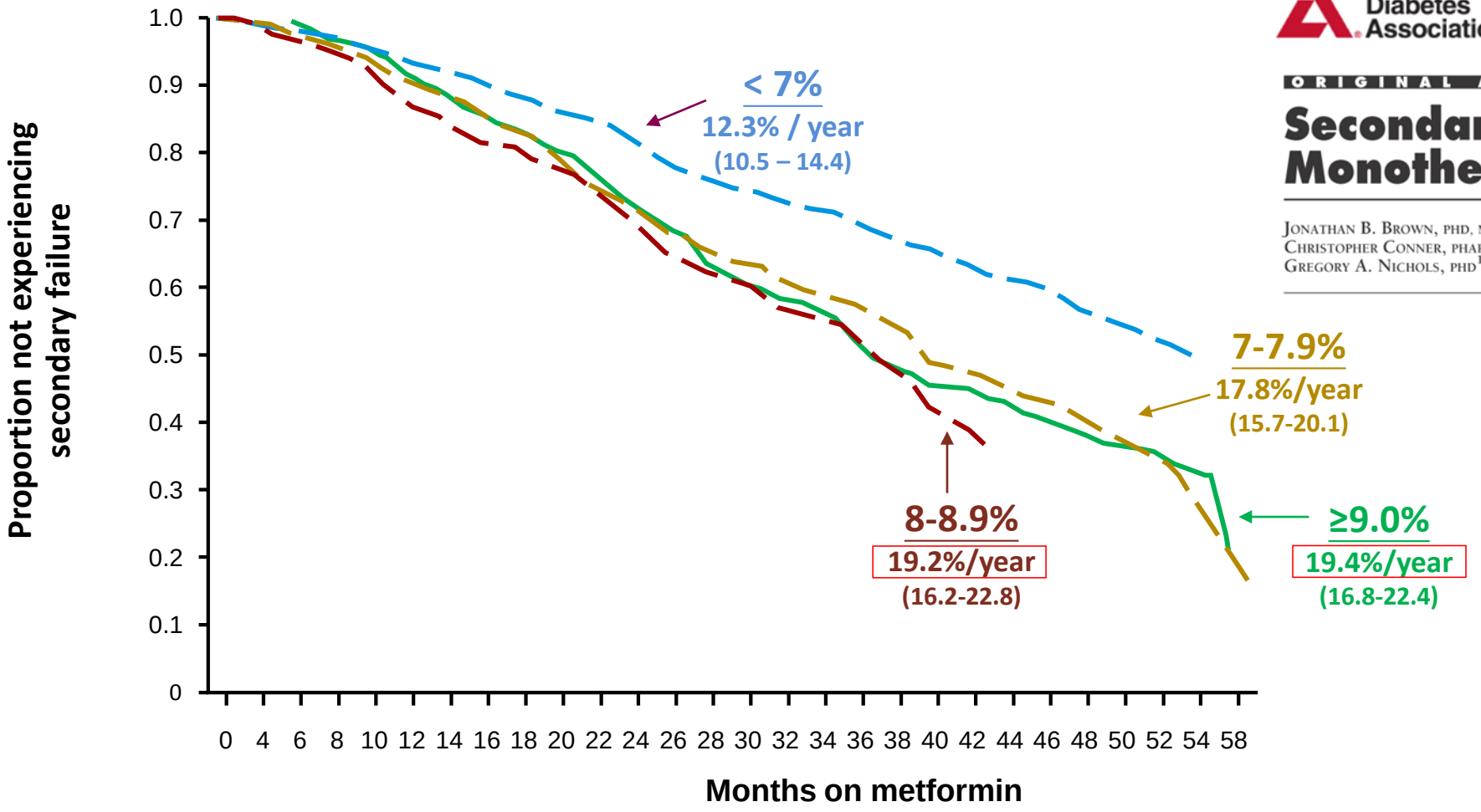
No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

ADOPT Study:
initial treatment for 4360 patients with recently diagnosed type 2 diabetes

Monotherapy failure at 5 years:
15% with rosiglitazone
21% with metformin
34% with glyburide

Primary outcome: time to monotherapy failure (defined as fasting plasma glucose >180 mg per deciliter)
Steven E. Kahn et al. N Engl J Med 2006;355:242743.

Time to failure of metformin monotherapy



American Diabetes Association. Diabetes Care

ORIGINAL ARTICLE

Secondary Failure of Metformin Monotherapy in Clinical Practice

JONATHAN B. BROWN, PHD, MPP[1]
CHRISTOPHER CONNER, PHARMD, PHD[2]
GREGORY A. NICHOLS, PHD[1]

Of the 1,799 patients studied, 42% (n = 748) experienced secondary failure; the mean failure rate was 17% per year.

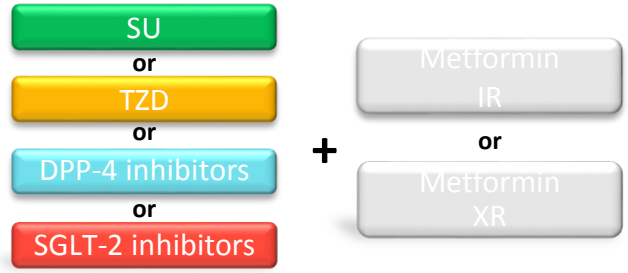
Failure of metformin monotherapy is increased when initial HbA1c is ≥ 8%

Secondary failure is defined as a subsequent A1C ≥7.5% or the addition or substitution of another anti-hyperglycemic agent.
Diabetes Care 2010 Mar; 33(3): 501-506.

Recommendation of starting dual therapy

Association	Latest version	Circumstance	Consider treatment
ADA	2018	• Entry A1c **≥ 9%** • A1c target is not achieved after 3-month monotherapy	Dual combination
AACE/ACE	2018	• Entry A1c **≥ 7.5%** • A1c target is not achieved after 3- month monotherapy	Dual Therapy
Canadian Diabetes Association	2016	• Entry A1c **> 8.5%** • A1c target is not achieved after metformin treatment	Dual combination
NICE (UK)	2017	• If A1c rises to **7.5%** after metformin treatment • Support the person to aim for an HbA1c level of 7%	Dual Therapy
中華民國糖尿病學會	2018	• 初診斷或已治療，但糖化血色素 ≥ **8.5%** 的病人	使用兩種或多種口服抗糖尿病藥物

Choices of second-line therapy



Cardiovascular profile consideration:

SGLT-2 inhibitors

vs

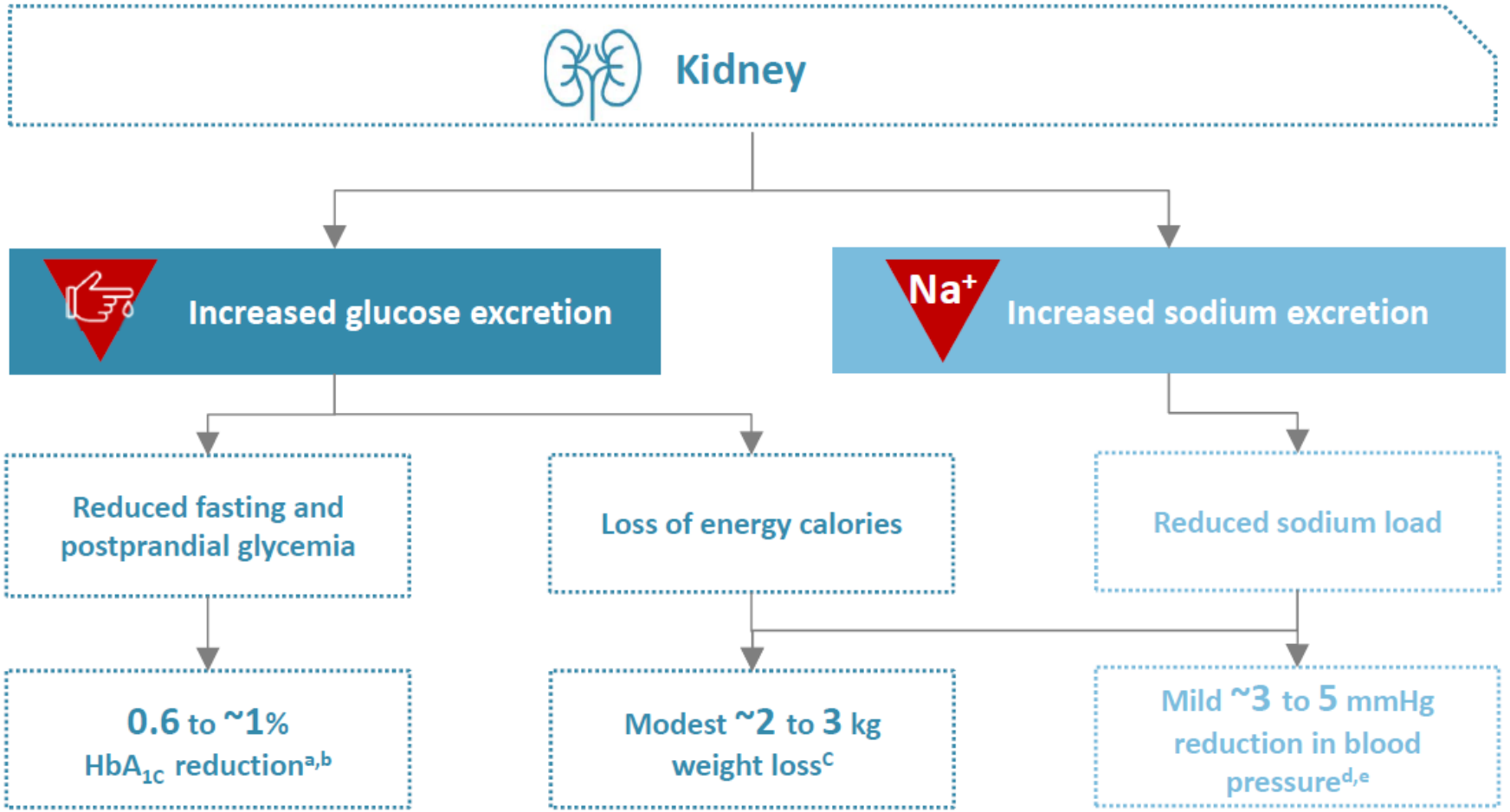
SU

TZD

DPP-4 inhibitors

?

Clinical Benefits of SGLT2 Inhibitors



a. Wilding JP, et al. Diabetes Obes Metab. 2014; 16:124-136; b. Forst T, et al. Diabetes Obes Metab. 2014; 16:467-477; c. Valentine V. Clin Diabetes. 2012; 30:151-155; d. Rosenstock J, et al. Diabetes Obes Metab. 2014; 15:1154-1160; e. Goring S, et al. Diabetes Obes Metab. 2014; 16:433-442.

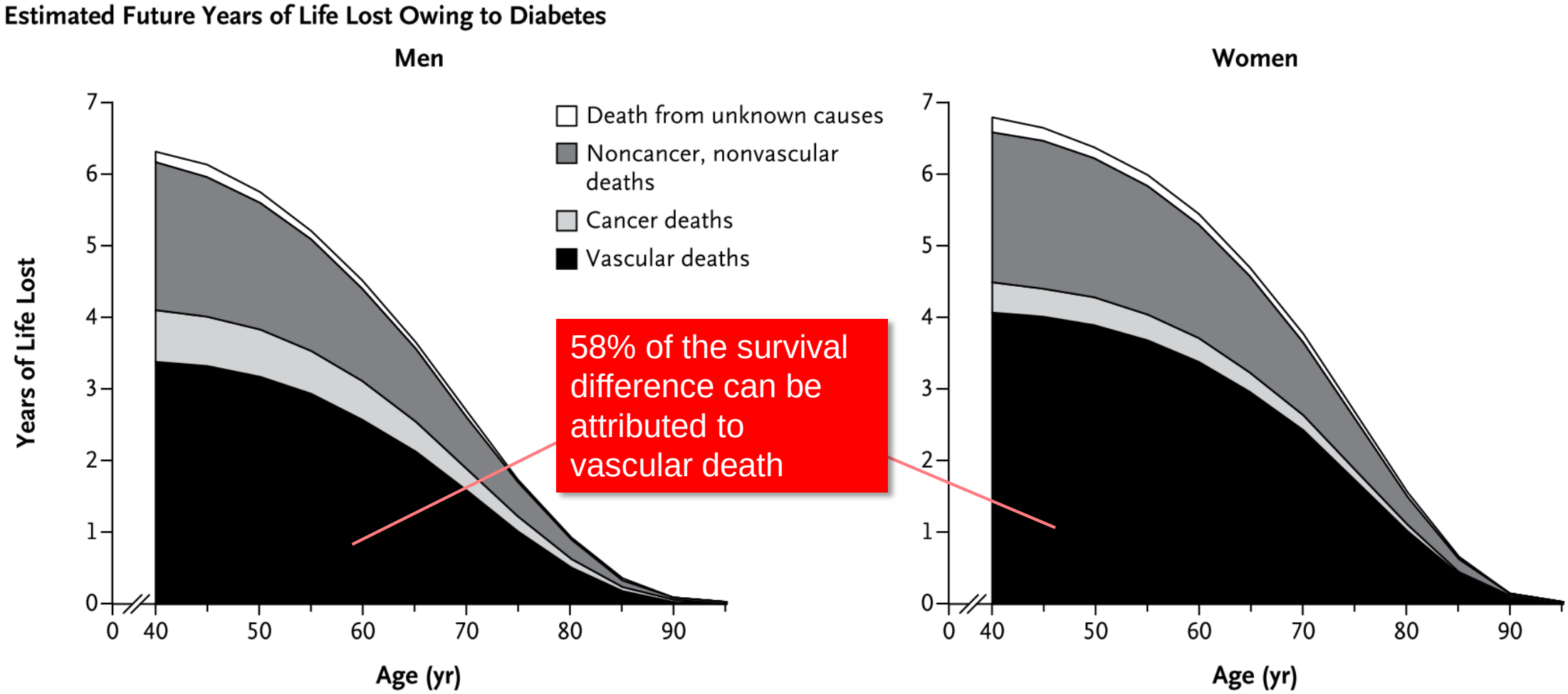
口服抗糖尿病藥的建議與考量

鈉-葡萄糖共同輸送器-2 抑制劑 (SGLT2i)

Canagliflozin、Dapagliflozin、Empagliflozin

- 較少發生低血糖
- 會增加泌尿道與生殖器感染的風險
- 使用後通常可降低體重與血壓
- 可減少糖尿病腎臟病惡化與因心臟衰竭住院的風險

Diabetes is associated with significant loss of life years

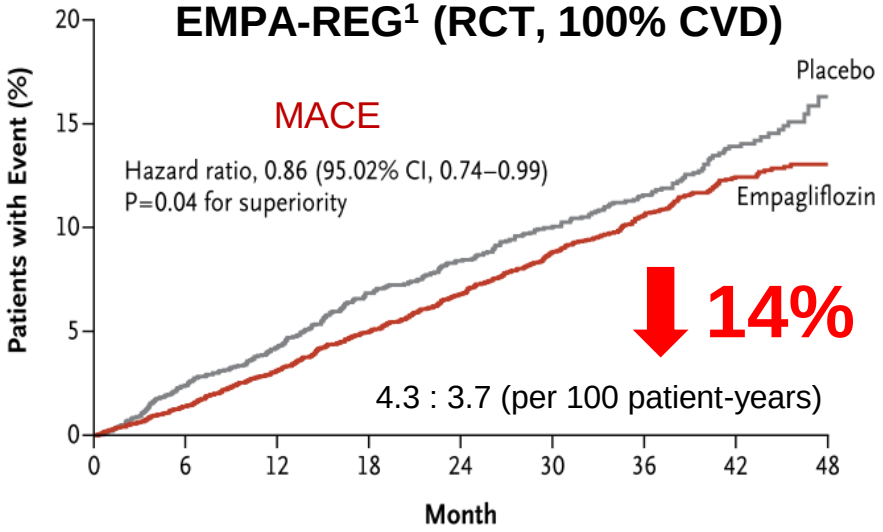


At 40, 50, and 60 years of age, men with diabetes would incur about 6.3, 5.8, and 4.5 years of life lost.
At 40, 50, and 60 years of age, women with diabetes would incur about 6.8, 6.4, and 5.4 years of life lost

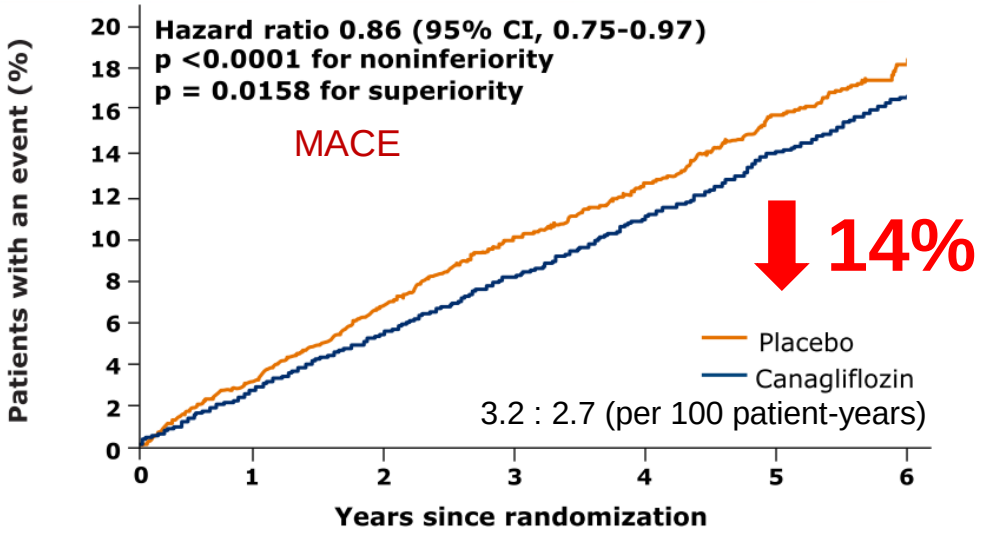
Seshasai et al. N Engl J Med 2011;364:829-41

Lower MACE incidence of SGLT2i in both RCT and RWE

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

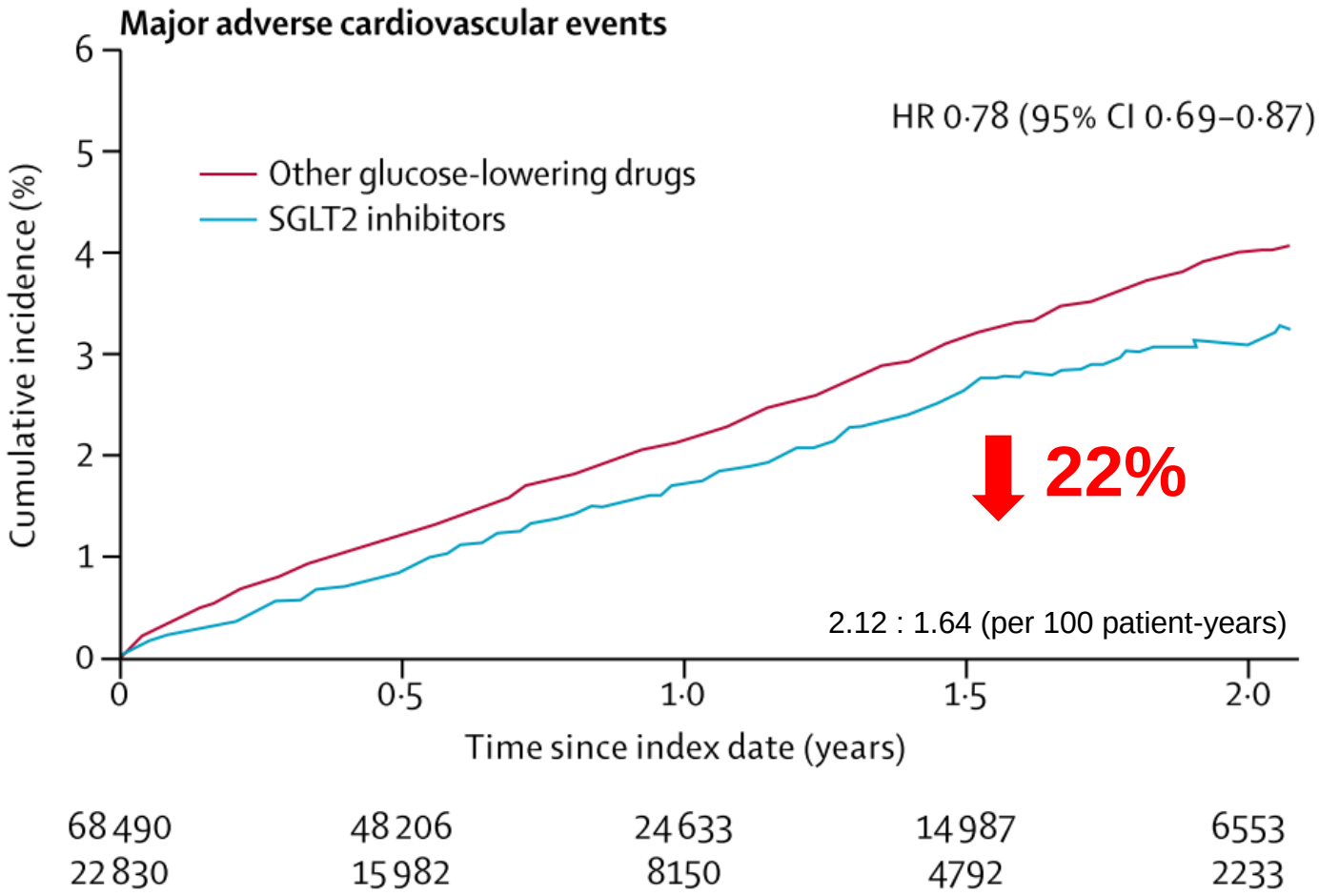


CANVAS[2] (RCT, 66% CVD)



CVD-REAL Nordic[3]

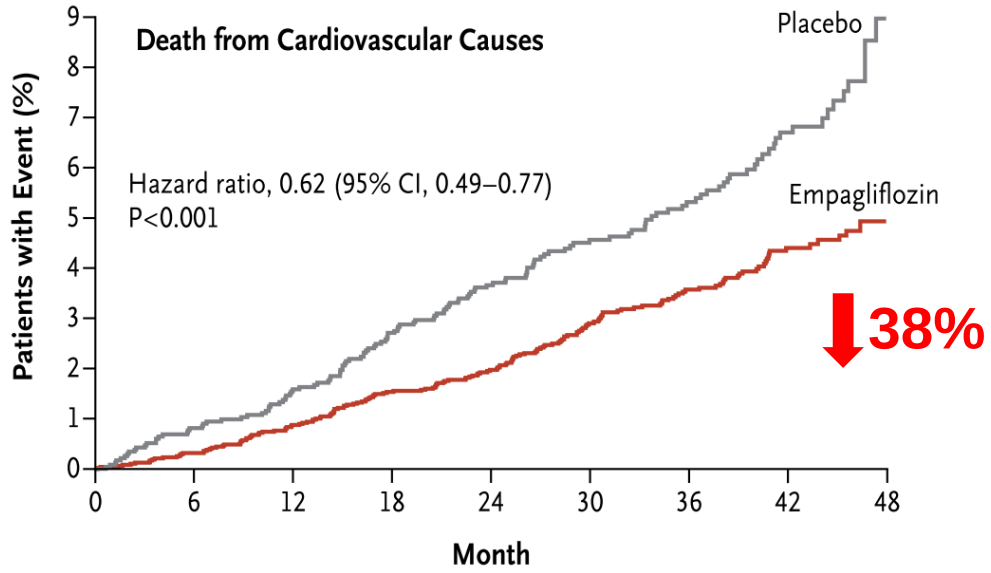
(real-world evidence, 24% CVD)



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 both RCT and RWE

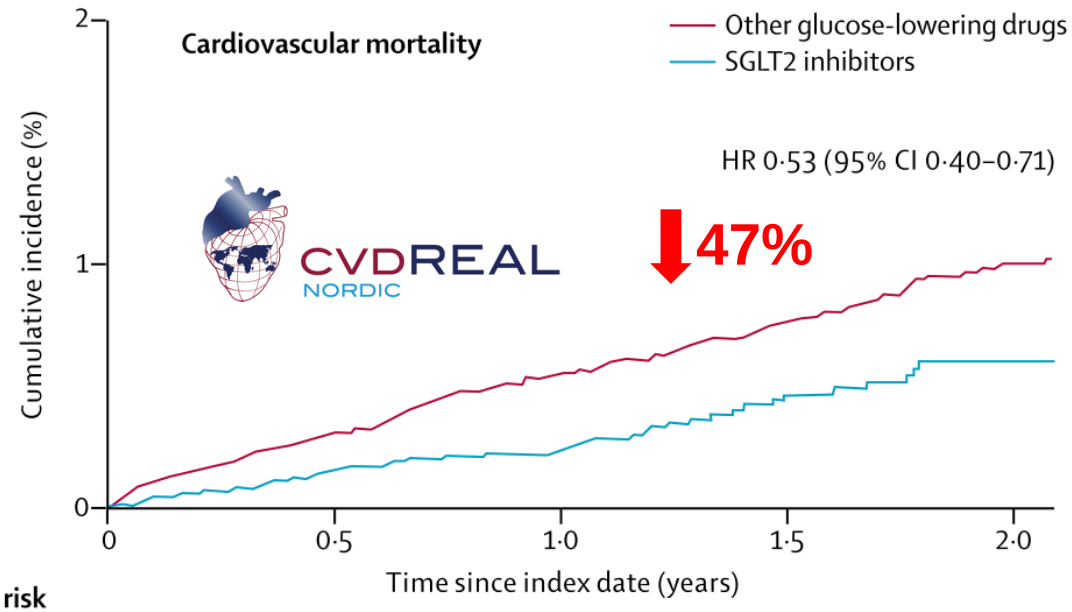
EMPA-REG[1] (100% CVD)



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 vs 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

THE LANCET
Diabetes & Endocrinology

0.53 vs 0.27 events per 100 patient-years

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

Summary of CV Outcome Trial and Real-world Evidence of SGLT2i

	EMPA-REG[1]	CANVAS program[2]	DECLARE[3]	CVD-Real[4]	CVD-Real Nordic[5]
Medication	Empa	Cana	Dapa	41.8% Dapa 52.7% Cana 5.5% Empa	94% Dapa 1.3% Cana 4.7% Empa
Study type	RCT	RCT	RCT	RWE	RWE
Patients	7,020	10,143	17,160	309,056	91,320
History of CVD, %	100	66	40.6	13	25
Follow-up, year	3.1	3.9 (6.0/2.5)	4.5	2012-2016	2012-2015
Primary MACE Outcome, %	**-14**	**-14**	-	-	**-22**
CV Death, %	-38	-13*	-	-	-47
MI, %	-13*	-15*	-	-	-13*
Stroke, %	24*	-10*			-14*
All-Cause Mortality, %	-31	-13 (no significant)	-	-51 CVD: -53 Non-CVD: -46	-49
Hospitalization for HF, %	**-35**	**-33**		**-39** **CVD: -31** **Non-CVD: -55**	**-30**

*No significant

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. Mikhail Kosiborod et al. Circulation July 11, 2017, Volume 136, Issue 2. doi: https://doi.org/10.1161/CIRCULATIONAHA.117.029190; 5. Kåre I Birkeland et al. The 77th Scientific Sessions of the American Diabetes Association, San Diego, California, June 9-13, 2017; 1205-P

Lower Risk of Cardiovascular Events and Death Associated with Initiation of SGLT-2 Inhibitors versus Other Glucose Lowering Drugs - Real World Data Across Three Major World Regions with More Than 400,000 Patients: The CVD-REAL 2 Study

Mikhail Kosiborod[1], Carolyn Su Ping Lam [2], Shun Kohsaka[3], Dae Jung Kim[4], Avraham Karasik[5], Jonathan Shaw[6], Navdeep Tangri[7], Su-Yen Goh[8], Marcus Thuresson[9], Hungta Chen[10], Filip Surmont[11], Niklas Hammar[12,13], Peter Fenici[14] on behalf of the CVD-REAL Investigators and Study Group. Presented at the 67th Scientific Sessions of the American College of Cardiology meeting; March 10-12, 2018; Orlando, FL.

[1]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, USA; [2]National Heart Centre, Singapore and SingHealth Duke-NUS, Singapore; [3]Keio University School of Medicine, Tokyo, Japan; [4]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Republic of Korea; [5]Tel Aviv University, Ramat Aviv, and Maccabi Healthcare Israel; [6]Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia; [7]Department of Medicine, University of Manitoba, Winnipeg MB, Canada; [8]Singapore General Hospital, Singapore; [9]Statisticon AB, Uppsala, Sweden; [10]AstraZeneca, Gaithersburg, MD, USA; [11]AstraZeneca, Luton, UK; [12]Karolinska Institutet, Stockholm, Sweden; [13]AstraZeneca, Gothenburg, Sweden; [14]AstraZeneca, Cambridge, UK

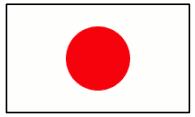
Kosiborod M, Lam CSP, Kohsaka S, et al. Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study.
J Am Coll Cardiol (in press). DOI: 10.1016/j.jacc.2018.03.009

Countries and Data Sources

Australia – National Diabetes Services Scheme (NDSS)*

Canada – Manitoba Population Health Research Data Repository

Israel – The Maccabi Health Management Organization



Japan – Medical Data Vision

Singapore – SingHealth Diabetes Registry

South Korea – National Health Insurance Service (NHIS)

87% Asian

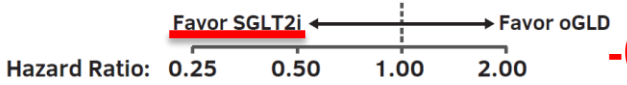
Kosiborod M, Lam CSP, Kohsaka S, et al. Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study. J Am Coll Cardiol (in press). DOI: 10.1016/j.jacc.2018.03.009

*Included in the ACD analysis only

Observations from CVD-REAL 2 (real-world evidence, 87% Asian, 26.6% CVD)

All-Cause Death

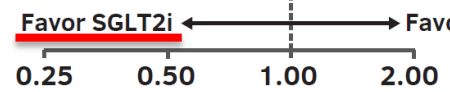
Database	N	# of events	HR (95% CI)
Korea	336,644	3445	0.72 (0.67, 0.77)
Japan	67,780	557	0.56 (0.47, 0.67)
Singapore	2726	36	0.75 (0.38, 1.47)
Israel	19,472	199	0.41 (0.30, 0.55)
Canada	16,064	261	0.51 (0.41, 0.65)
Australia	27,442	718	0.32 (0.27, 0.38)
Total	470,128	5216	0.51 (0.37, 0.70)



-0.49

Hospitalization for Heart Failure

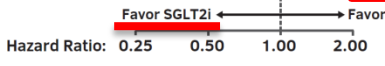
Database	N	# of events	HR (95% CI)
Korea	336,644	5149	0.87 (0.82, 0.92)
Japan	67,780	565	0.75 (0.63, 0.89)
Singapore	2726	67	0.62 (0.38, 1.02)
Israel	19,472	128	0.53 (0.37, 0.75)
Canada	16,064	88	0.36 (0.24, 0.56)
Total	442,686	5997	0.64 (0.50, 0.82)



-0.36

Composite of All-Cause Death or HHF

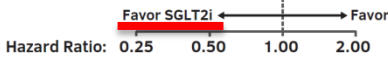
Database	N	# of events	HR (95% CI)
Korea	336,644	7990	0.81 (0.78, 0.85)
Japan	67,780	1061	0.65 (0.57, 0.74)
Singapore	2726	93	0.62 (0.41, 0.95)
Israel	19,472	313	0.45 (0.36, 0.57)
Canada	16,064	331	0.48 (0.39, 0.59)
Total	442,686	9788	0.60 (0.47, 0.76)



-0.40

Myocardial Infarction

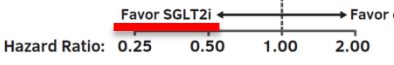
Database	N	# of events	HR (95% CI)
Korea	336,644	1901	0.81 (0.74, 0.89)
Japan	67,780	91	0.75 (0.50, 1.14)
Singapore	2726	70	0.79 (0.49, 1.27)
Israel	19,472	59	1.09 (0.66, 1.80)
Canada	16,064	128	0.75 (0.56, 1.01)
Total	442,686	2249	0.81 (0.74, 0.88)



-0.19

Stroke

Database	N	# of events	HR (95% CI)
Korea	336,644	5972	0.82 (0.78, 0.86)
Japan	67,780	272	0.66 (0.52, 0.84)
Singapore	2726	34	0.34 (0.15, 0.75)
Israel	19,472	116	0.66 (0.47, 0.94)
Canada	16,064	45	0.55 (0.32, 0.94)
Total	442,686	6439	0.68 (0.55, 0.84)



-0.32

Are all SGLT2 inhibitors the same?

Label information of marketed (summer 2017) SGLT2 inhibitors, and emerging preclinical and clinical data

Two operational definitions of "sameness"

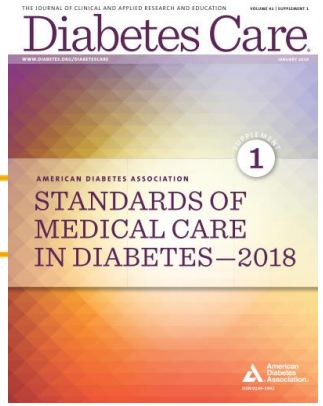
Regulatory (FDA) view: Label

- Indications
- Safety and warnings
- Data from registrational trials within each drug (including sponsored RCTs of head to head comparisons)
- Pharmacokinetic and pharmacodynamic analyses of sponsored registrational trials

Clinical & basic science view

- Outcomes
- Adverse events
- Indirect comparisons by payors
- Indication for specific patients (e.g. glucose lowering v.s. hard outcomes)
- Preclinical and clinical data not reflected in the label

2018 ADA guideline



A1C is greater than or equal to 9%, **consider Dual Therapy.**

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

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Dual Therapy — Lifestyle Management + Metformin + Additional Agent

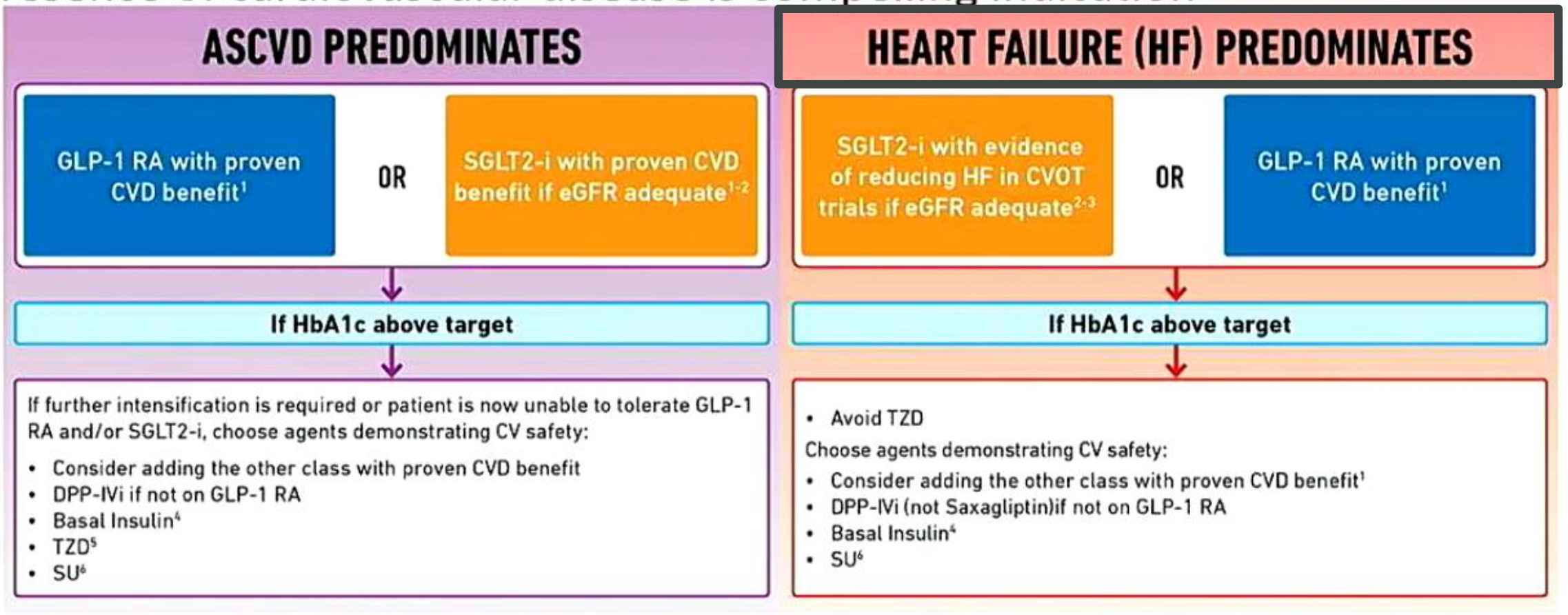
ASCVD?

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)

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

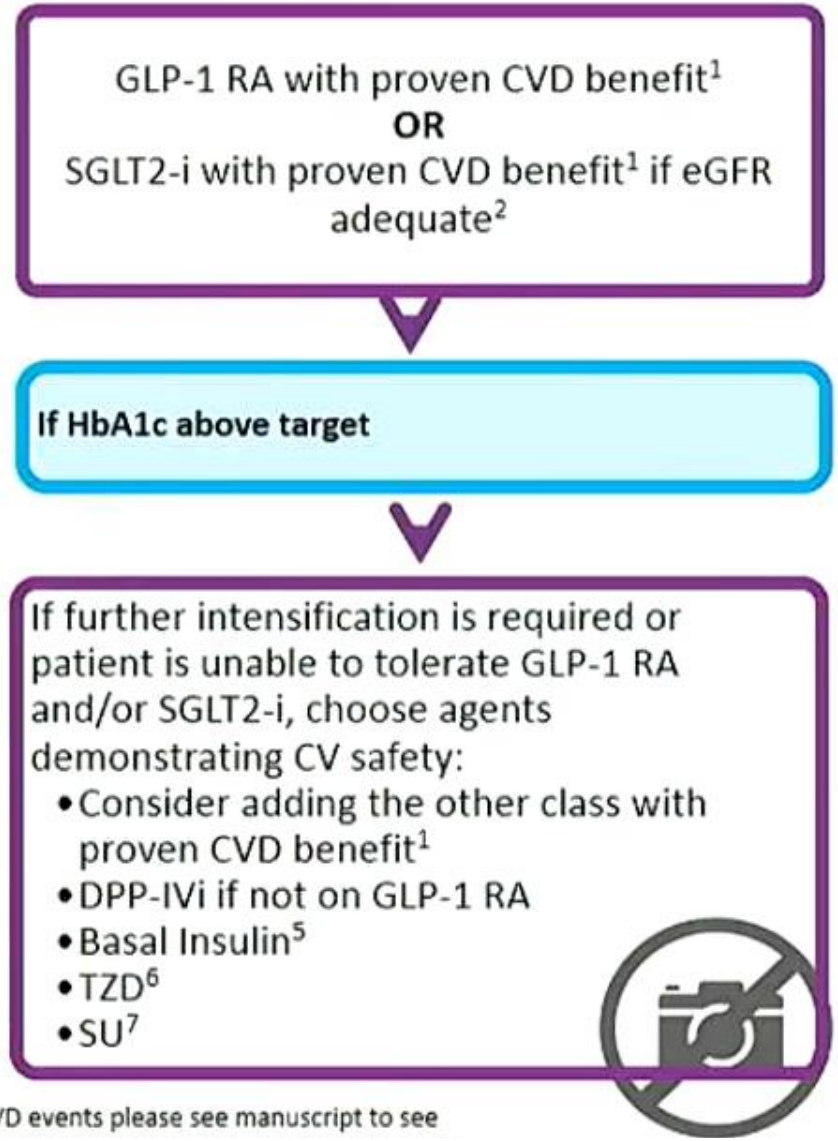
American Diabetes Association.

EASD European Association for the Study of Diabetes

Caveats and Questions

No evidence of CVD benefit in those at lower cardiovascular risk

The combination of SGLT2-i and GLP-1 RA has not been tested in cardiovascular outcome trials



1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see manuscript to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i clas level of eGFR for initiation and continued use, 5. Degludec or U100 Glargine have dem CVD effects, 7. Choose later generation SU with lower risk of risk of 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/2018EASDconsensu

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Available online at www.sciencedirect.com

ScienceDirect

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

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

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 TSOC and DAROC consensus

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 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		

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			

https://doi.org/10.1016/j.jcma.2018.01.001

鈉-葡萄糖共同輸送器-2 抑制劑 (SGLT-2 inhibitors)

目前美國食品藥物管理局核准之 SGLT-2 inhibitors 藥物有三項

- Canagliflozin
- Dapagliflozin
- Empagliflozin

Canagliflozin：於 2017 年 3 月取得台灣衛生福利部的藥品許可證

Dapagliflozin、Empagliflozin：已於台灣臨床使用於第 2 型糖尿病的治療

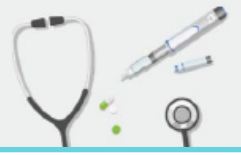
使用方法：
可單一或**併用**
其他**口服抗糖尿病藥物**或**胰島素**

優點：
- 較少發生低血糖
- 降低體重
- 降低血壓

療效：
HbA_{1C} 約可降低 **0.7%**

主要的副作用：
增加泌尿道及
生殖器感染的風險

Pharmacological Properties of SGLT2 Inhibitors



Each drug in the class as different from the others

	Empagliflozin	Dapagliflozin	Canagliflozin
Therapeutic dose (mg/day) **Starting dose**	10-25 10	5-10 5	100-300 100
Administration	QD With or without food	QD With or without food	QD Before the first meal of the day
Peak plasma concentration (hours post-dose)	1.5	Within 2	1–2
Absorption (mean oral bioavailability)	≥ 60%	~ 78%	~ 65%
Metabolism	Primarily glucuronidation, No active metabolite		
Elimination (half-life, hours)	Hepatic:renal 44:56 [12.4]	Hepatic:renal 22:78 [12.9]	Hepatic:renal 67:33 [13.1]*
Selectivity over SGLT1	1:5000	> 1:1400	> 1:160[1]
Glucose excretion with higher dose (g/day)	78 (25 mg dose)	~ 70 (5 or 10mg dose)	87 (100mg dose)

SGLT, sodium glucose cotransporter; **QD**, once daily.;*For the 300 mg dose.

http://www.ema.europa.eu/.

1. Sha S, et al. *Diab Obes Metab*. 2015; 17:188–197.

SGLT-2 inhibitors dosage adjustments based on renal function

Each drug in the class as different from the others

TABLE 2. SGLT2 INHIBITOR DOSAGE ADJUSTMENTS BASED ON RENAL FUNCTION

eGFR mL/min/1.73 m²	Canagliflozin	Dapagliflozin	Empagliflozin
≥60	No dosage adjustment 100-300 mg/day	No dosage adjustment 5-10 mg/day	No dosage adjustment 10-25 mg/day
45-60	100 mg daily	Not recommended eGFR <60	No dosage adjustment 10-25 mg/day
30-45	Not recommended eGFR <45	N/A	Not recommended eGFR <45
<30	Contraindicated	Contraindicated	Contraindicated

eGFR - estimated glomerular filtration rate; SGLT2 - sodium-glucose cotransporter-2.

Which SGLT-2 inhibitor to use ?

Efficacy comparison* as monotherapy compared to placebo in 24 weeks trial

	Empagliflozin (10mg,25mg)	Dapagliflozin (5mg,10mg)	Canagliflozin (100mg,300mg)
HbA1C reduction (%)	0.7-0.9	0.5-0.7	0.91-1.16
FPG reduction (mg/dL)	31-36	19.9-24.7	36-43
Weight Loss (in Kg)	2.5-2.8	2.8-3.2	2.2-3.3
SBP reduction (mmHg)	2.6-3.4	2.3-3.6	3.7-5.4

Each drug in the class as different from the others

*Note: comparison in individual trials and not in head to head clinical trials

鈉-葡萄糖共同輸送器-2 抑制劑 (SGLT-2 inhibitors)

Each drug in the class as different from the others

在 canagliflozin 的大型研究中，觀察到以 canagliflozin 治療的患者		在 empagliflozin 的大型研究中
較高的骨折風險 Hazard Ratio: **1.26** 95% CI : 1.04-1.52 *p*=0.02	較高的下肢截肢風險 Hazard Ratio: **1.97** 95% CI : 1.41-2.75 *p*<0.001	並未觀察到此類不良反應事件風險上升的情況

鈉-葡萄糖共同輸送器-2 抑制劑是否會增加骨折與下肢截肢的風險，仍待更進一步的研究

A meta-analysis of trials evaluating combined safety outcomes of canagliflozin, dapagliflozin and empagliflozin did not support a harmful effect of SGLT2 inhibitors on bone.
The fracture event rate was 1.59% in the SGLT2 inhibitor group and 1.56% in the control group. Moreover, the incidence of fracture events was similar among the three SGLT2 inhibitors.

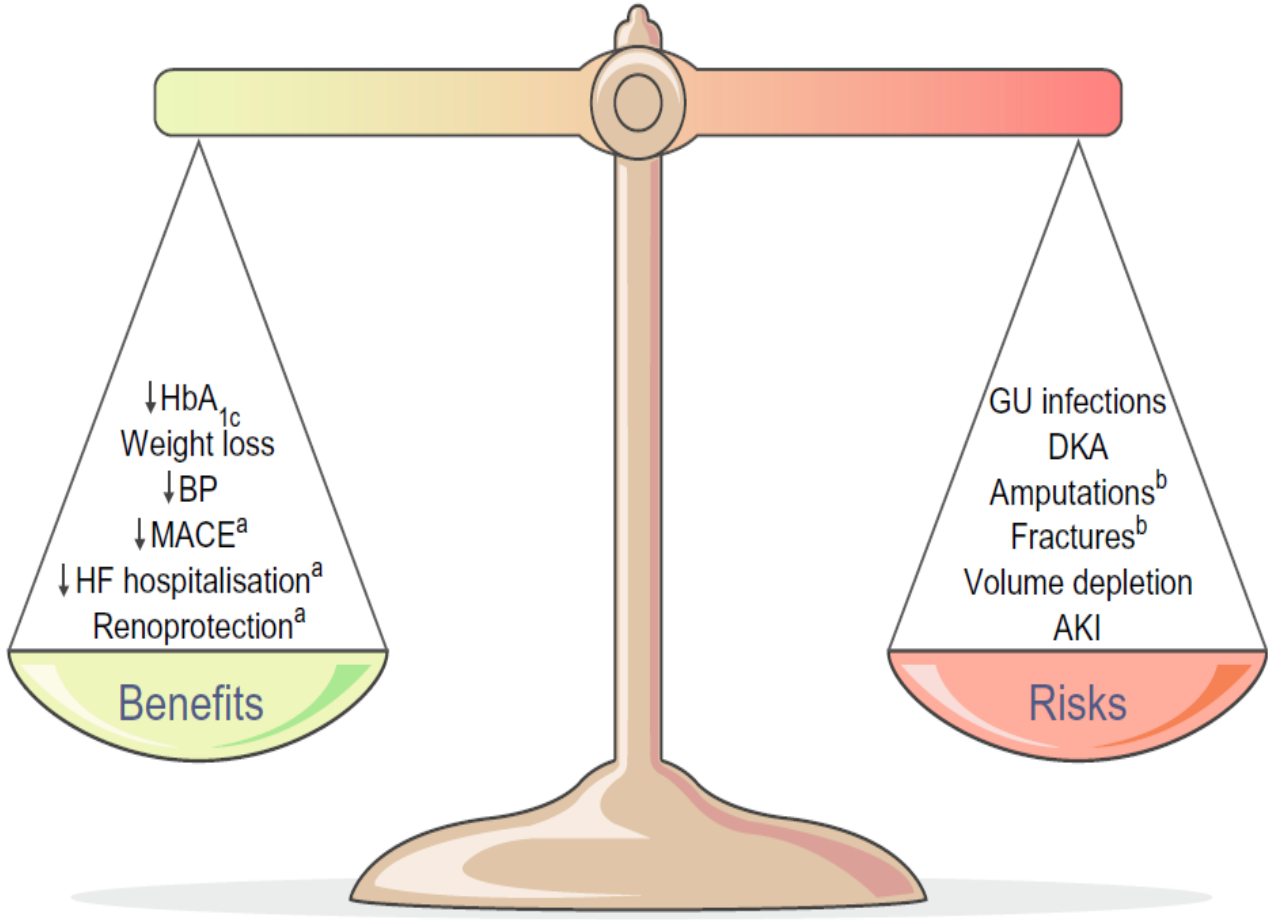
Diabetes Obes Metab 18:1199–1206

Weighting risk and benefits

•There are no published head-to-head trials comparing empagliflozin, dapagliflozin with canagliflozin, so we can't directly compare the three agents.

•Amputation/fracture → CANA ?
•AKI → DAPA/CANA ?
⇨ An analysis of SGLT2 users and nonusers: no differences

•Trend in stroke → EMPA-REG ?
⇨ trend for cardiovascular mortality was similar in individuals with and without a history of stroke at baseline



When a second drug is going to be added…

Free combination

vs

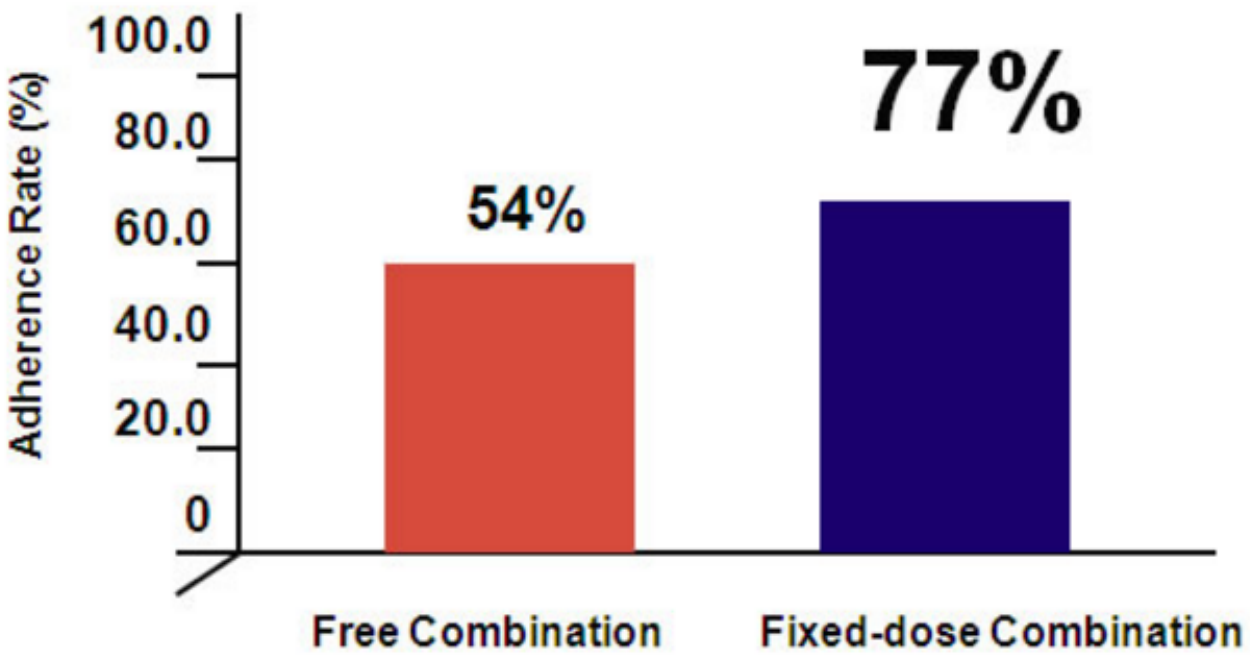
Fixed-dose combination

?

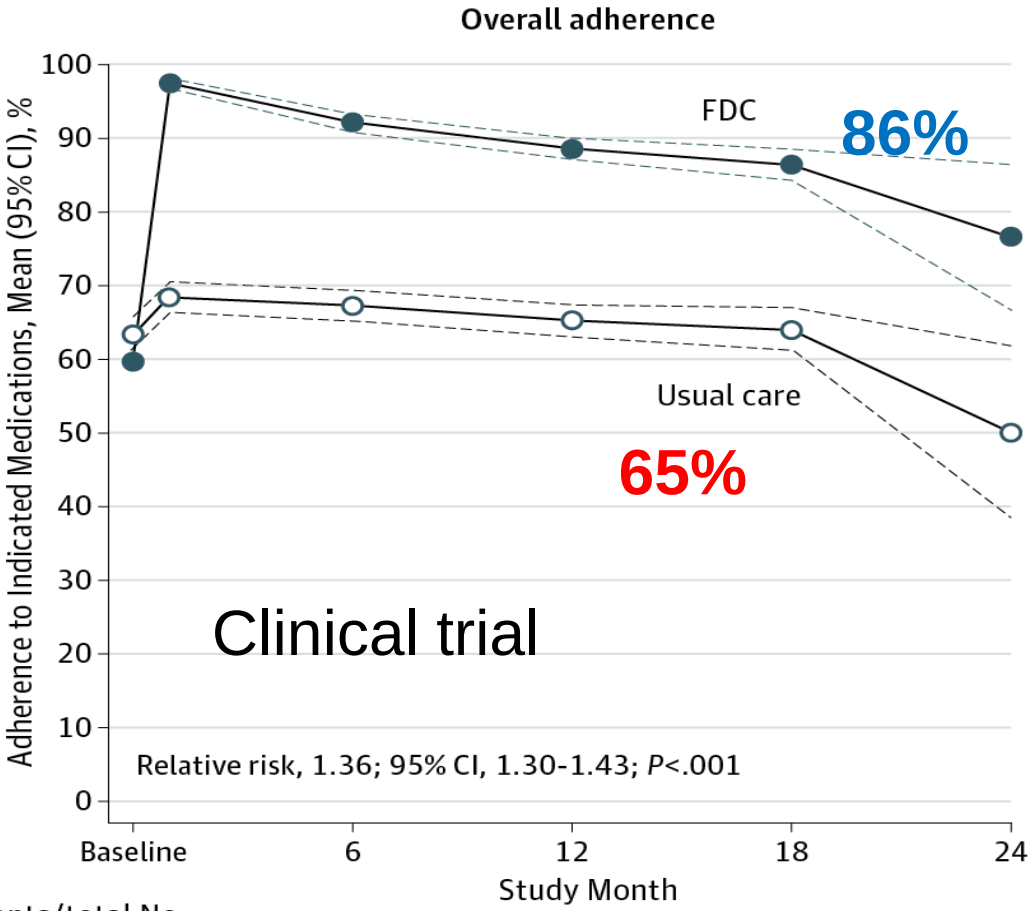
Jardiance-Duo (12.5/850 mg)
Xig-Duo (10/1000 mg)

Fixed-dose combinations (FDC) improve adherence

Real-world evidence



Retrospective analysis, 6502 patients, glyburide/metformin, 180 days[1]
The adherence rate was defined as the sum of the days' supply of oral antidiabetic medication obtained by the patient during the follow-up period divided by the total number of days in the designated follow-up period



No. of events/total No.					
FDC	598/1002	899/977	827/935	452/524	26/34
Usual care	635/1002	657/978	602/925	334/522	18/36

Randomized, open-label trial, 2004 patients with established CVD or at risk of CVD, aspirin/simvastatin/lisinopril/ hydrochlorothiazide, 15 months[2] *P<0.001

1. Melikian C et al. Clin Ther. 2002 Mar;24(3):460-7
2. Simon Thom et al. JAMA. 2013;310(9):918-929. doi:10.1001

After reducing number of pills,

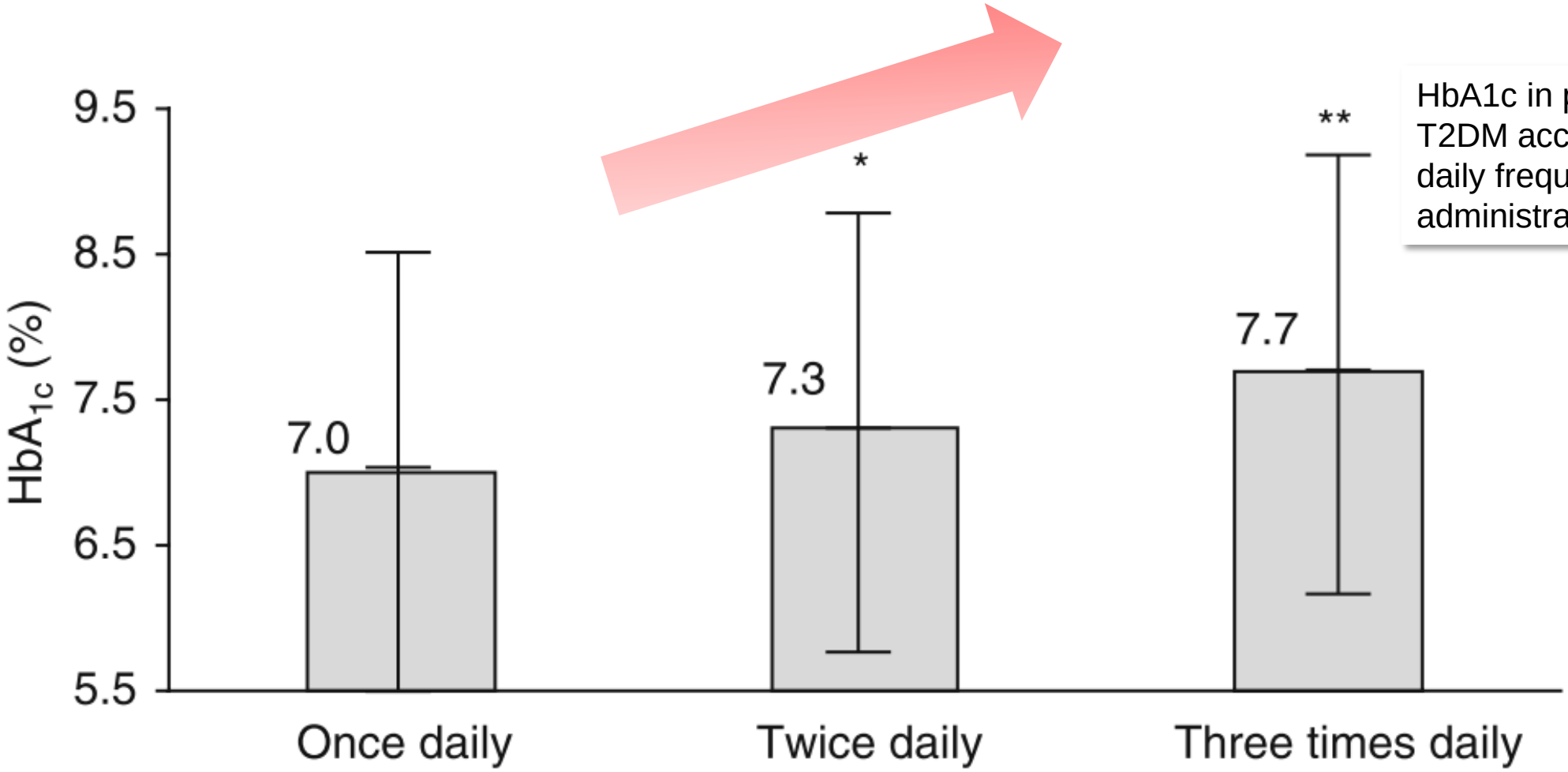
Once Daily

vs

≥2 time Daily

?

Frequency of daily doses of OAD and HbA1c



HbA1c in patients with T2DM according to the daily frequency of administration of OAD

* p < 0.05, ** p < 0.01 vs once-daily administration

Prospective assessment of self-reported compliance with a standardized questionnaire in an cohort of 11,896 T2DM patients

OAD: oral antidiabetic drug

1. Guillausseau PJ et al. Treat Endocrinol. 2005;4(3):167-75. 2. Diabetes Metab. 2003 Feb;29(1):79-81.

TW-4292_XIG_28/03/2018

Which class? What kind of metformin?

SU

or

TZD

or

DPP-4 inhibitors

or

SGLT-2 inhibitors

+

Metformin IR

or

Metformin XR

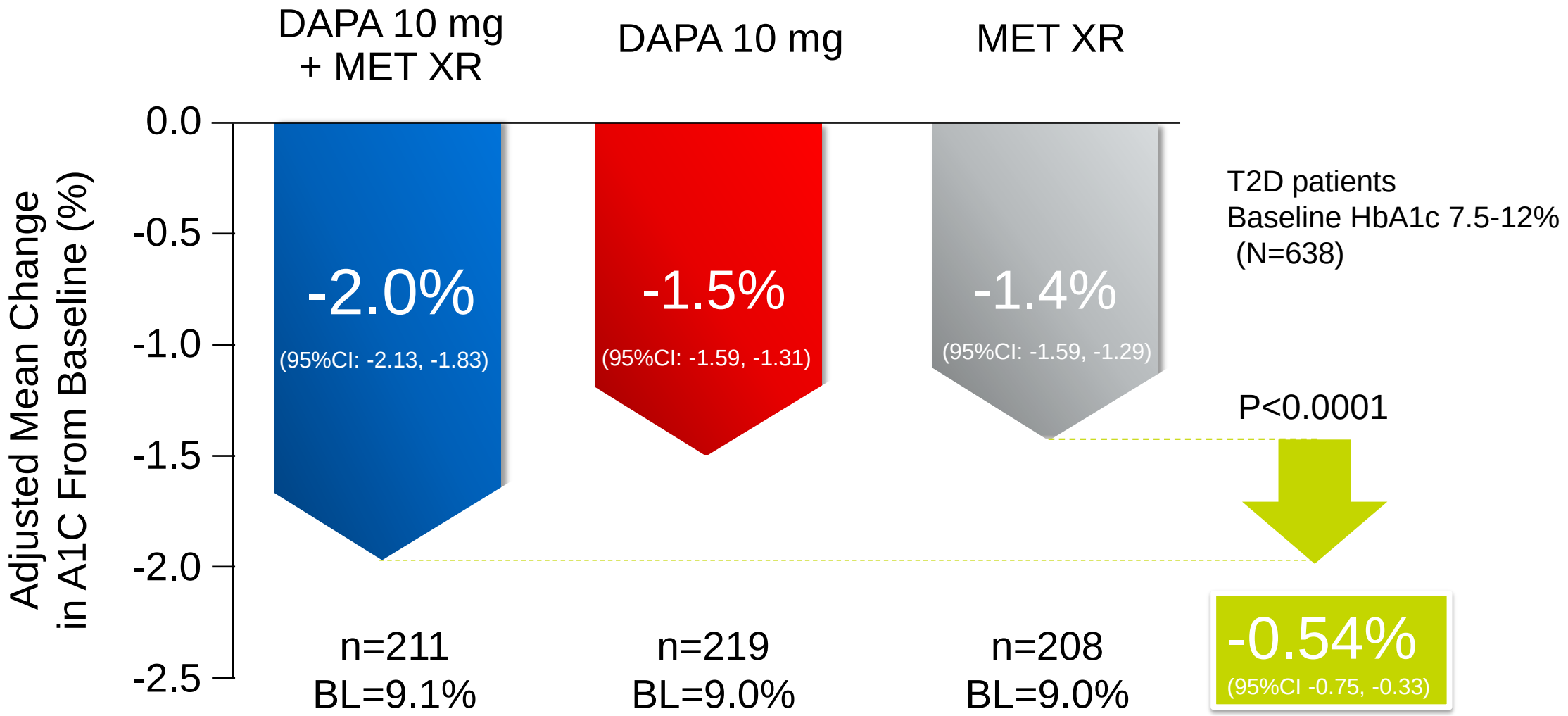
=

xigduo® XR
Extended-Release Tablets
(dapagliflozin/metformin HCl)

- ✓ **Once-daily dosage**
- ✓ **Less GI side effects**

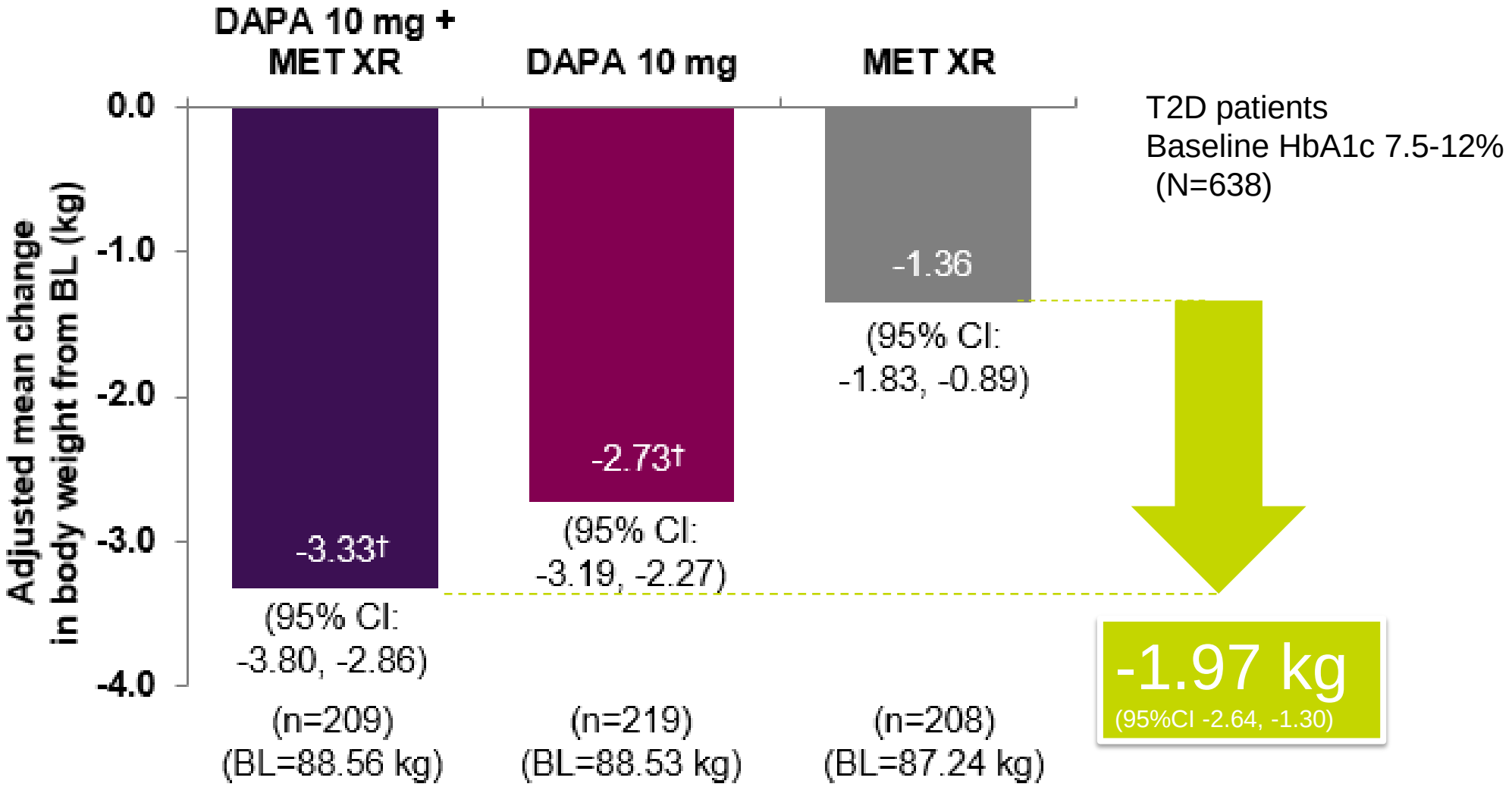
- ✓ **Superior glycemic effect and durability**
- ✓ **Additional benefits that other classes do not provide**

HbA1c reduction of 2% at week 24



Mean metformin XR doses for combination and metformin groups were 1928.6 mg and 1949.7 mg
DAPA: Dapagliflozin, MET XR: metformin XR, XR: extended release; BL: mean baseline
Henry RR, et al. Int J Clin Pract 2012;66(5):446–456.

Weight loss of 3.3 kg at week 24

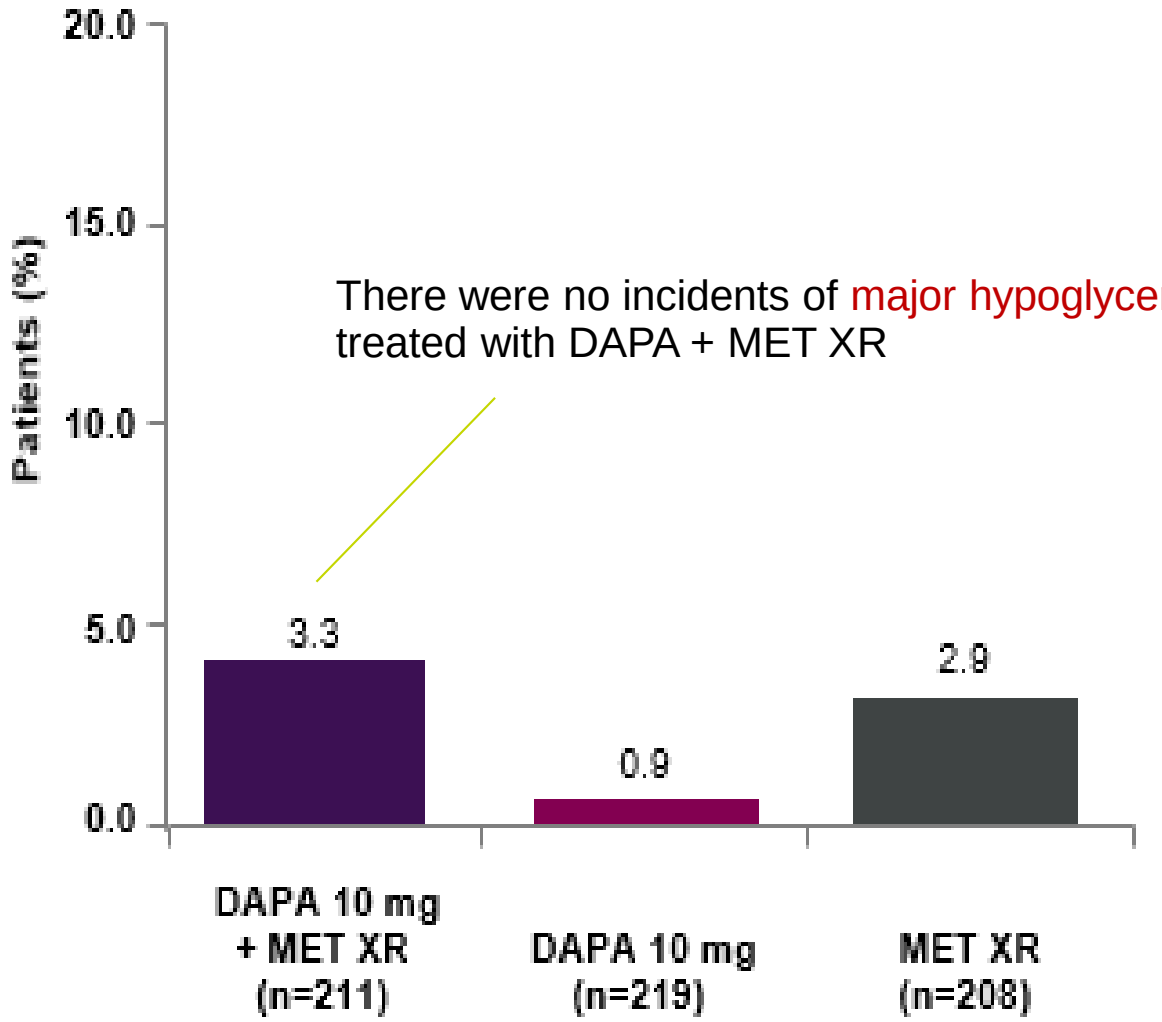


Dapagliflozin is not indicated for the management of weight loss.

Mean metformin XR doses for combination and metformin groups were 1928.6 mg and 1949.7 mg

Henry RR, et al. Int J Clin Pract 2012;66(5):446–456.

Hypoglycemia incidence at week 24



There were no incidents of major hypoglycemia in patients treated with DAPA + MET XR

T2D patients
Baseline HbA1c 7.5-12%
(N=638)

Mean metformin XR doses for combination and metformin groups were 1928.6 mg and 1949.7 mg

Henry RR, et al. Int J Clin Pract 2012;66(5):446–456.

Take home message

- Diabetes: complex management
- Monotherapy fails…combination therapy can be started with A1c of 8.5%
- SGLT-2i (RCT and RWD) CV protection (MACE/heart failure) , considered as priority use in those with high risk for CAD (low risk: DECLARE)
- Which SGLT-2i? No direct hear-to head study comparing efficacy or safety
- The viewpoint of physician using them to treat diabetes (cardiorenal events) in a safe manner.
- SLGT-2 inhibitors are appropriate for patients who are at risk of hypoglycemia, overweight, or with CVD.

- Wait for more data: CKD study, heart failure study, more safety data (fractures, amputations…)

Chung Shan Medical University

Affiliated Hospital