糖尿病藥物治療最新指引
Target organ driven or glycemic driven- Where are we now?

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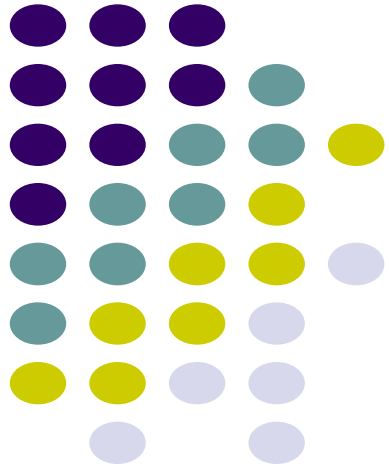
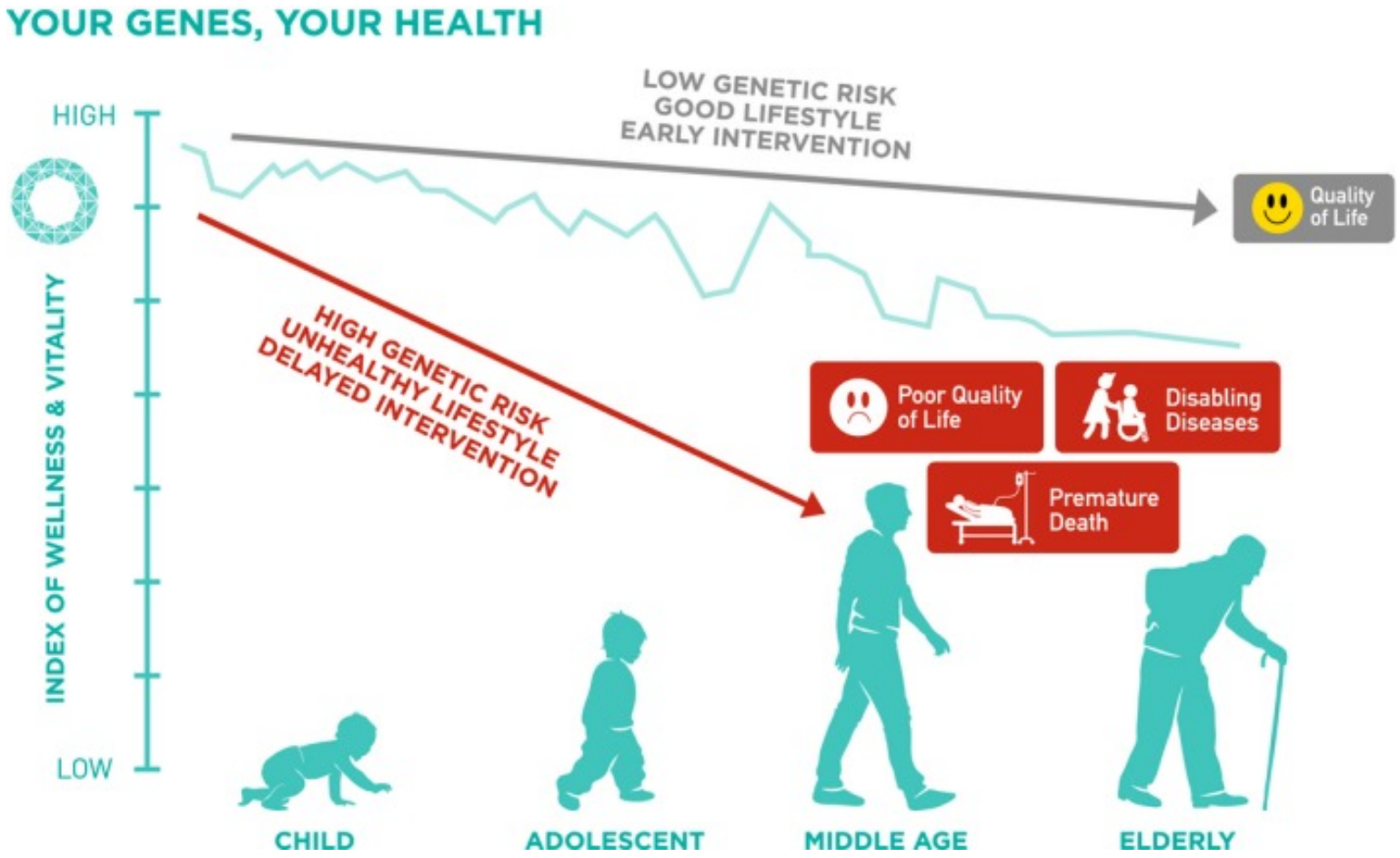
Dec,5. 2021

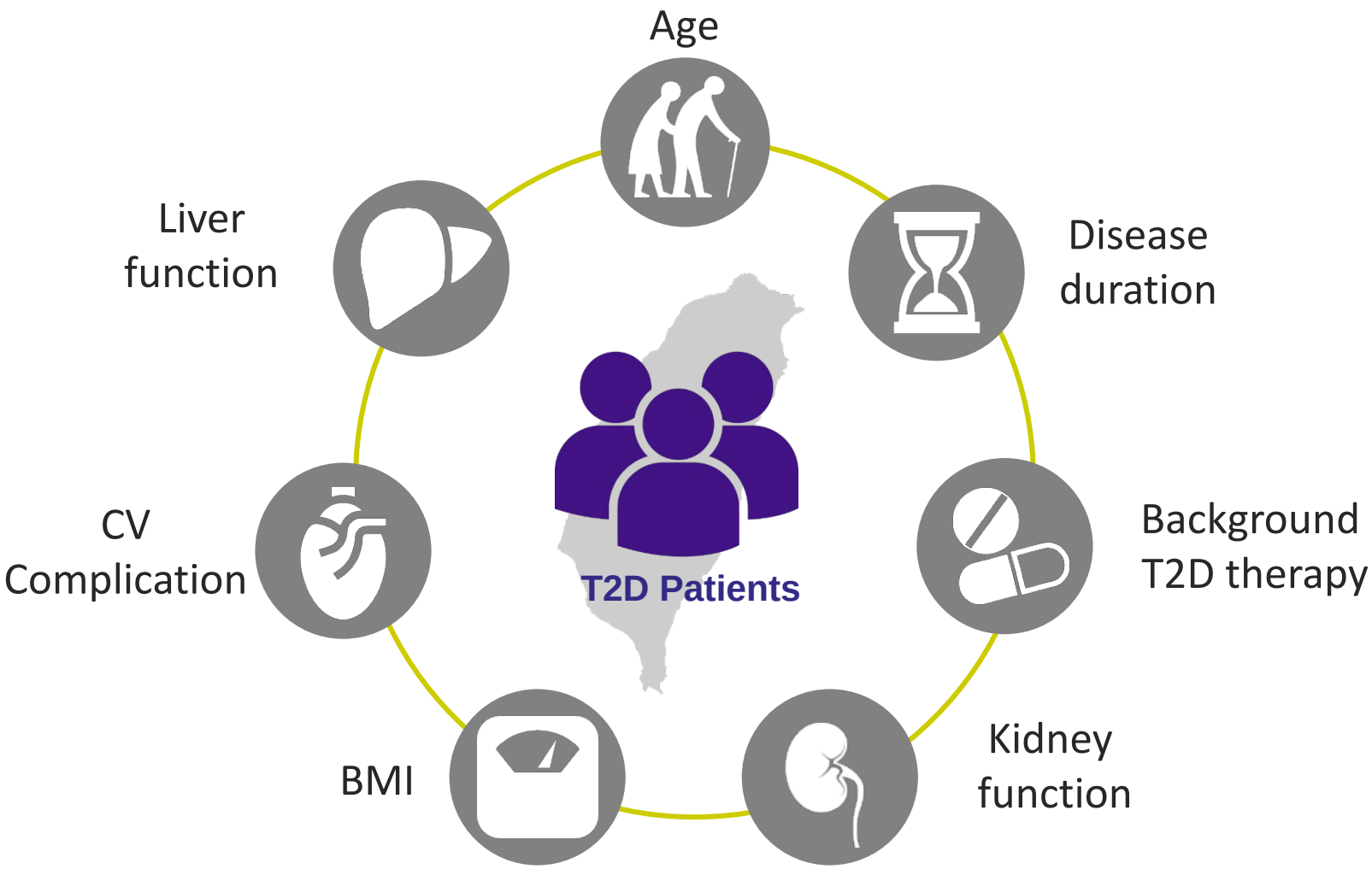


Life course of diabetes



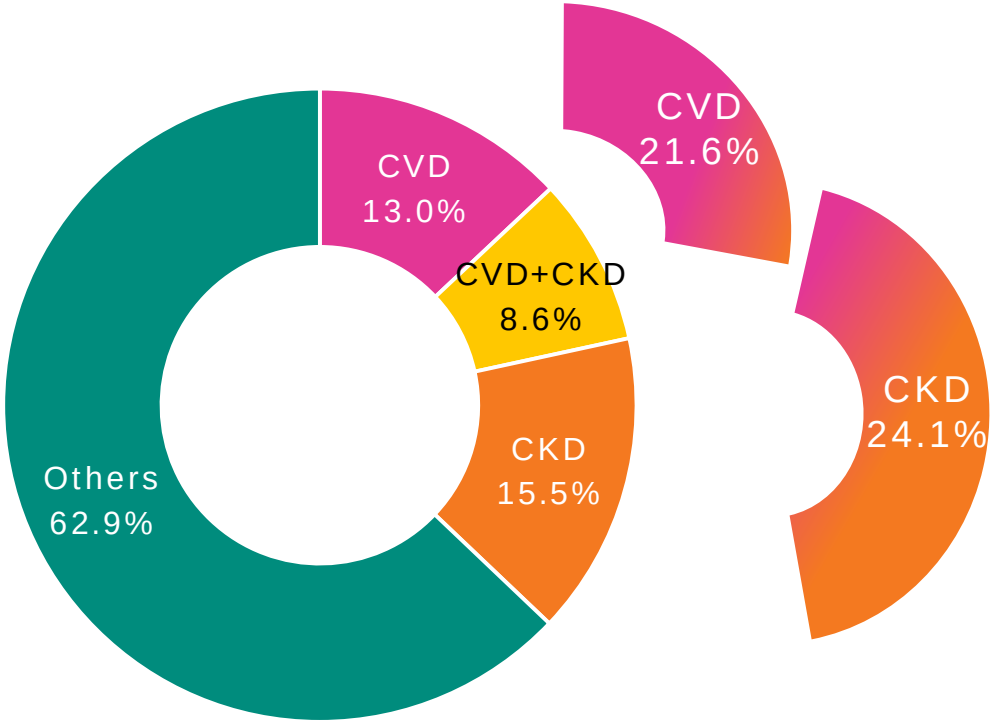
Xie F et al. 2018 Sep;9(5):998-1015. doi: 10.1111/jdi.12830. Epub 2018 Apr 25.

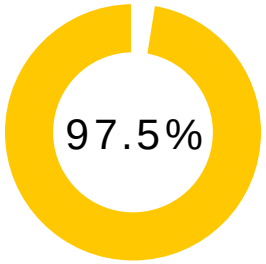
Diversity of T2D patients



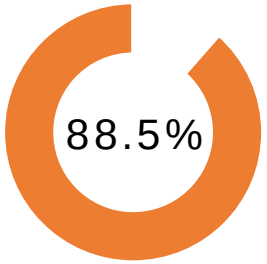
多數第二型糖尿病人合併有心腎共病-- Cross-sectional

A retrospective study of T2DM patients via Q-EMR from 2014 to 2015





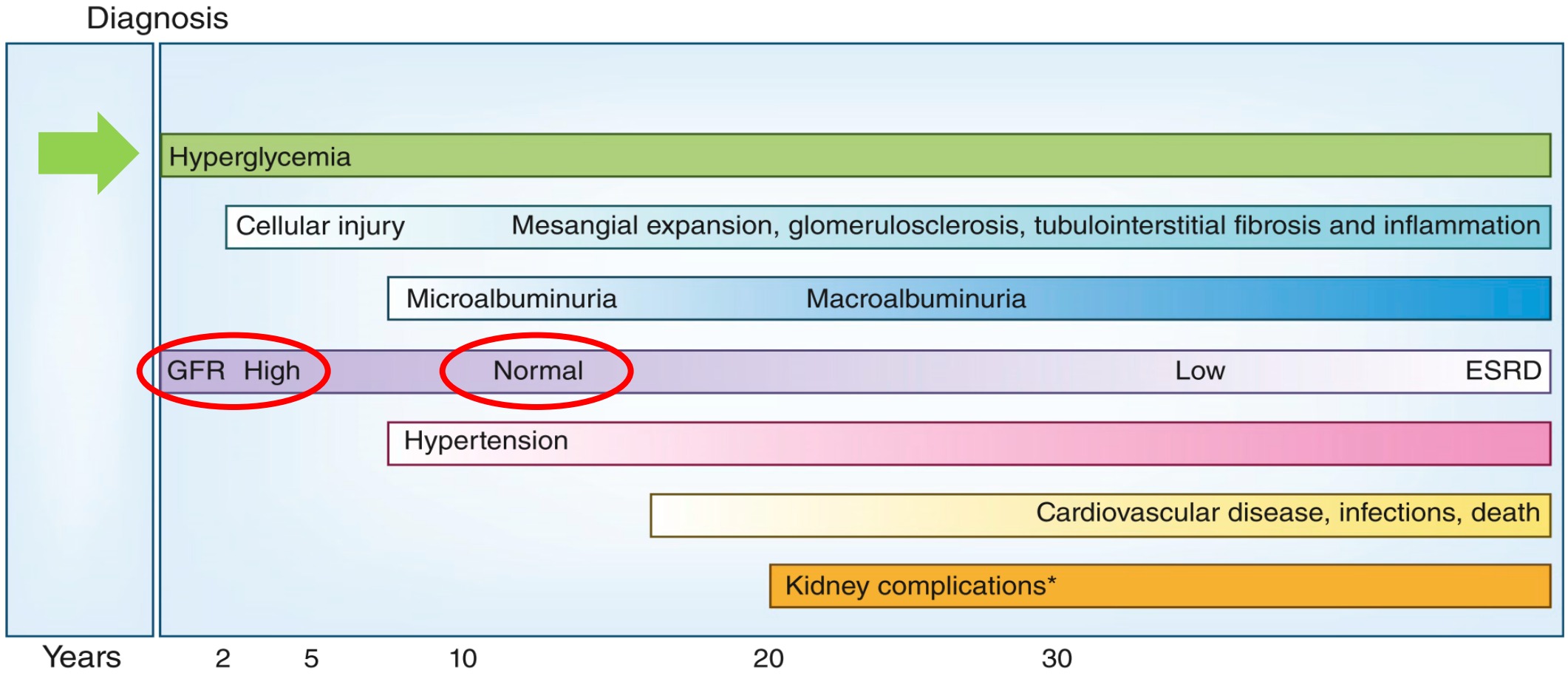
had ≥ 1 comorbid condition



had ≥ 2 comorbid condition

Q-EMR, Quintiles Electronic Medical Record (EMR) research database
Iglay K, et al. *Curr Med Res Opin* 2016 Jul;32(7):1243-52.

Longitudinal--
Progressive disease with early onset complications



*Kidney complications: anemia, bone and mineral metabolism, retinopathy, and neuropathy
CJASN December 2017, 12 (12) 2032-2045
Timeline is well characterized for type 1 diabetes mellitus; for type 2 diabetes mellitus, timeline may depart from the illustration due to the variable timing of the onset of hyperglycemia

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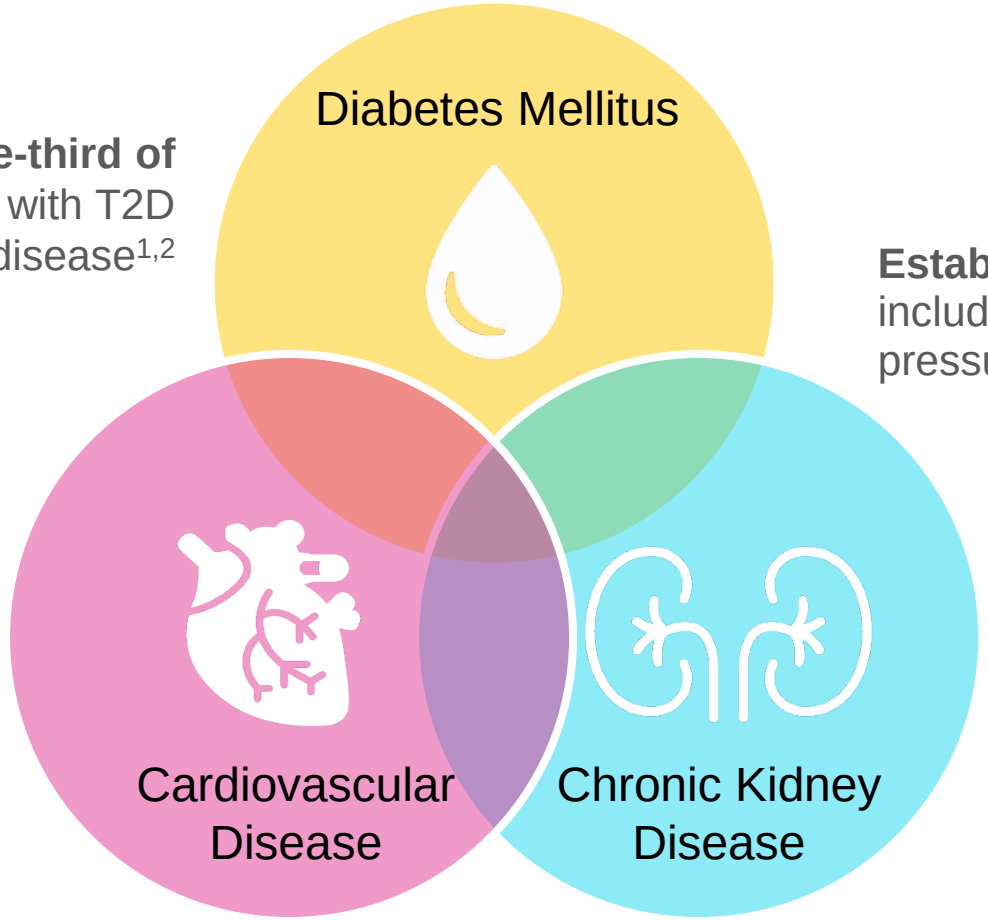
TW2009853796

血糖與心臟腎臟彼此互相影響

~One-third of patients with T2D have CV disease[1,2]

2× increased risk of death with a history of MI, stroke or diabetes[5]



Established risk factors for CKD include CV disease, high blood pressure, obesity and diabetes[4]

Diabetes and/or hypertension is the cause of **>80% of ESKD** cases worldwide[2]

1. Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83; 2. International Diabetes Federation. IDF Diabetes Atlas. 9th edn. 2019. https://www.diabetesatlas.org/ (accessed March 2020); 3. Kannel WB *et al. Am J Cardiol* 1974;34:29; 4. Siemens Healthineers. Chronic kidney disease: a global crisis. 2018. www.siemens-healthineers.com/en-uk/news/chronic-kidney-disease.html (accessed March 2020); 5. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52; 6. Sarraf M *et al. Clin J Am Soc Nephrol* 2009;4:2013

2019 台灣糖尿病年鑑讓我們看到除了控制血糖對於共病的控制仍然有很多進步空間

- 第二型糖尿病人數: 2,189,401
- 2014年新病人數: 159,047
- 心血管併發症盛行率: 25.19%
- 死亡主因排行榜: 心臟病12% (第三名)
- 糖尿病併發腎疾病比率: 17.92%

2019臺灣糖尿病年鑑

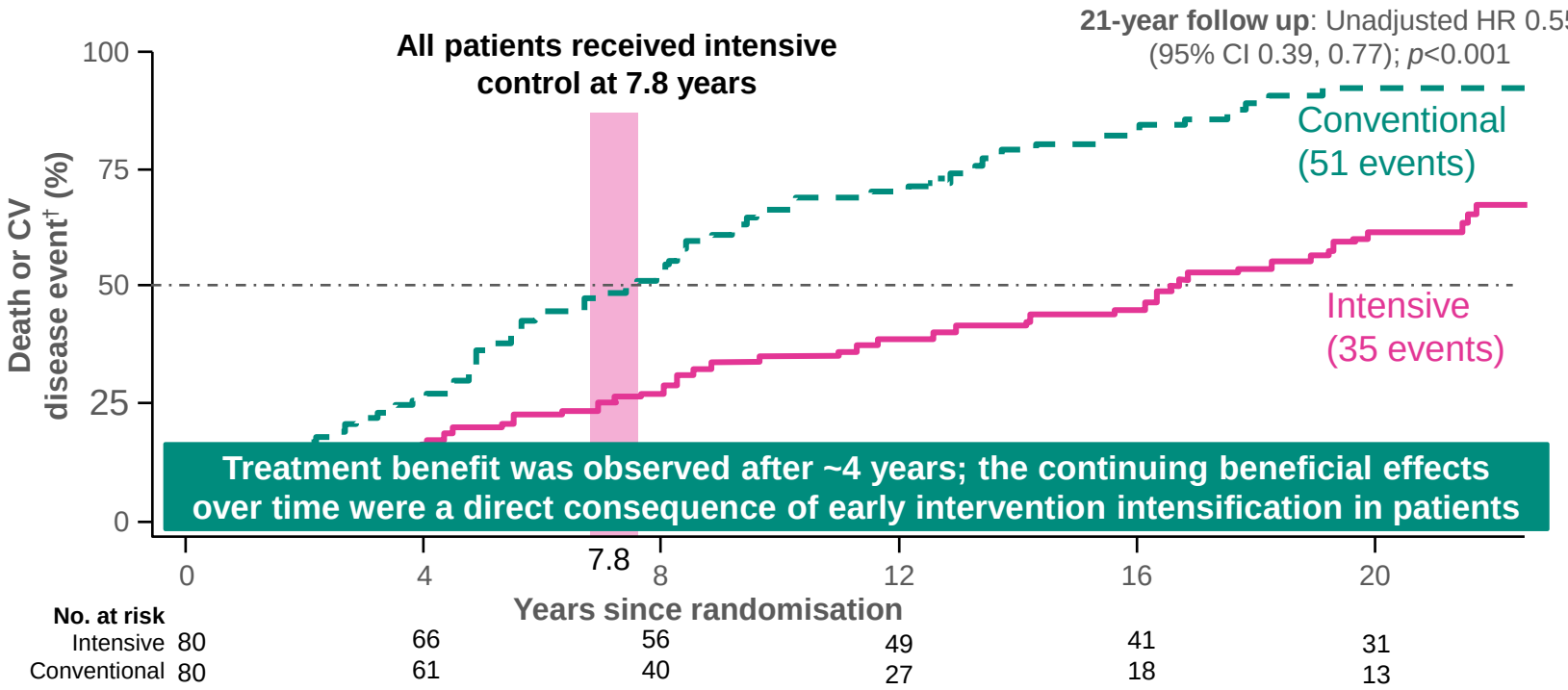
各項目評比》台灣慢性病表現不佳

項目	日本	韓國	新加坡	台灣
慢性腎病（洗腎）	79	73	57	55
糖尿病	100	74	100	60
膽囊和膽道疾病	90	74	86	64
高血壓心臟病	99	90	56	61
腦血管疾病	76	62	74	63
先天性心臟異常	84	91	88	69
整體分數	94	90	91	85

註：滿分100分，僅列舉台灣表現特別不佳的項目（2016年分數）

STENO-2 試驗顯示:
積極控制心血管風險因子能減少病人死亡或心血管事件發生

Steno-2: Intensive multifactorial control* of CV risk factors reduces CV risk in patients with T2D and microalbuminuria[1,2]



Changes in key clinical and biochemical variables at 7.8 years[2]

Variable	Conventional (n=63)	Intensive (n=67)	*p*-value
Systolic BP (mmHg)	-3±3	-14±2	<0.001
Diastolic BP (mmHg)	-8±2	-12±2	0.006
LDL cholesterol (mg/dl)	-13±6	-47±5	<0.001
HbA1c (%)	0.2±0.3	-0.5±0.2	<0.001
BMI (men)	0.4±0.4	0.7±0.4	0.61
BMI (women)	1.3±1.3	2.3±1.2	0.29
Current smoker (no. of patients)	-6	-5	0.73

*Intensive multifactorial control consisted of reduced targets for blood pressure, cholesterol, triglycerides and HbA1c, as well as treatment with aspirin and ACEi; †Composite secondary endpoint: time to incident CV disease, number of CV events, mortality and CV disease rates
ACEi, angiotensin-converting enzyme inhibitor, BMI, body mass index; LDL, low-density lipoprotein

1. Gaede P *et al. Diabetologia* 2016;59:2298; 2. Gaede P *et al. N Engl J Med* 2003;348:383

多重心血管風險因子的控制是目前第二型糖尿病的標準治療[1,2]

- ADA and ESC guidelines focus on reducing the risk of CV death in patients with T2D[1,2]

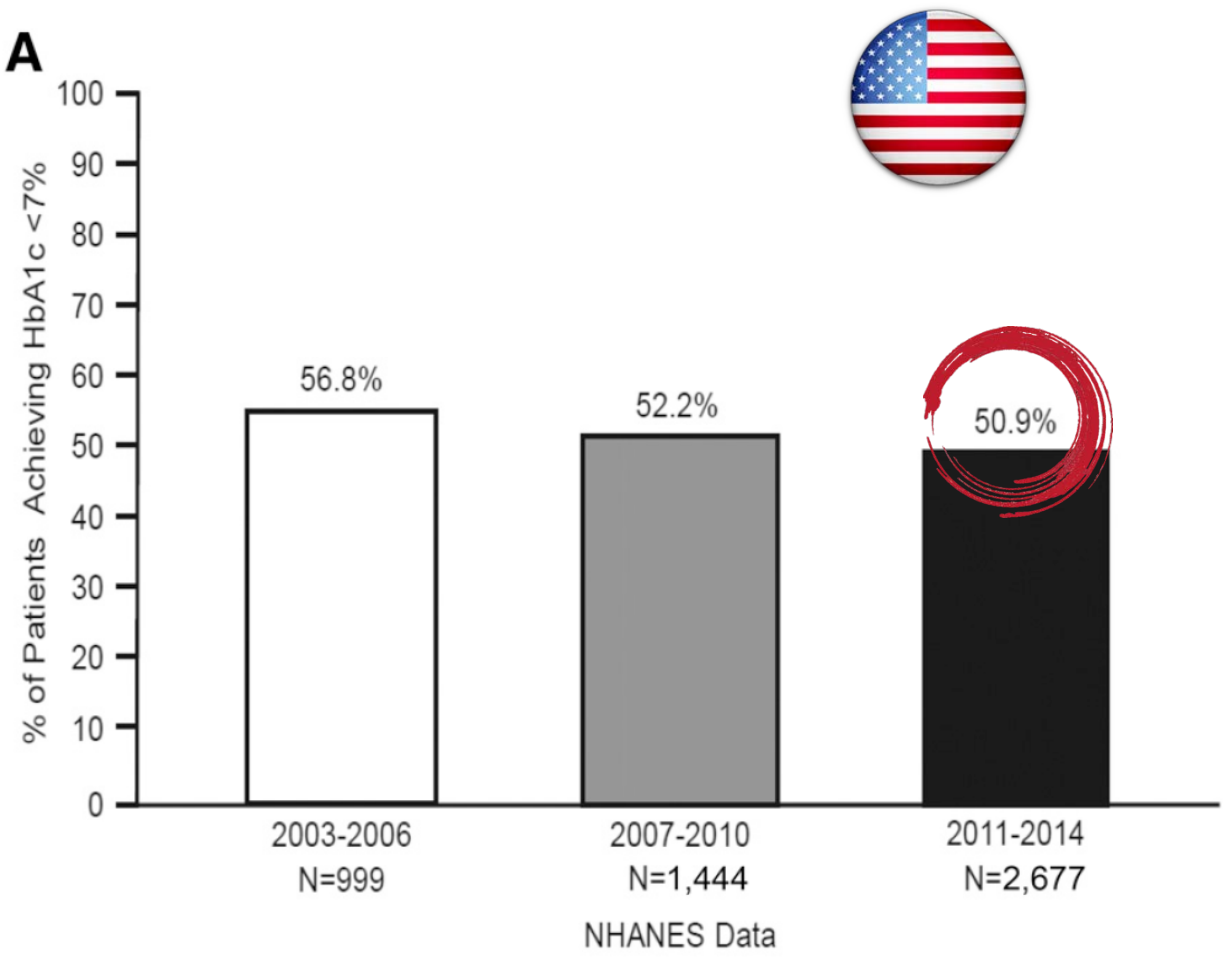
	Target	Treatment
 Glucose control	**Targets are individualised – for many patients HbA1c <7%[1,2]**	• Metformin, SGLT2 inhibitors*, GLP-1 receptor agonists†, DPP-4 inhibitors, sulphonylureas, thiazolidinediones, insulin[1,2]
 Blood pressure-lowering	For individuals with T2D and hypertension, a blood pressure target of: • **<130/80 mmHg if at higher CV risk‡[1]** • **<140/90 mmHg if at lower risk for CV disease§[1]**	• RAAS blocker (ACEi/ARB), calcium channel blocker, thiazide-like diuretics[1,2] • Dual therapy is recommended as first-line treatment[2]
 LDL cholesterol-lowering	• **<1.8 mmol/l (<70 mg/dl) with LDL-C reduction of ≥50% if at high CV risk[1,2]** • **<2.6 mmol/l (<100 mg/dl) if at moderate CV risk[2]**	• Statins, ezetimibe or PCSK9 inhibitor[1,2]
 Individualised diet and lifestyle	**Weight loss and smoking cessation[1,2]**	• Diet[1,2] • Physical activity[1,2] • Behavioural therapy[1]

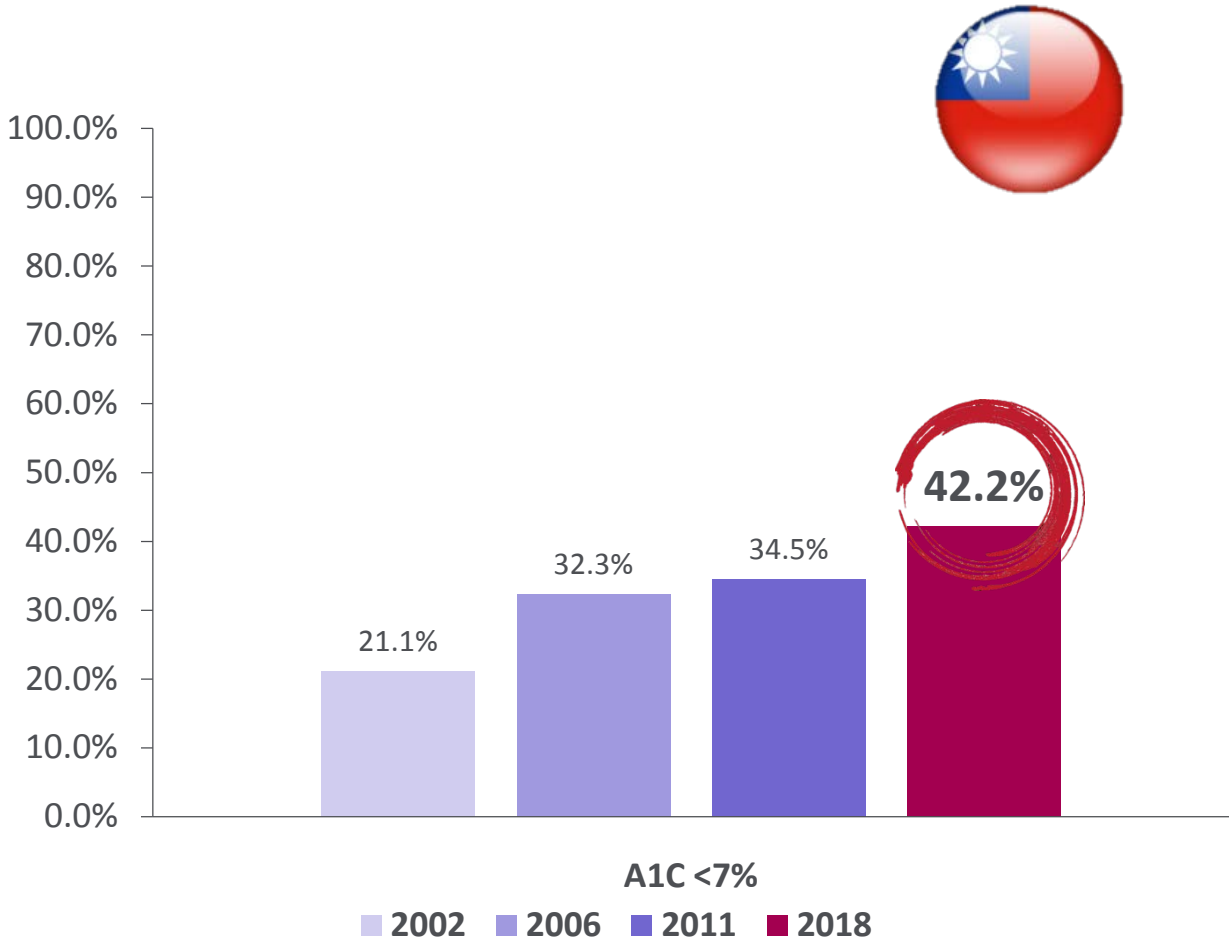
For full recommendations, please refer to the individual references

*Empagliflozin, canagliflozin and dapagliflozin reduce CV events in patients with diabetes and CV disease or who are at very high/high CV risk; †Liraglutide, semaglutide and dulaglutide reduce CV events in patients with diabetes and CV disease or who are at very high/high CV risk; ‡Existing ASCVD or 10-year ASCVD risk ≥15%; §10-year ASCVD risk <15%. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9; RAAS, renin-angiotensin-aldosterone system

1. American Diabetes Association. *Diabetes Care* 2020;43:S1; 2. Cosentino F *et al. Eur Heart J* 2020;7:255

Proportion of T2D patients achieving HbA1C < 7% is relatively lower in Taiwan

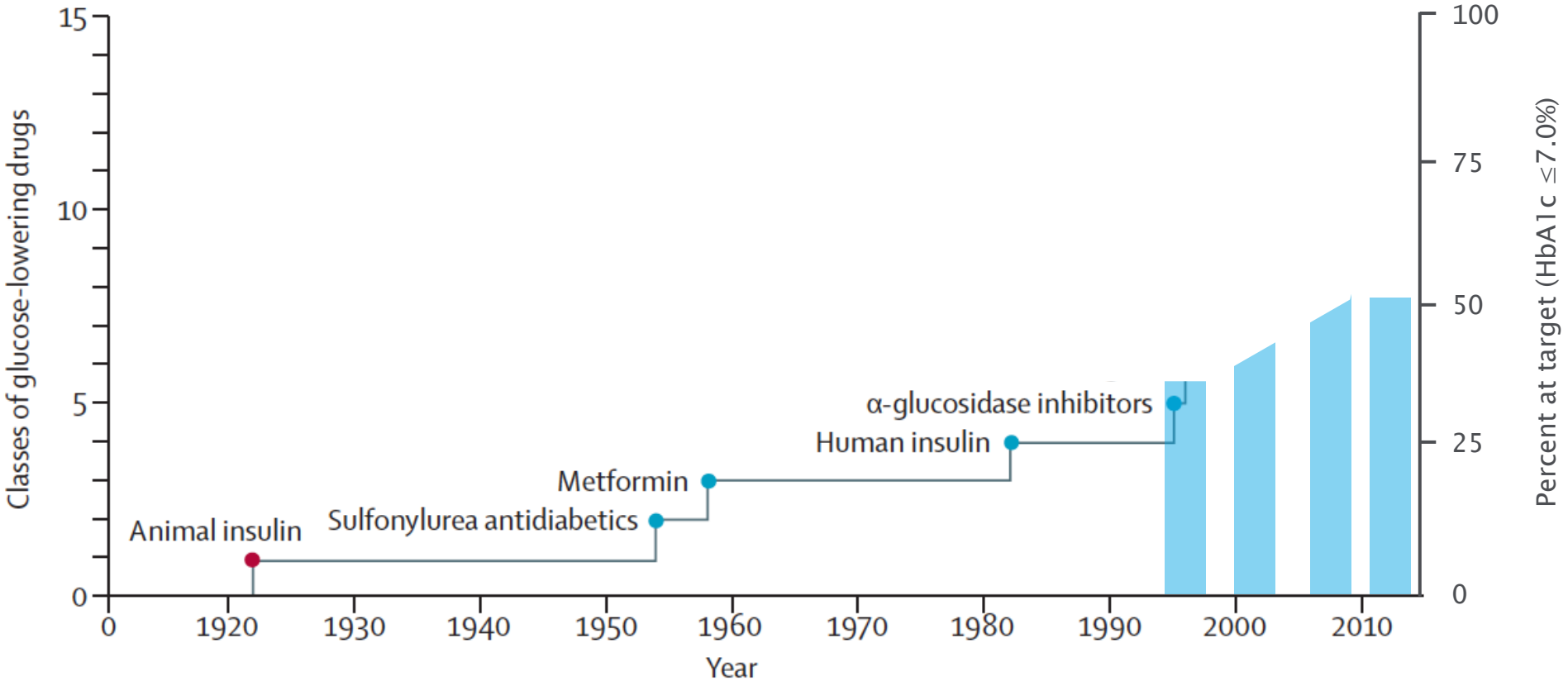




1.Diabetes Care 2017;40:1425–1432
2. 2018 台灣糖尿病健康促進機構之品管調查研究

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

Drugs development to Treat Type 2 Diabetes



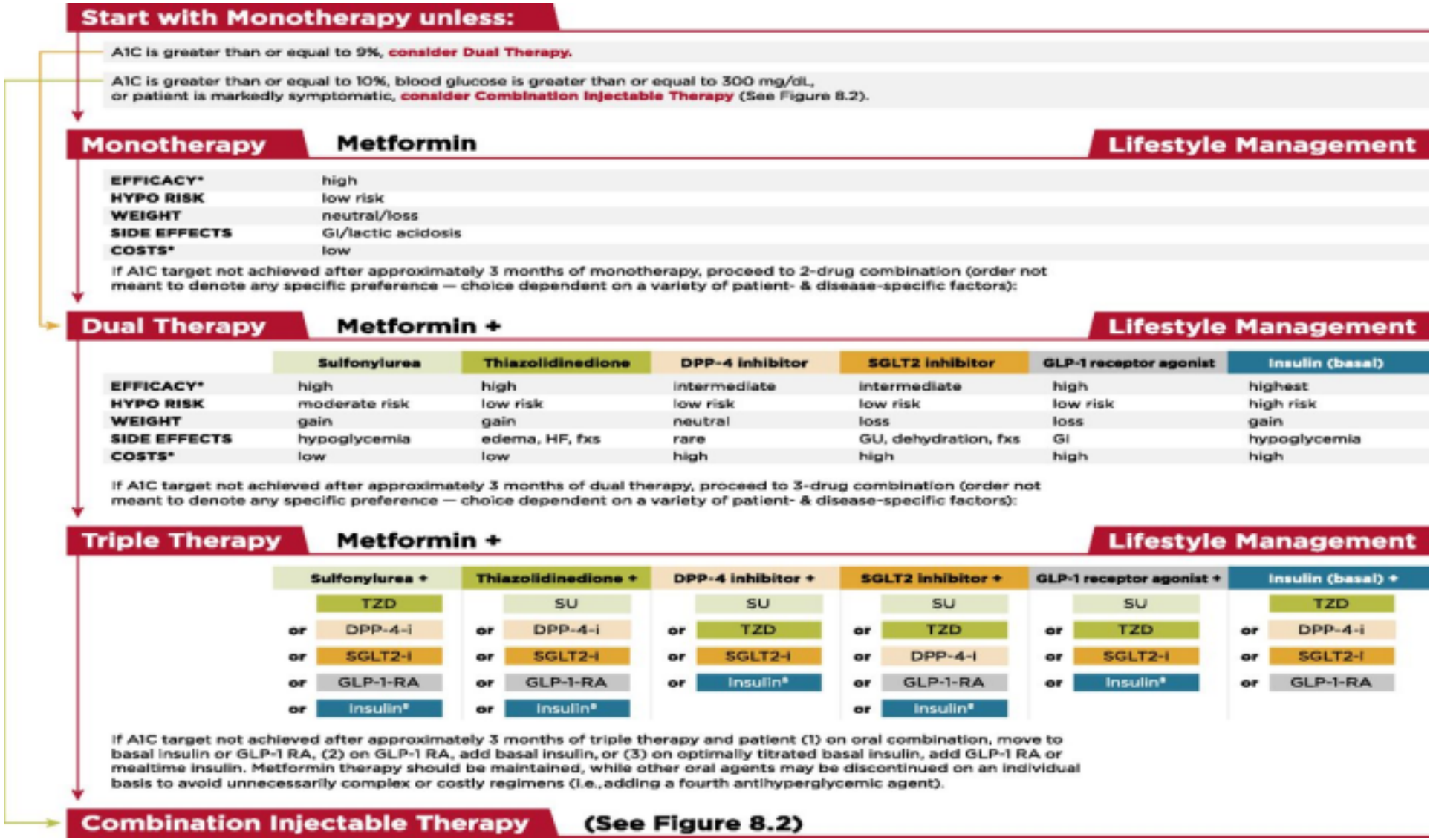
Kahn S, Cooper M, Del Prato S. ***Lancet*** 2014; 383: 1068–83

Trajenta® (linagliptin) 5mg tablets

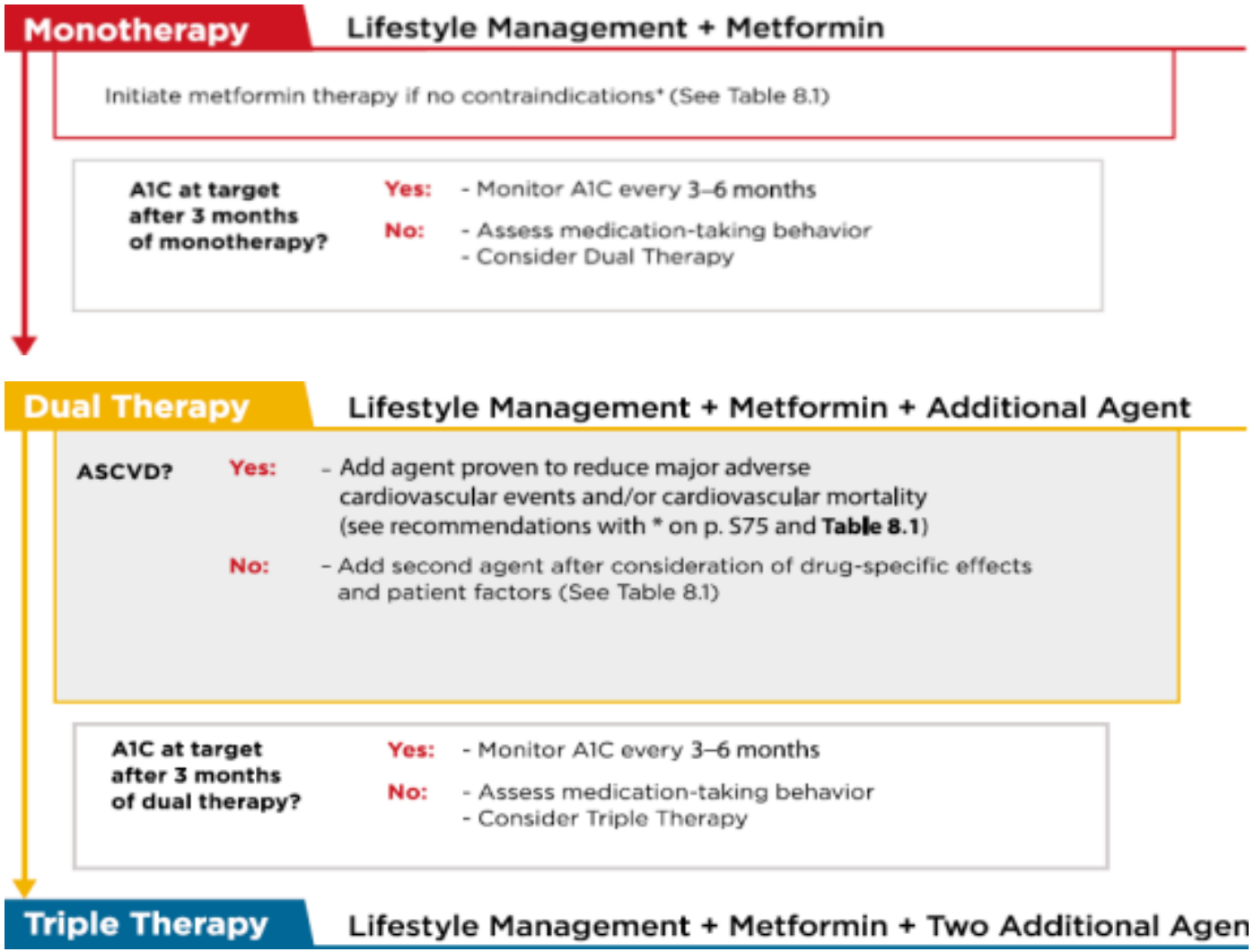
TrajentaDuo® (linagliptin/metformin HCl)

What's Your Choice?

2017 ADA Guidelines are Glycemic focused treatment algorithm



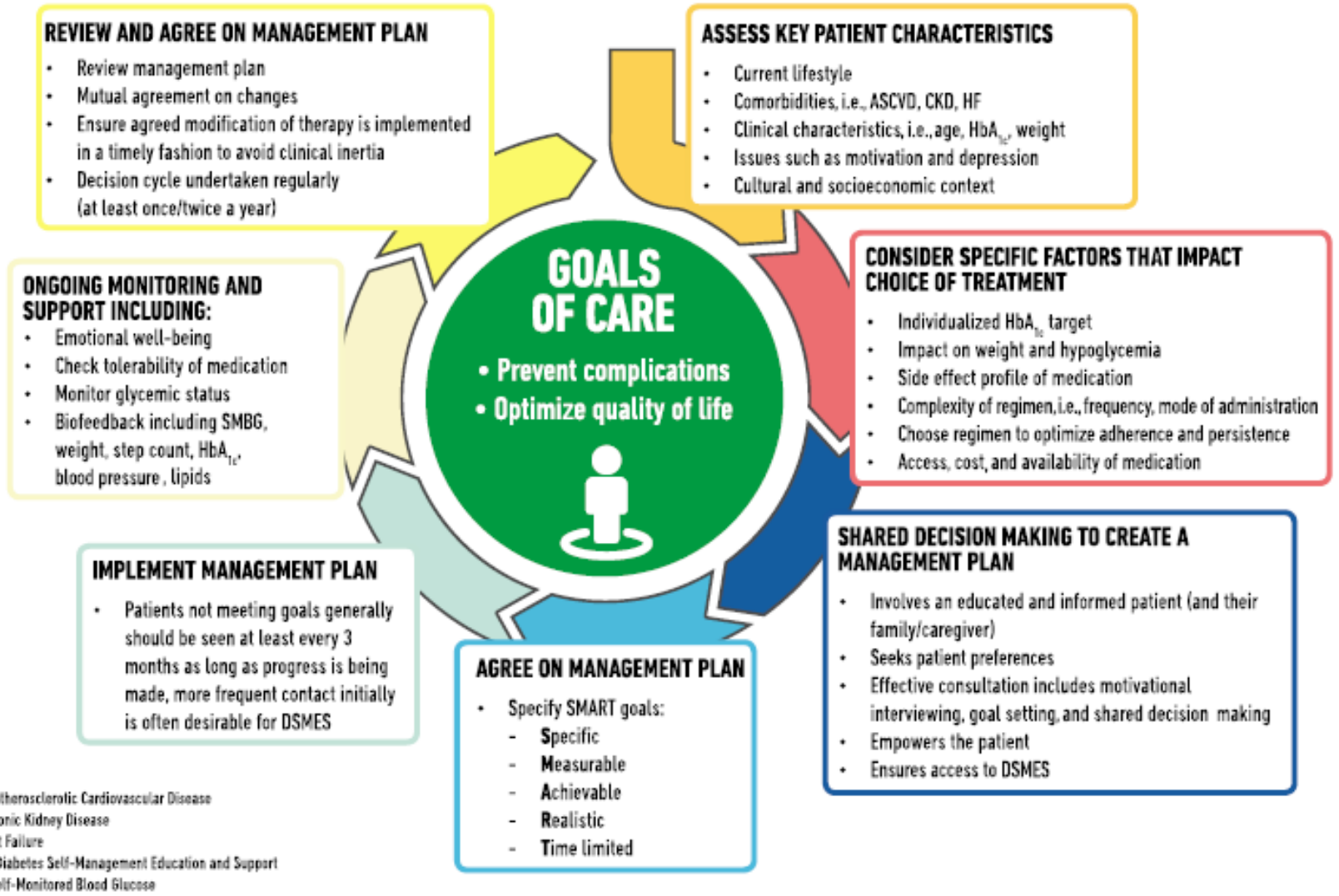
2018 ADA Guidelines turned to ASCVD focused



In patients with **T2DM** and established **ASCVD**, anti hyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to **reduce major adverse CV events and CV mortality** (currently empagliflozin and liraglutide), after considering drug specific and patient factors(Table 8.1).

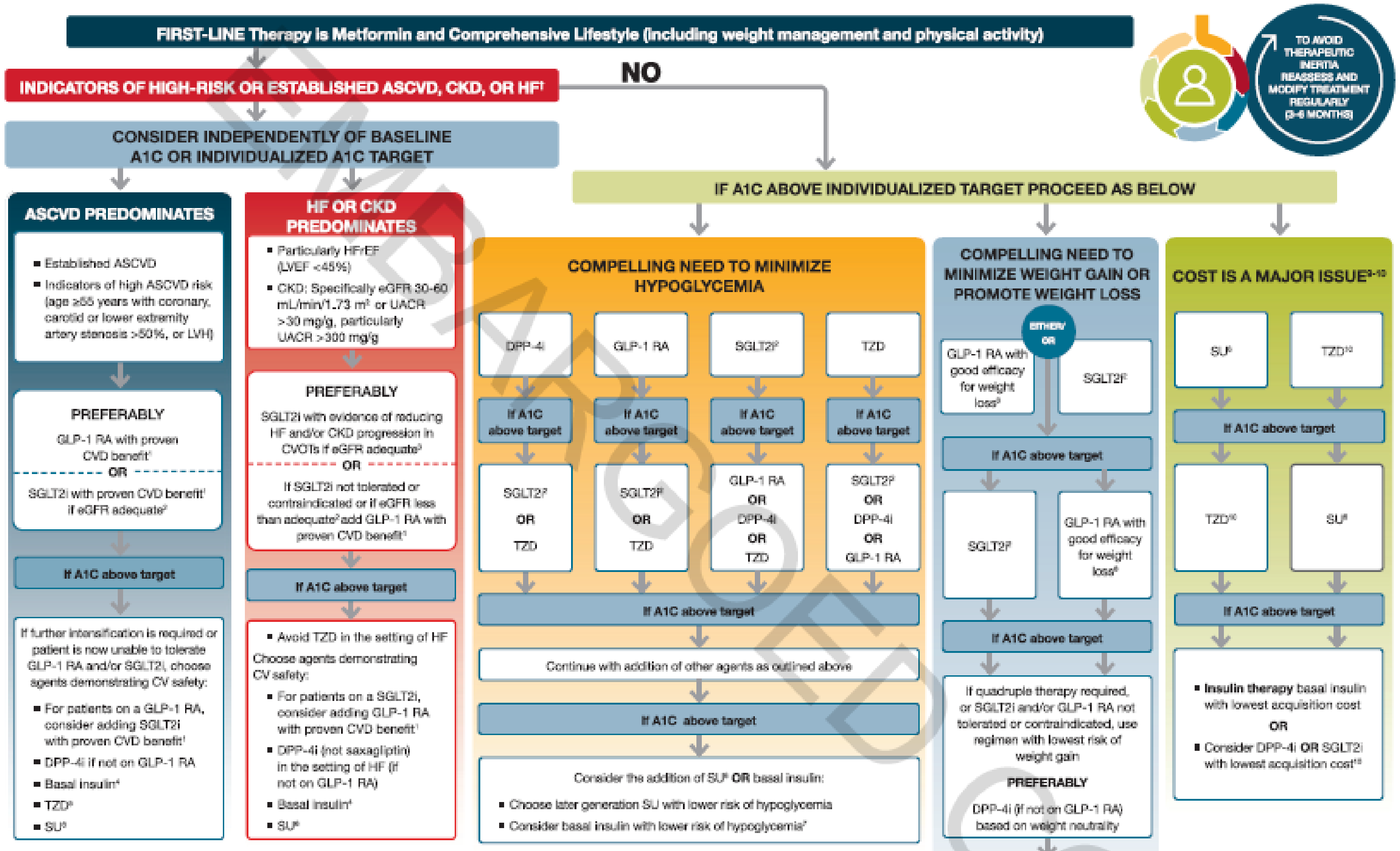
Diabetes Care 2018;41(Suppl. 1):S73–S85

2019 ADA Guidelines based on patient centric



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

2020 ADA guidelines treatment algorithm is similar to 2019


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
NO
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit¹
OR
SGLT2i with proven CVD benefit¹ if eGFR adequate²
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
DPP-4i if not on GLP-1 RA
Basal insulin⁴
TZD⁵
SU⁶
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹
If A1C above target
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin⁴
SU⁶
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i²
TZD
If A1C above target
SGLT2i² OR TZD
SGLT2i² OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i² OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU⁶ OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia⁷
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/OR
GLP-1 RA with good efficacy for weight loss⁸
SGLT2i²
If A1C above target
SGLT2i²
GLP-1 RA with good efficacy for weight loss⁸
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
SU⁶ · TZD⁵ · Basal insulin
COST IS A MAJOR ISSUE⁹⁻¹⁰
SU⁶
TZD¹⁰
If A1C above target
TZD¹⁰
SU⁶
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-4i OR SGLT2i with lowest acquisition cost¹⁰

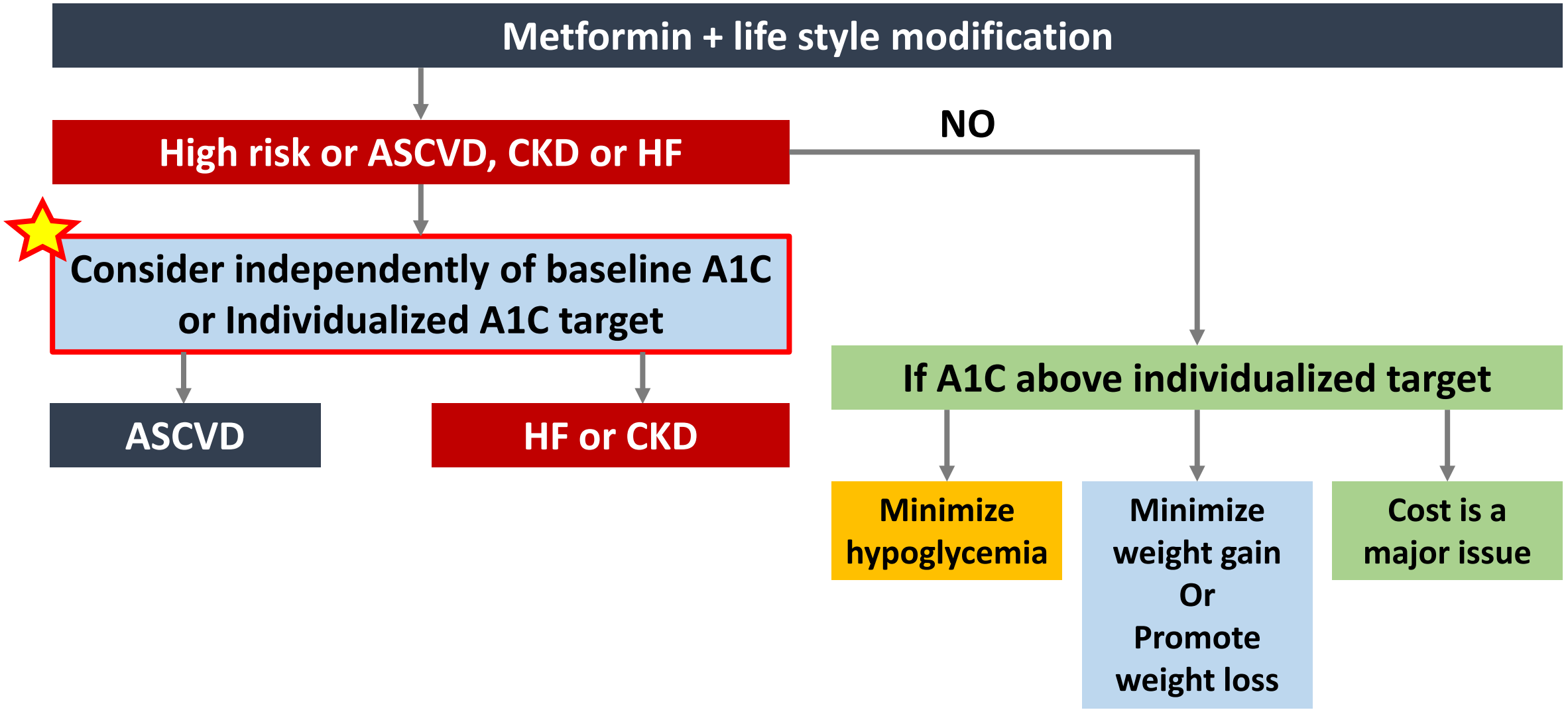
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
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 to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

American Diabetes Association.

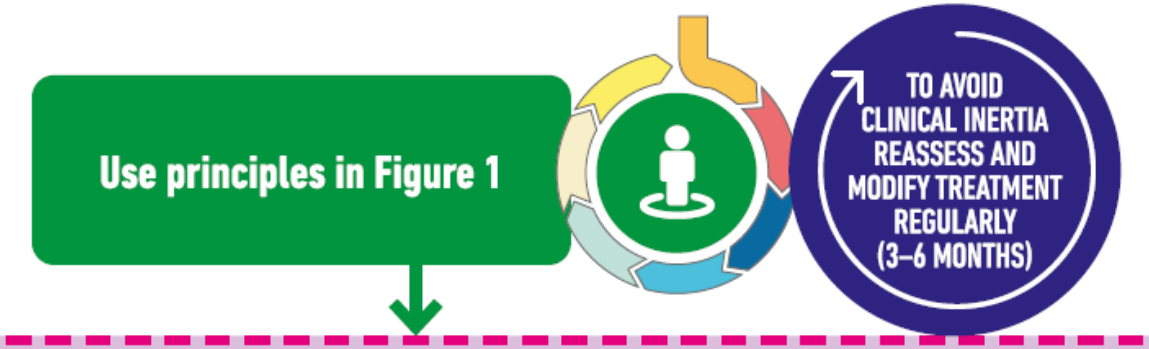
Individualized A1C target is a key consideration for treatment diabetes



American Diabetes Association.

Individualized A1C target is a key consideration for treatment diabetes

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH INDICATORS OF HIGH-RISK OR ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD), CHRONIC KIDNEY DISEASE (CKD) OR HEART FAILURE (HF)

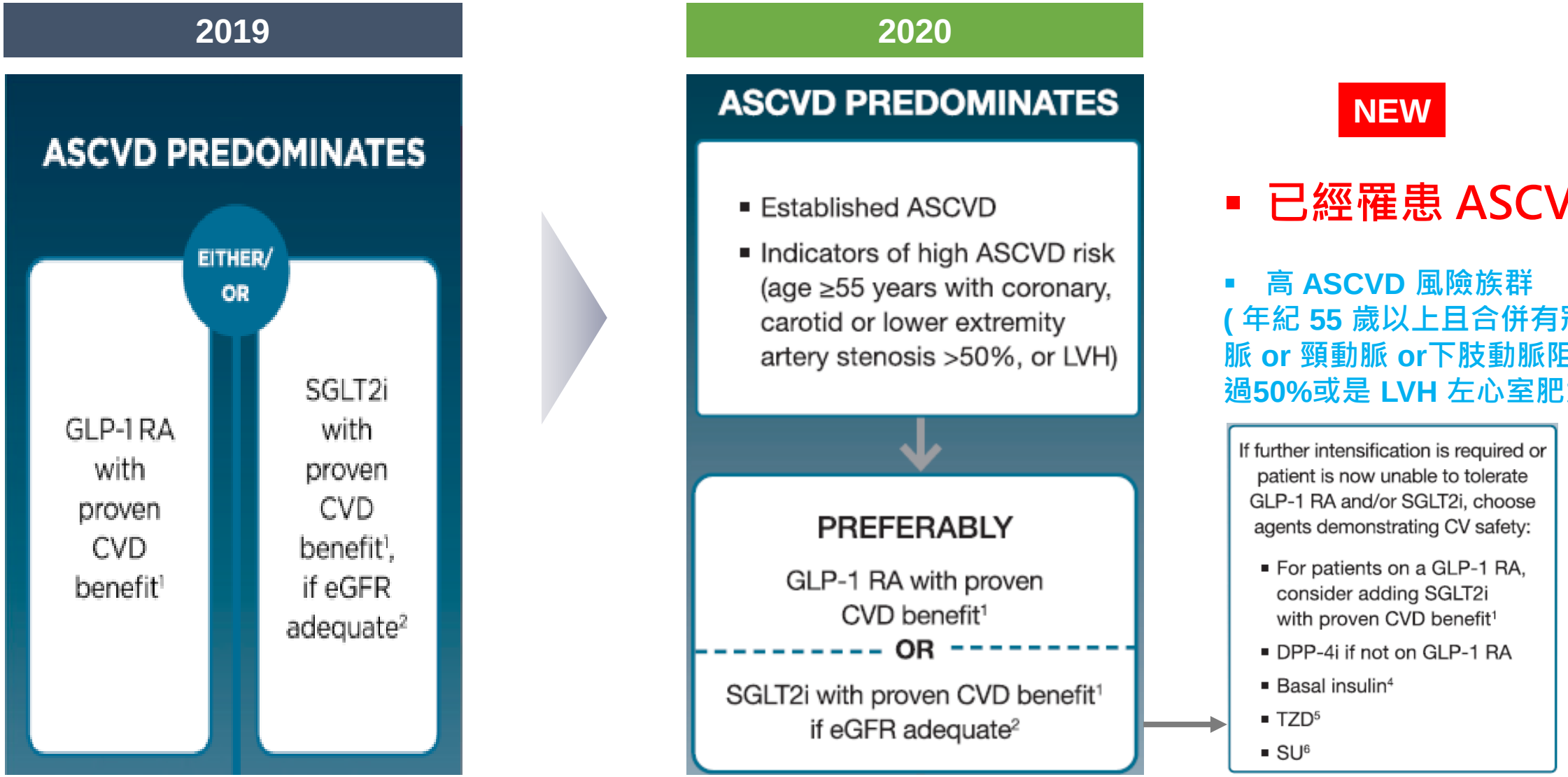


Use metformin unless contraindicated or not tolerated

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add an SGLT2i or GLP-1 RA with proven CVD benefit[1] (consider adding independently of individualised HbA_{1c} target)
- If individualised HbA_{1c} target achieved and already on dual therapy or multiple glucose-lowering therapies when adding SGLT2i or GLP-1 RA, consider stopping or reducing dose of other glucose-lowering therapy to reduce the risk of hypoglycaemia

American Diabetes Association.

ASCVD and high risk patients are suggested to add SGLT2i or GLP-1 RA



NEW

- 已經罹患 ASCVD
- 高 ASCVD 風險族群
(年紀 55 歲以上且合併有冠狀動脈 or 頸動脈 or下肢動脈阻塞超過50%或是 LVH 左心室肥大)

American Diabetes Association.

More definition of HF and CKD patients in 2020 ADA guidelines

2019

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

2020

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m^2 or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

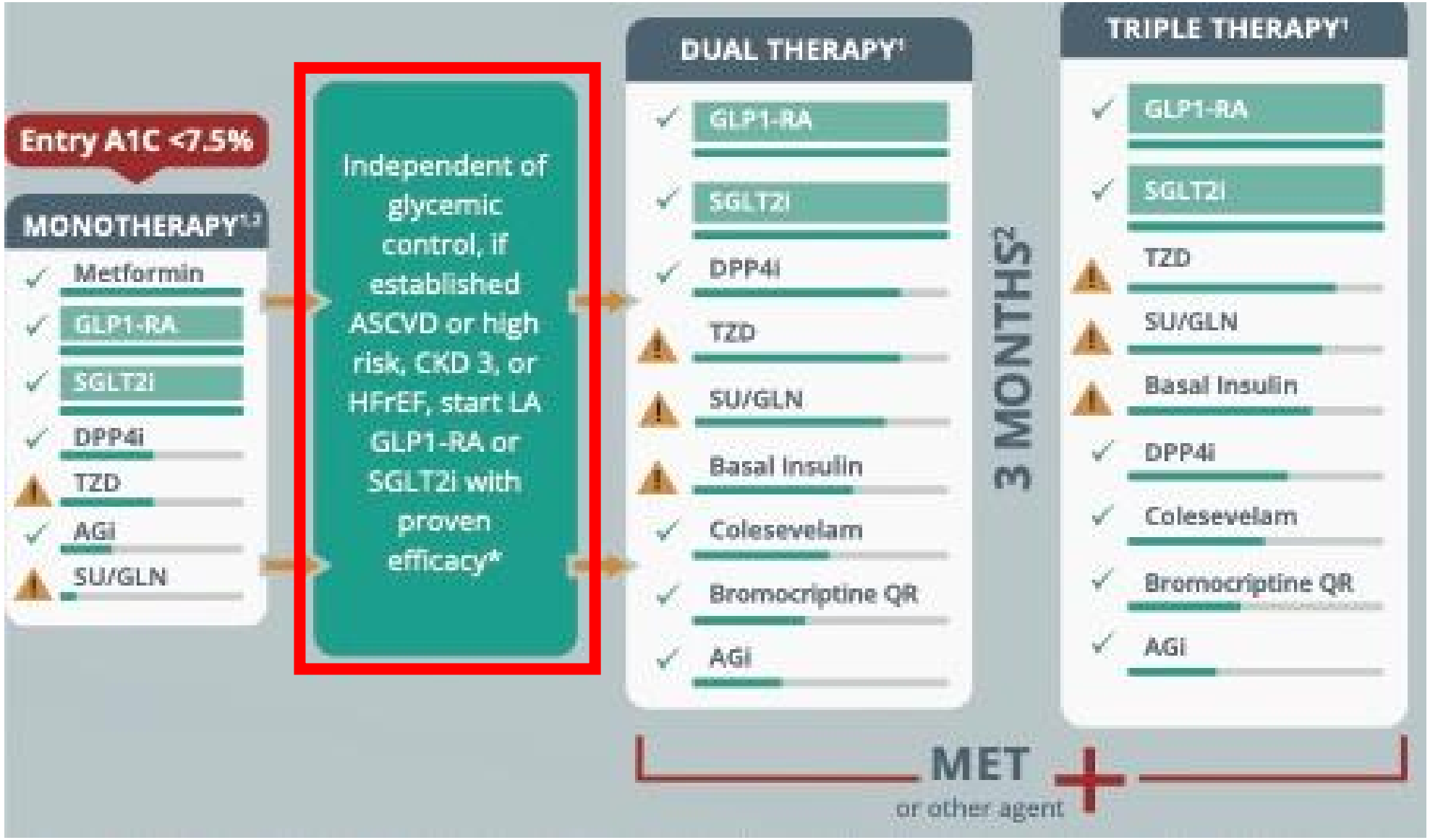
NEW

- **HFrEF (LVEF<45%)**
- **CKD:**
  1) **eGFR介於 30~60**
  2) **UACR > 30 mg/g, 特別是 UACR > 300 mg/g**

(urine albumin to creatinine ratio, UACR)

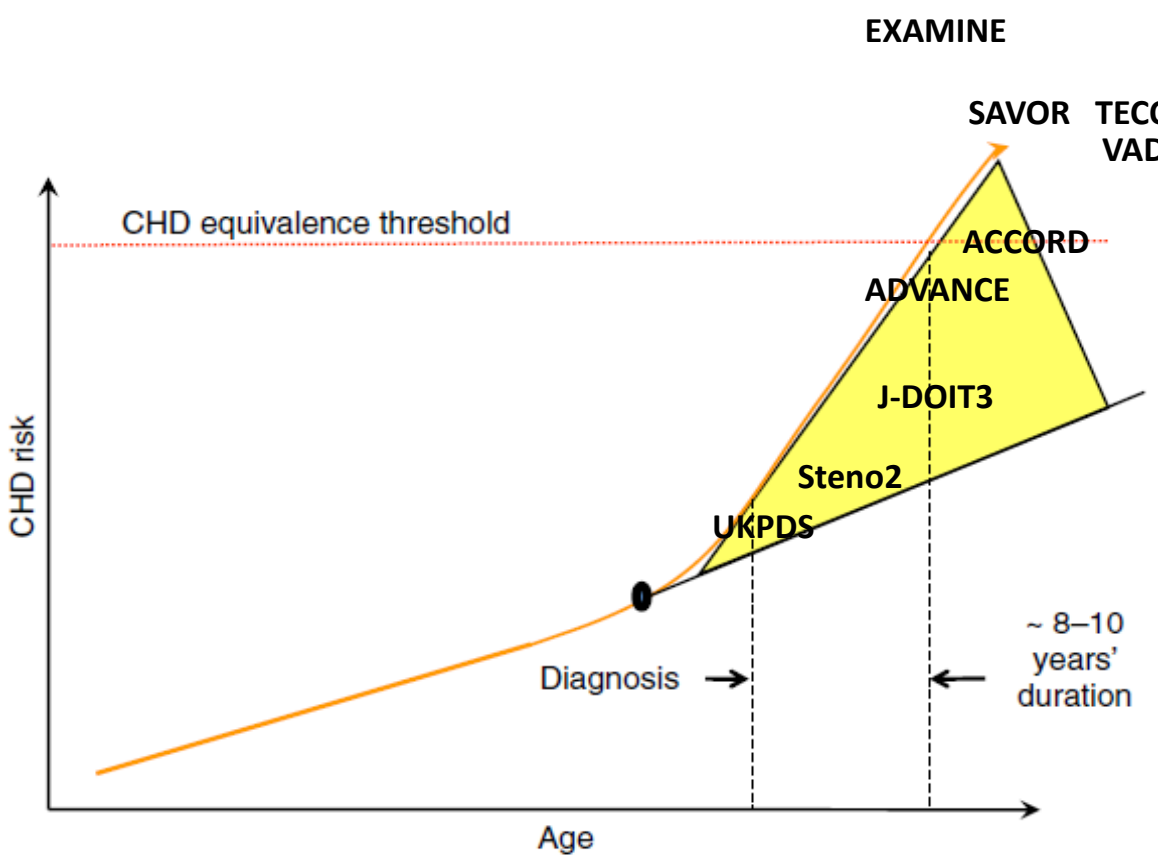
American Diabetes Association.

2020 AACE guidelines also recommend add-on SGLT2i or GLP1 RA to patient with High risk or ASCVD, CKD or HF




Why?

Vascular risk and its determinants before and during the course of type 2 diabetes

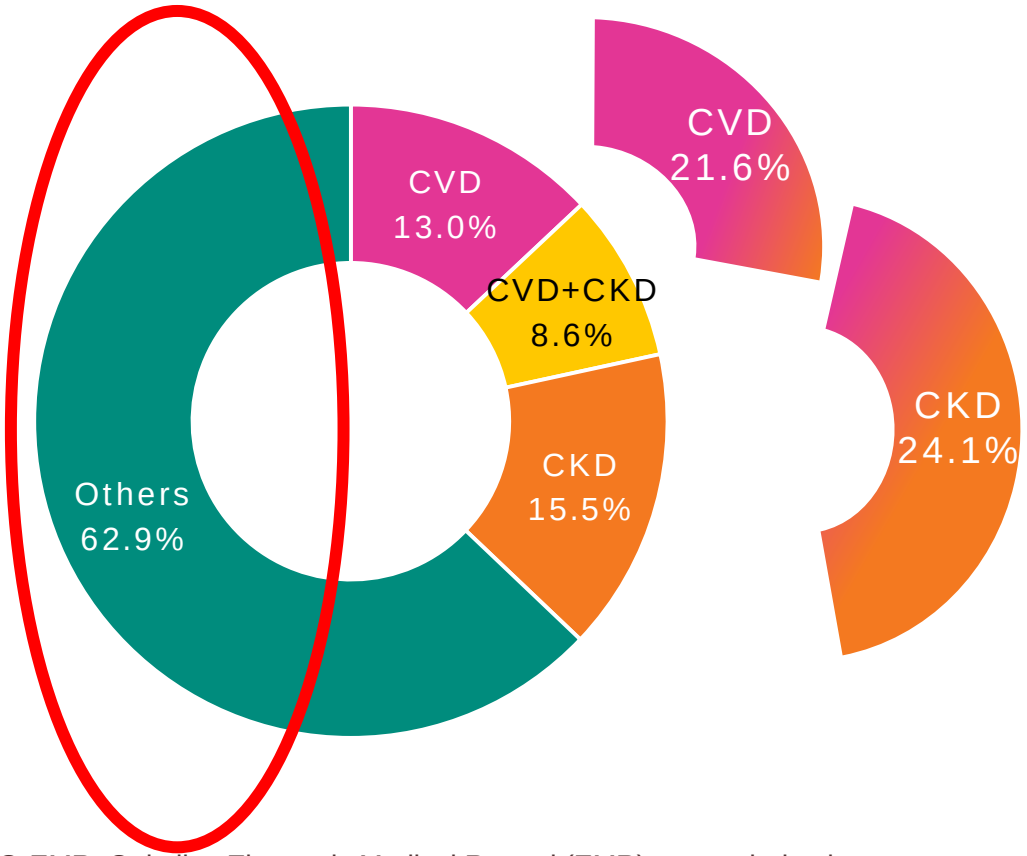


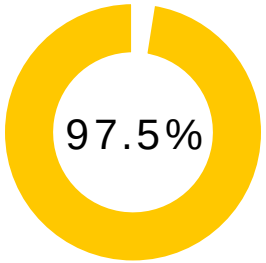
15-25% of the population with type 2 diabetes[2]

1. N. Sattar, Diabetologia (2013) 56:686–695
2. Melanie J. Davies, et al., Diabetologia. 2018 Oct 5.

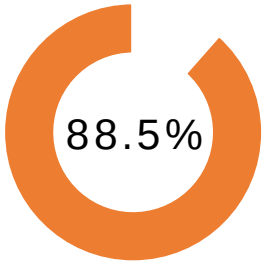
Cross-sectional—没有心肾共病

A retrospective study of T2DM patients via Q-EMR from 2014 to 2015





had ≥ 1 comorbid condition

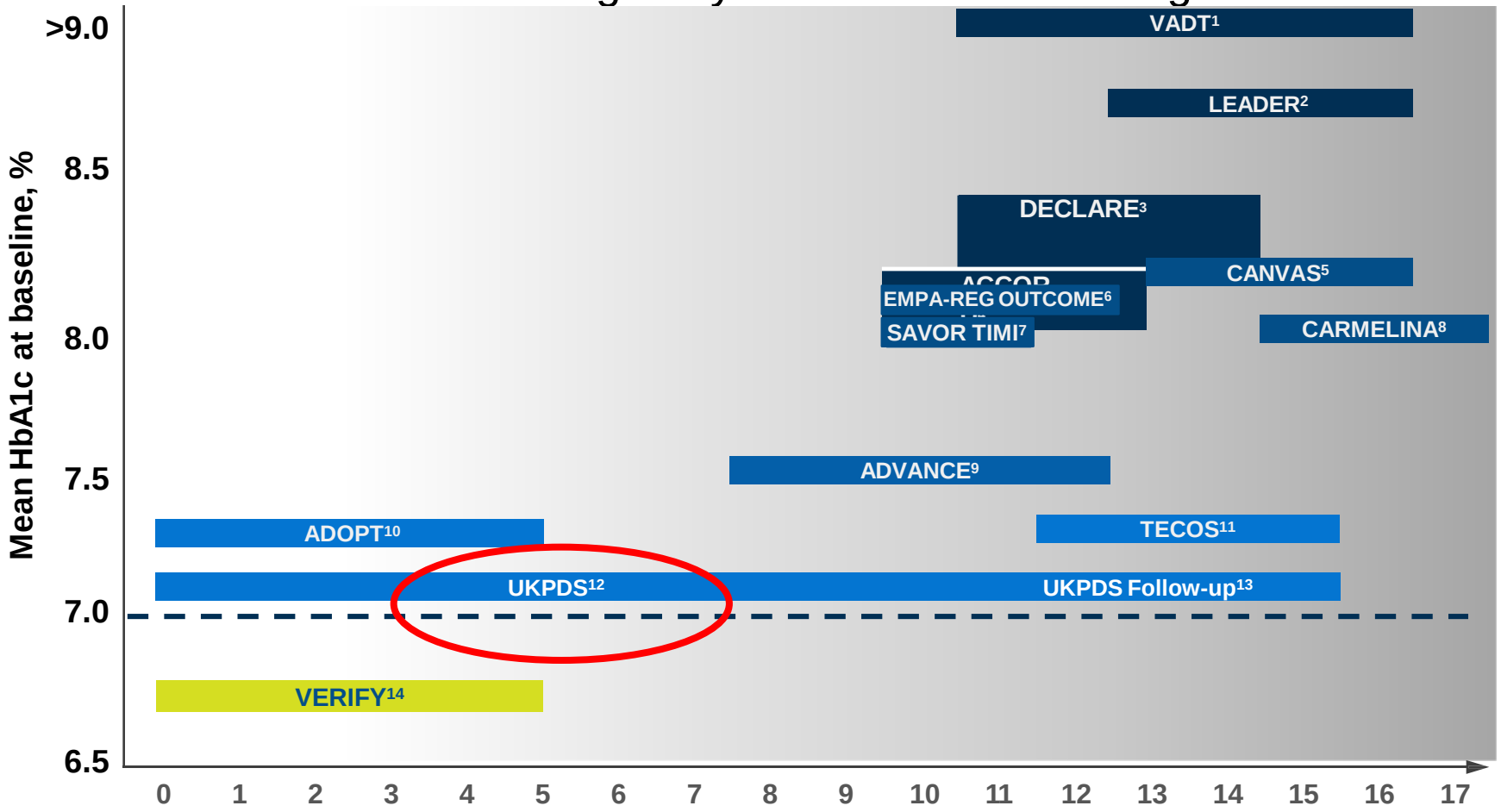


had ≥ 2 comorbid condition

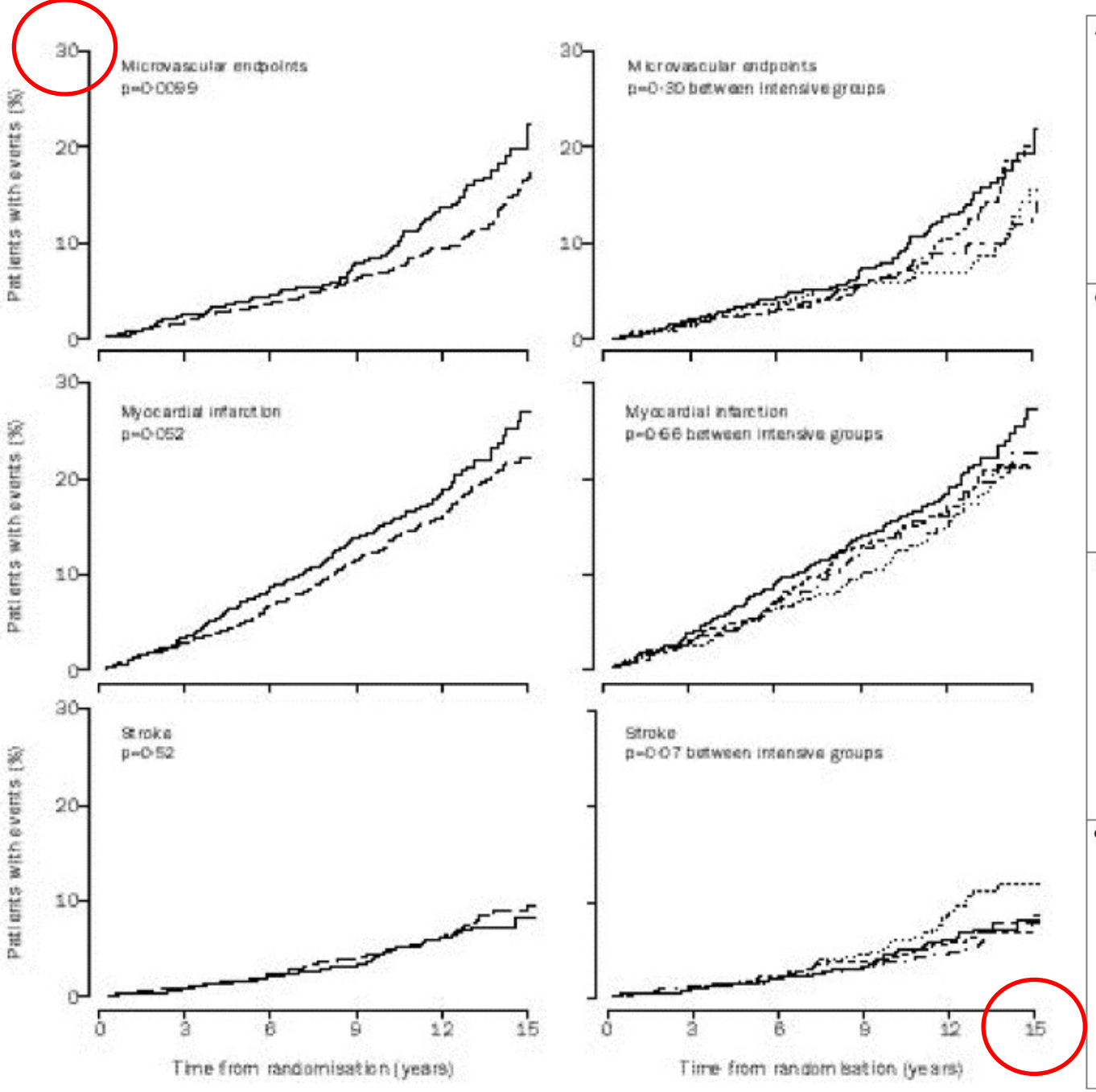
Q-EMR, Quintiles Electronic Medical Record (EMR) research database
Iglay K, et al. *Curr Med Res Opin* 2016 Jul;32(7):1243-52.

Clinical trials by diabetes progression periods

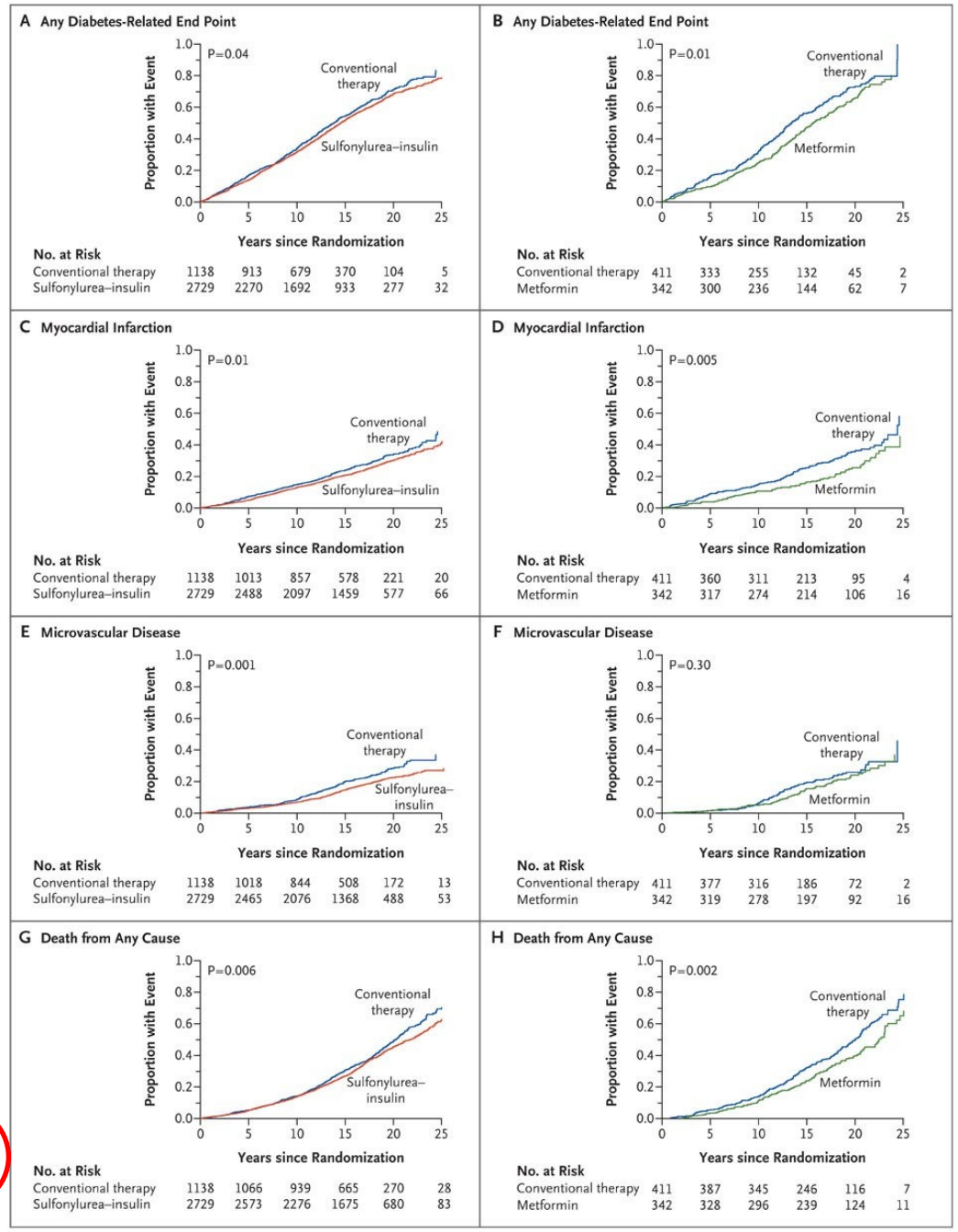
- Addressing early diabetes vs. later stage disease and



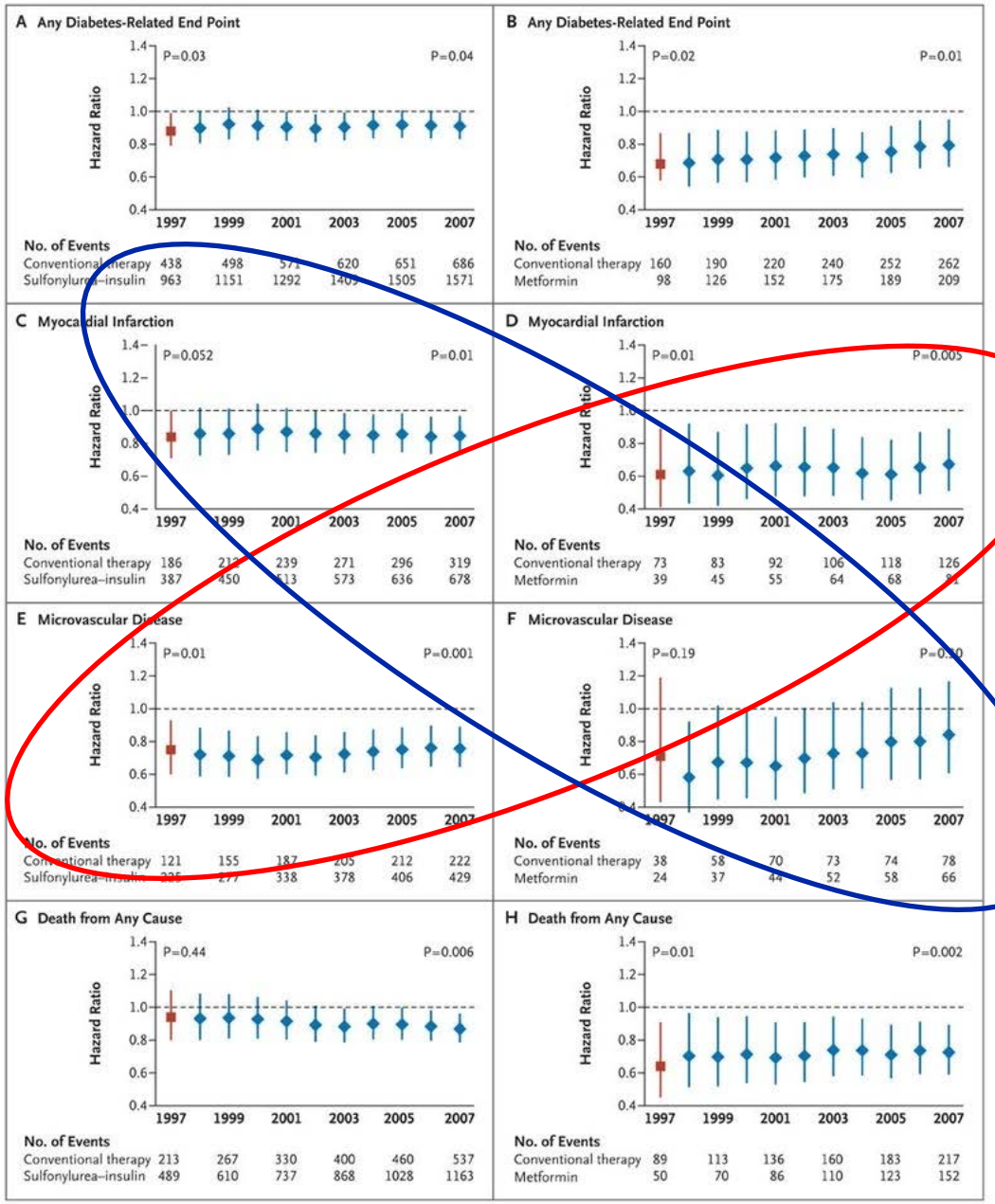
1. Duckworth W, et al. N Engl J Med. 2009;360(2):129-39. 2. Marso SP, et al. N Engl J Med 2016;375:311-22. 3. Wiviott SD, et al. N Engl J Med 2019;380:347-57. 4. ACCORD Study Group. N Engl J Med. 2008;358(24):2545-59. 5. Neal B, et al. N Engl J Med 2017;377:644-57. 6. Zinman B, et al. N Engl J Med 2015;373:2117-28. 7. Scirica BM, et al. N Engl J Med 2013;369:1317-26. 8. Rosenstock J, et al. JAMA. 2019;321(1):69-79. 9. ADVANCE Collaborative Group. N Engl J Med. 2008;358(24):2560-72. 10. Kahn SE, et al. N Engl J Med 2006;355:2427-43. 11. Green JB, et al. N Engl J Med 2015;373:232-42. 12. The UKPDS Group.Lancet. 1998;352(9131):837-53. 13. Holman RR, et al. N Engl J Med. 2008;359(15):1577-89. 14. Matthews D, et al. Diabet Med.2019;36:505-13.



Lancet. 1998;352:837-



N Engl J Med 2008; 359:1577-1589.



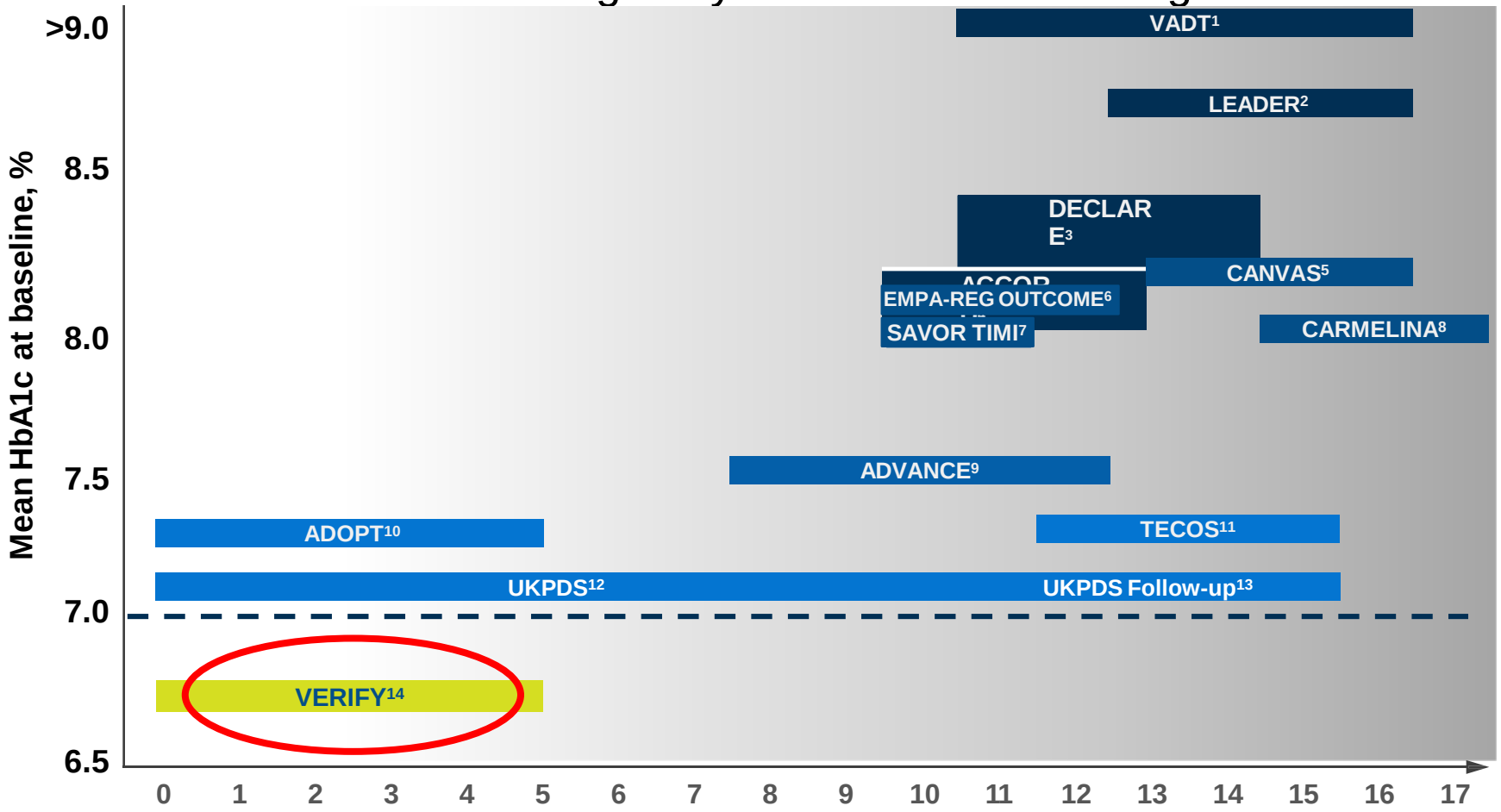
Good response

Fair response

N Engl J Med 2008; 359:1577-1589.

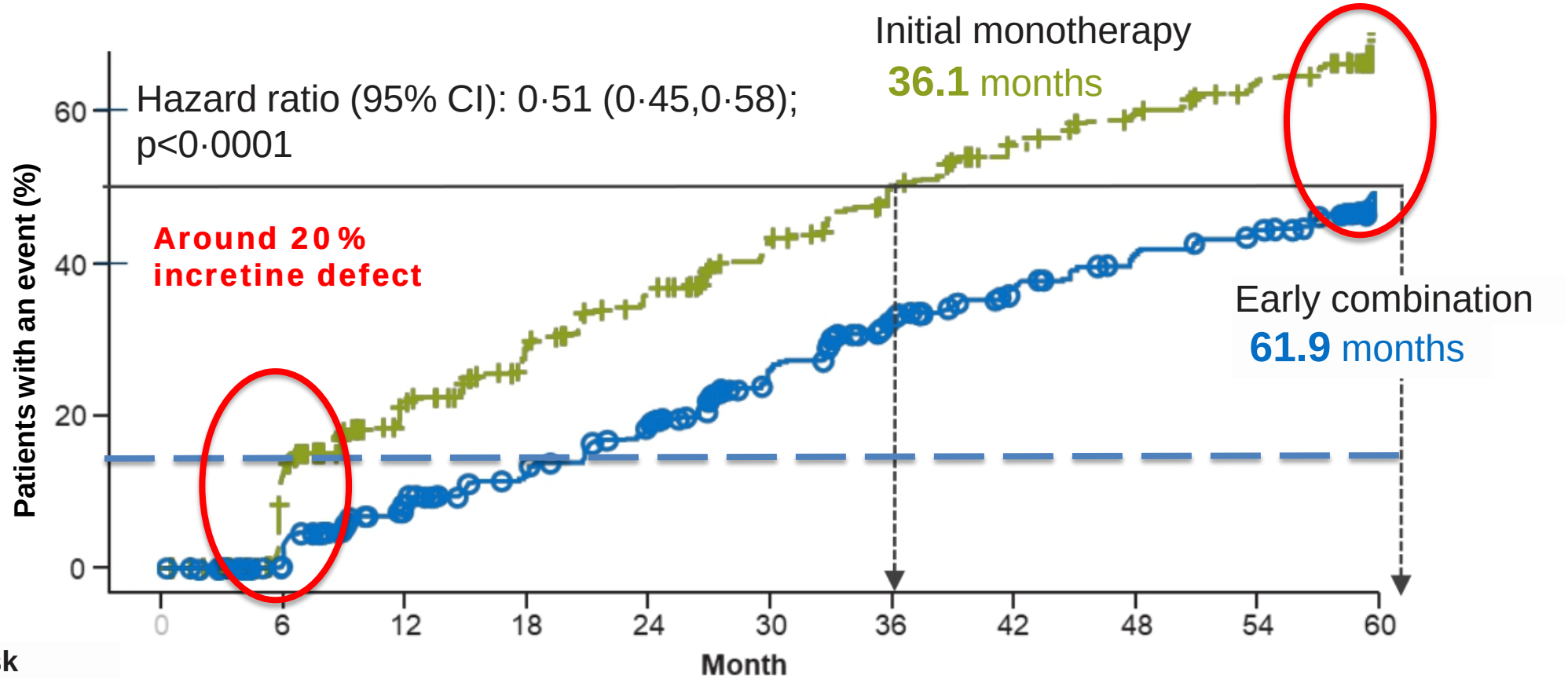
Clinical trials by diabetes progression periods

- Addressing early diabetes vs. later stage disease and



1. Duckworth W, et al. N Engl J Med. 2009;360(2):129-39. 2. Marso SP, et al. N Engl J Med 2016;375:311-22. 3. Wiviott SD, et al. N Engl J Med 2019;380:347-57. 4. ACCORD Study Group. N Engl J Med. 2008;358(24):2545-59. 5. Neal B, et al. N Engl J Med 2017;377:644-57. 6. Zinman B, et al. N Engl J Med 2015;373:2117-28. 7. Scirica BM, et al. N Engl J Med 2013;369:1317-26. 8. Rosenstock J, et al. JAMA. 2019;321(1):69-79. 9. ADVANCE Collaborative Group. N Engl J Med. 2008;358(24):2560-72. 10. Kahn SE, et al. N Engl J Med 2006;355:2427-43. 11. Green JB, et al. N Engl J Med 2015;373:232-42. 12. The UKPDS Group.Lancet. 1998;352(9131):837-53. 13. Holman RR, et al. N Engl J Med. 2008;359(15):1577-89. 14. Matthews D, et al. Diabet Med.2019;36:505-13.

Median time to initial treatment failure by strategy

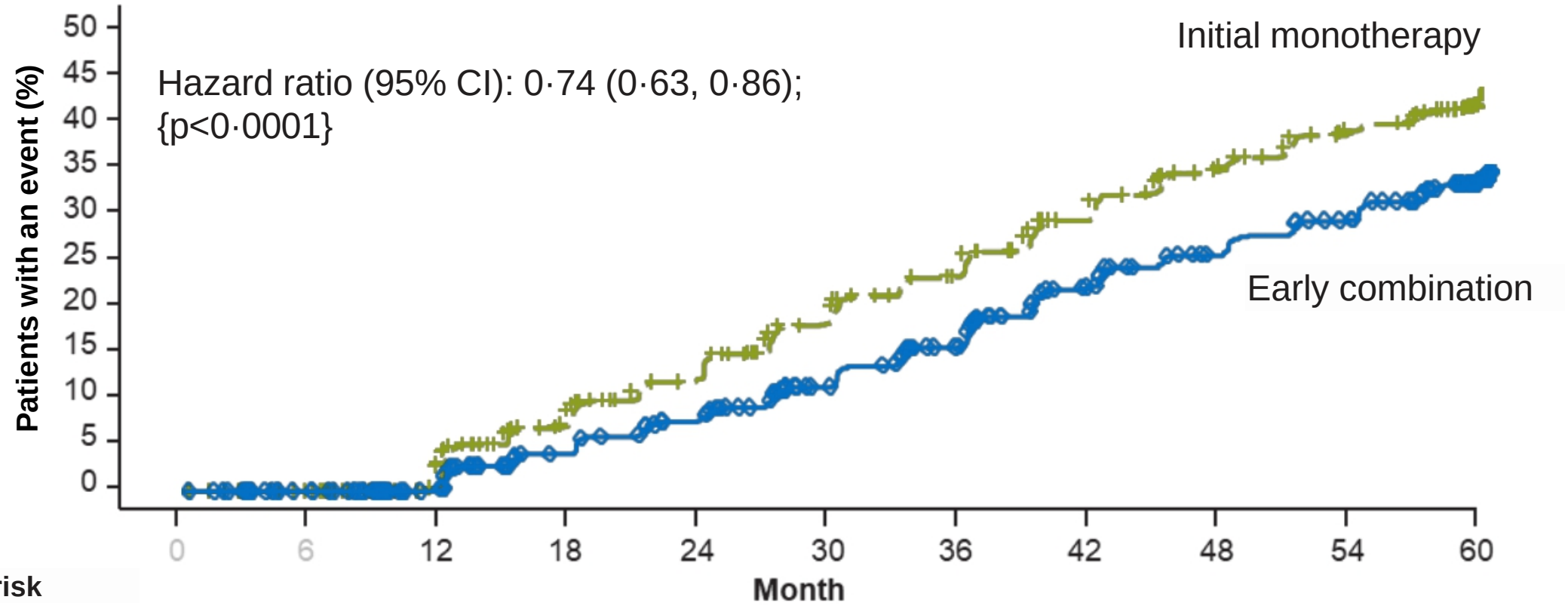


Patients at risk

Early combination	983	960	862	815	752	671	597	551	509	478	187
Initial monotherapy	989	937	733	661	576	503	434	377	337	299	108

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

Time to second failure

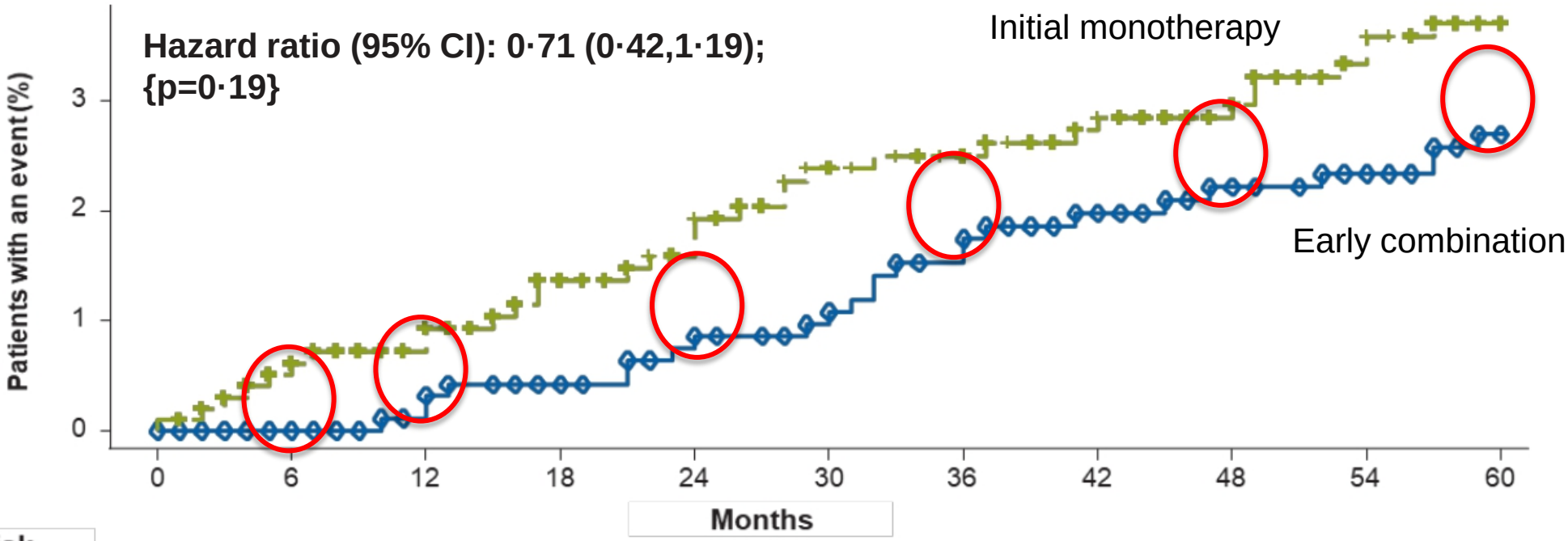


Patients at risk											
Early combination	983	966	918	870	830	768	715	644	602	565	221
Initial monotherapy	989	968	897	821	761	698	643	575	531	490	179

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

Time to first adjudicated macro-vascular event

Macro-CV event: CV death, MI , stroke and heart failure admission

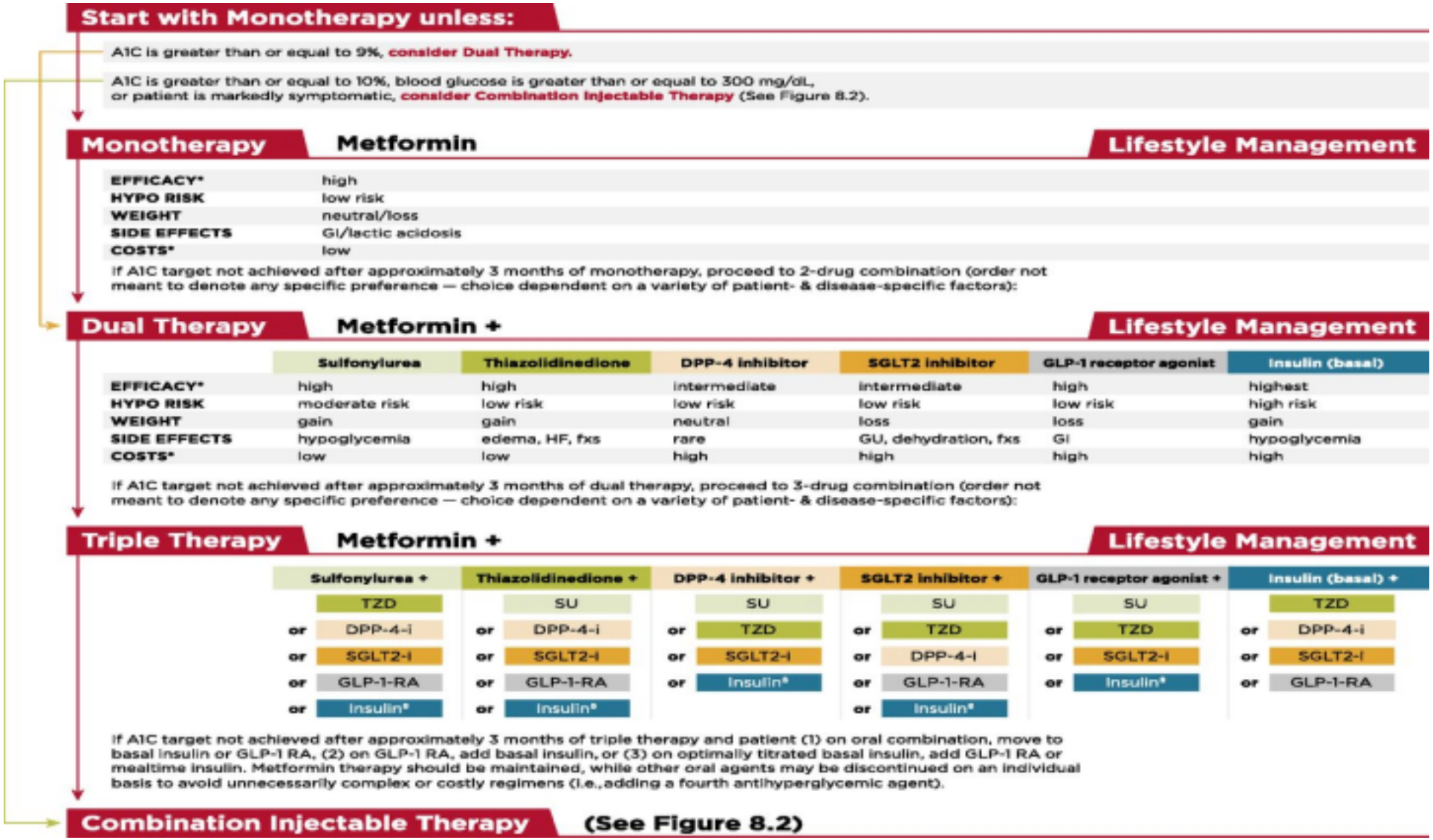


Patients at risk											
Initial monotherapy	1003	967	923	895	875	852	842	824	806	783	710
Early combination	996	970	947	924	912	890	874	846	822	809	731
Number of events											
Initial monotherapy	1	6	9	13	18	22	23	26	27	32	33
Early combination	0	0	3	4	8	10	16	18	20	21	24

Caveat! Small numbers, and wide confidence limits

Matthews DR et al. Lancet. 2019. doi.org/10.1016/S0140-6736(19)32131-2

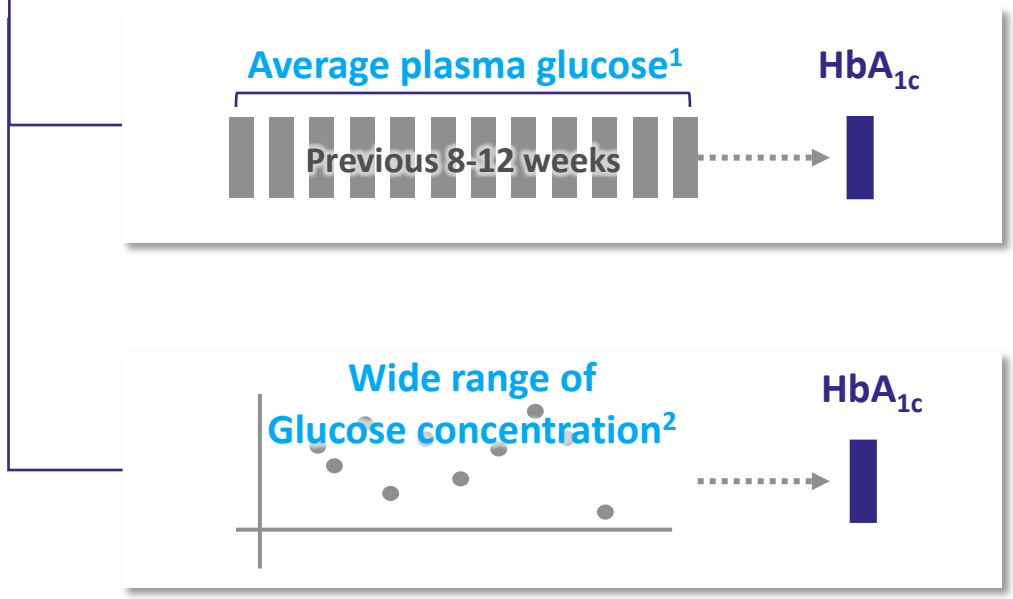
2017 ADA Guidelines are Glycemic focused treatment algorithm

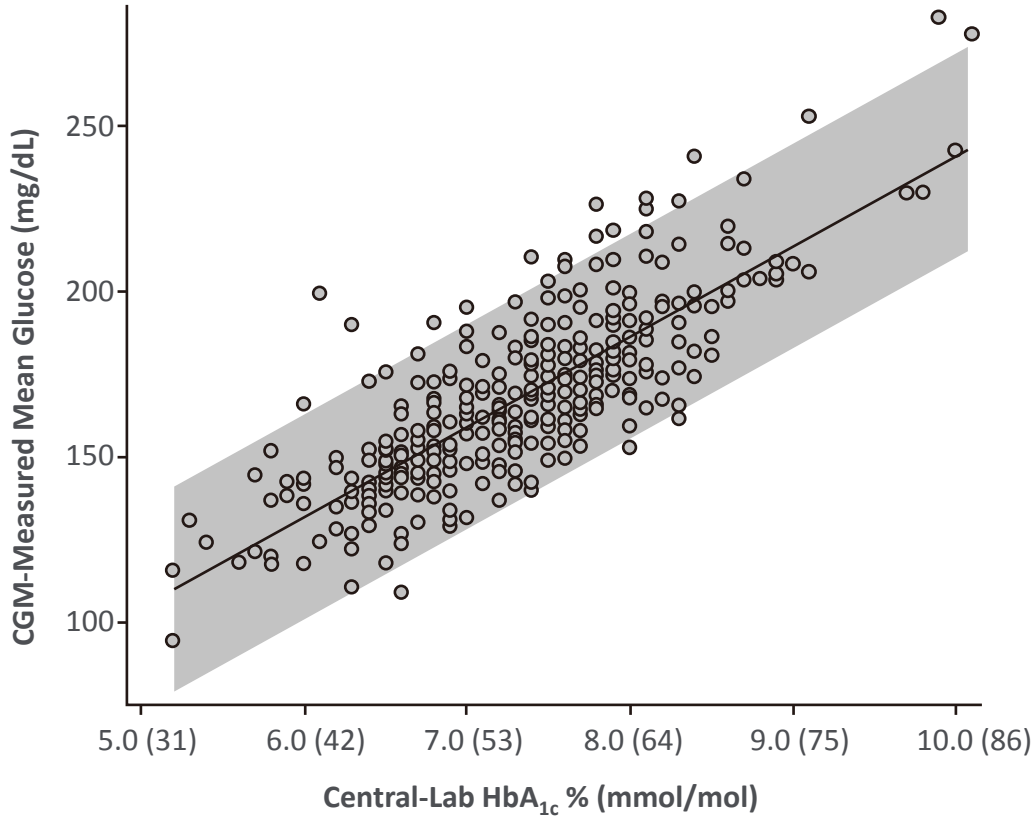


HbA_{1c} represents average plasma glucose levels

HbA_{1c}

The percentage of **circulating hemoglobin that is glycated**[1]





The shaded area represents the 95% prediction interval (analogous to an individual CI) for a patient's mean glucose concentration for a measured HbA_{1c} level

1. Chehregosha H, et al. Diabetes Ther. 2019;10(3):853–863. 2. Beck RW, et al. Diabetes Care. 2017;40(8):994–999.

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

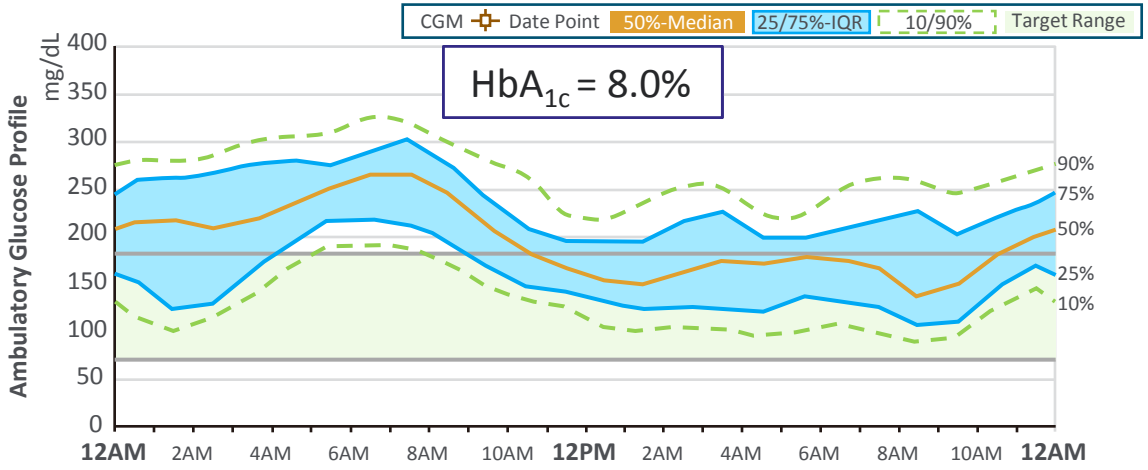
Two patients with same measured HbA_{1c} could have different continuous glucose monitoring profiles

Patient 1

Glucose Statistics

Avg Glucose mg/dL	Estimated HbA_{1c}	Serious Low	Low	In Target Range	High	Serious High	SD mg/dL	Coefficient of Variation	% Time CGM Active
195	8.4%	0.0%	0.5%	42.2%	57.3%	23.1%	64	32.9%	97.4%
88 - 116*	<6*	Below 54 mg/dL 0*	Below 70 mg/dL < 4*	70 - 180 mg/dL > 90*	Above 180 mg/dL <6*	Above 250 mg/dL 0*	10 - 26*	19.25*	
GLUCOSE EXPOSURE		GLUCOSE RANGES					GLUCOSE VARIABILITY		DATA SUFFICIENCY

*Reference ranges calculated from population without diabetes.
Curves/plots represent glucose frequency distributions by time regardless of date.

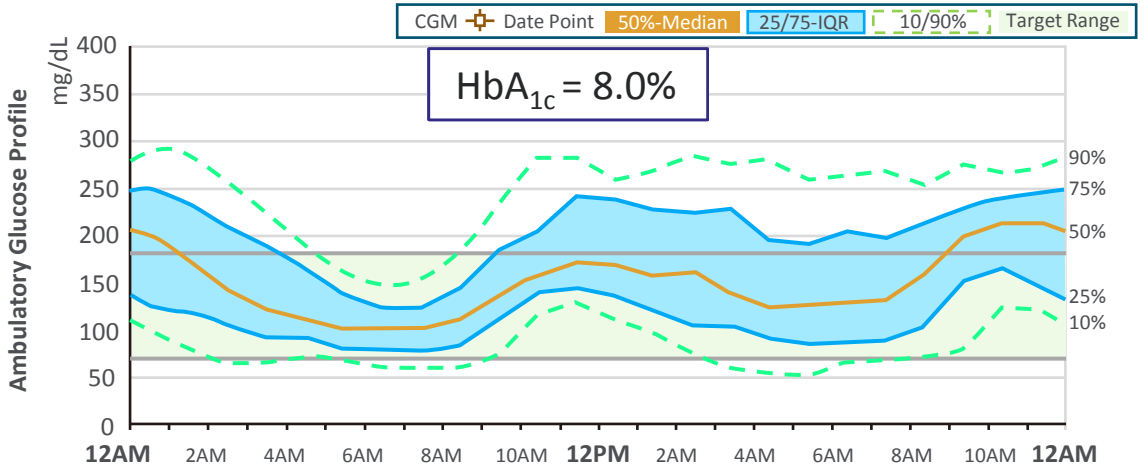


Patient 2

Glucose Statistics

Avg Glucose mg/dL	Estimated HbA_{1c}	Serious Low	Low	In Target Range	High	Serious High	SD mg/dL	Coefficient of Variation	% Time CGM Active
156	7.0%	4.4%	10.1%	54.5%	35.4%	11.3%	72	46.3%	70.6%
88 - 116*	<6*	Below 54 mg/dL 0*	Below 70 mg/dL <4*	70-180 mg/dL >90*	Above 180 mg/dL <6*	Above 250 mg/dL 0*	10 - 26*	19.25*	
GLUCOSE EXPOSURE		GLUCOSE RANGES					GLUCOSE VARIABILITY		DATA SUFFICIENCY

*Reference ranges calculated from population without diabetes.
Curves/plots represent glucose frequency distributions by time regardless of date.

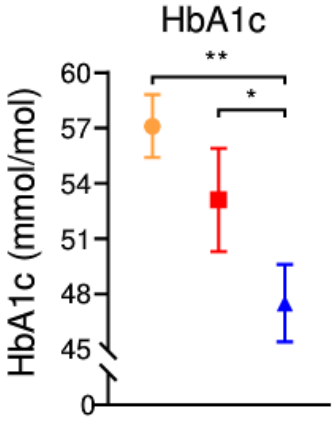


Beck RW, et al. Diabetes Care. 2017;40(8):994–999.

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

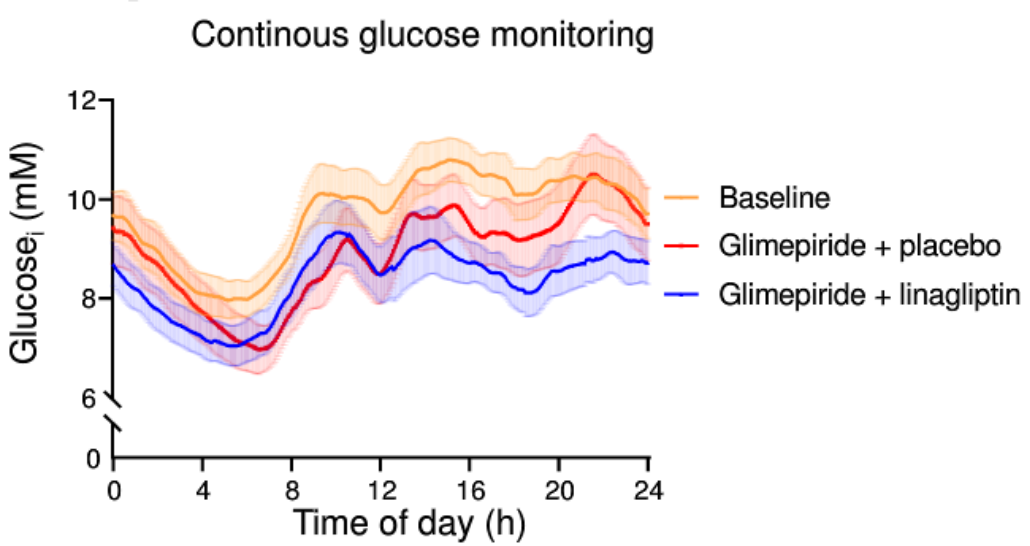
Glucose Fluctuation

Linagliptin + Glimepiride vs Glimipiride monotherapy



Baseline
Glimepiride + placebo
Glimepiride + linagliptin

Graphics: mean ± SEM
$Glucose_i$: interstitial glucose
CV: coefficient of variation
MAGE: mean amplitude of glycemic excursions
SD: standard deviation
** P<0.05, ** P<0.005*

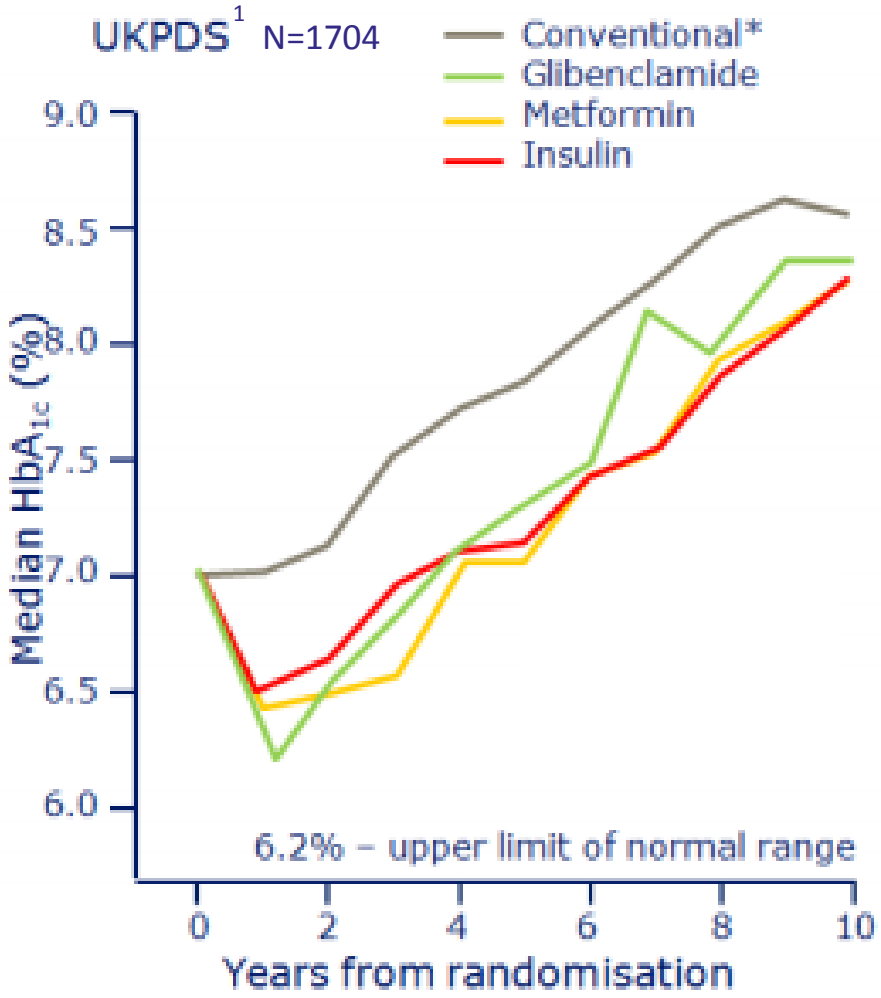


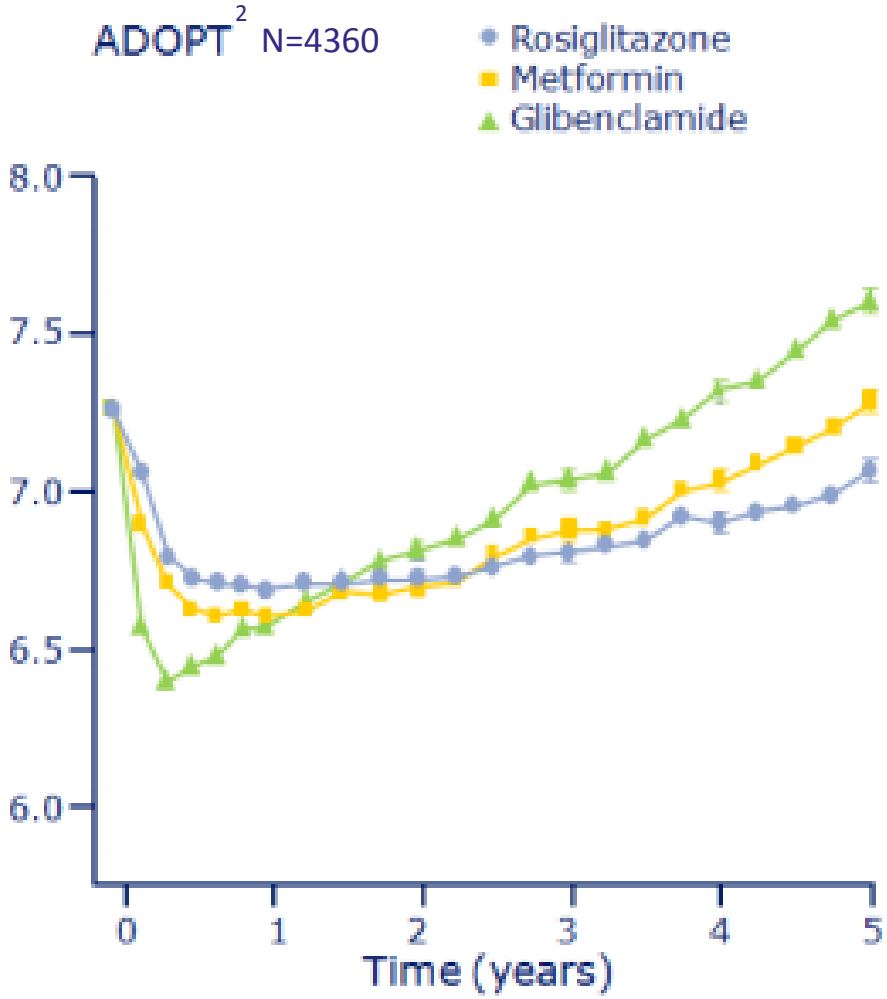
- SU可以降血糖，但無法改善患者的血糖波動。
- **加上Trajenta後，可進一步改善HbA_{1C}、血糖波動，且不增加低血糖風險。**

2020 ADA e-poster 923-P

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

Durable efficacy to different AHA





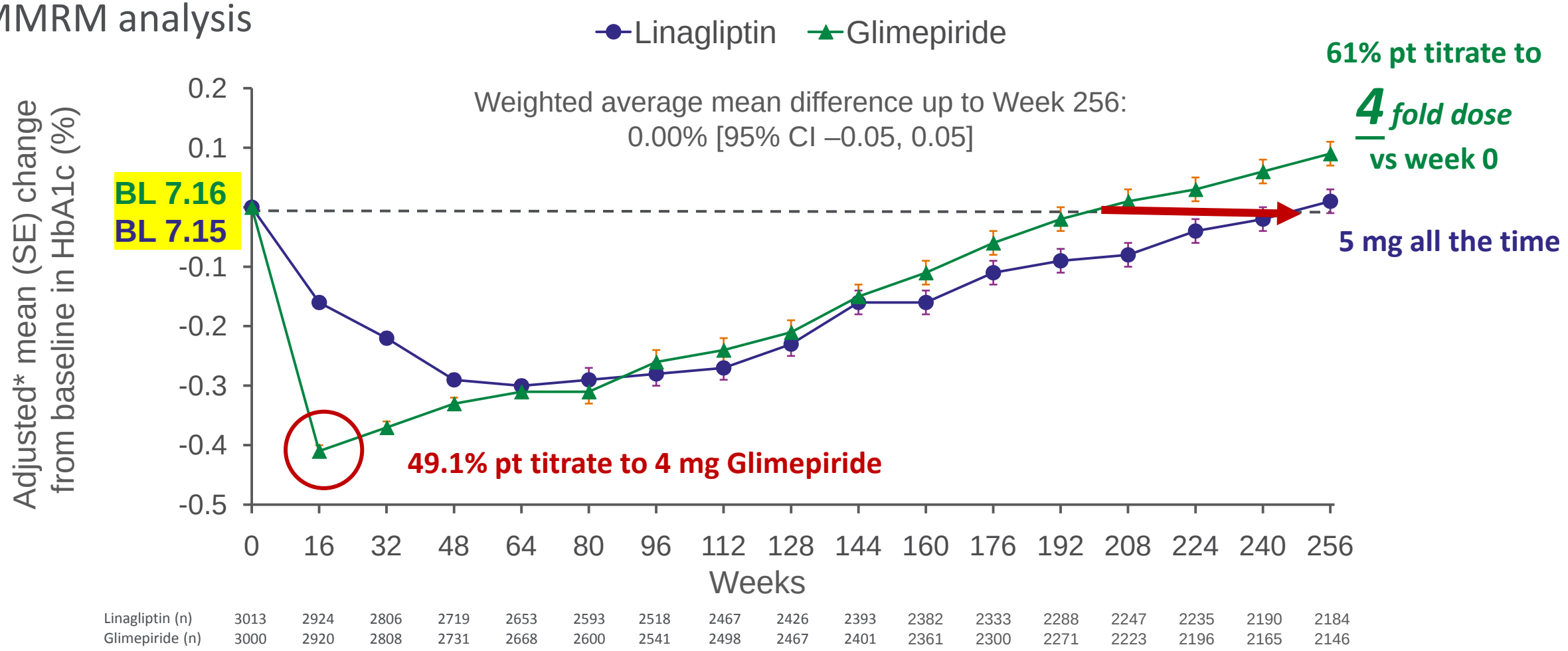
*Diet initially then sulphonylureas, insulin and/or metformin if FPG > 15 mmol/L

1.Lancet 1998:352:854-865
2.Kahn et al. NEJM 2006; 355:2427-43

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

Linagliptin demonstrated comparable and durable efficacy versus glimepiride over 6 years

MMRM analysis



Treated set without duplicates (observed cases - ALL). Comparisons are considered exploratory, as linagliptin did not meet superiority for the primary endpoint

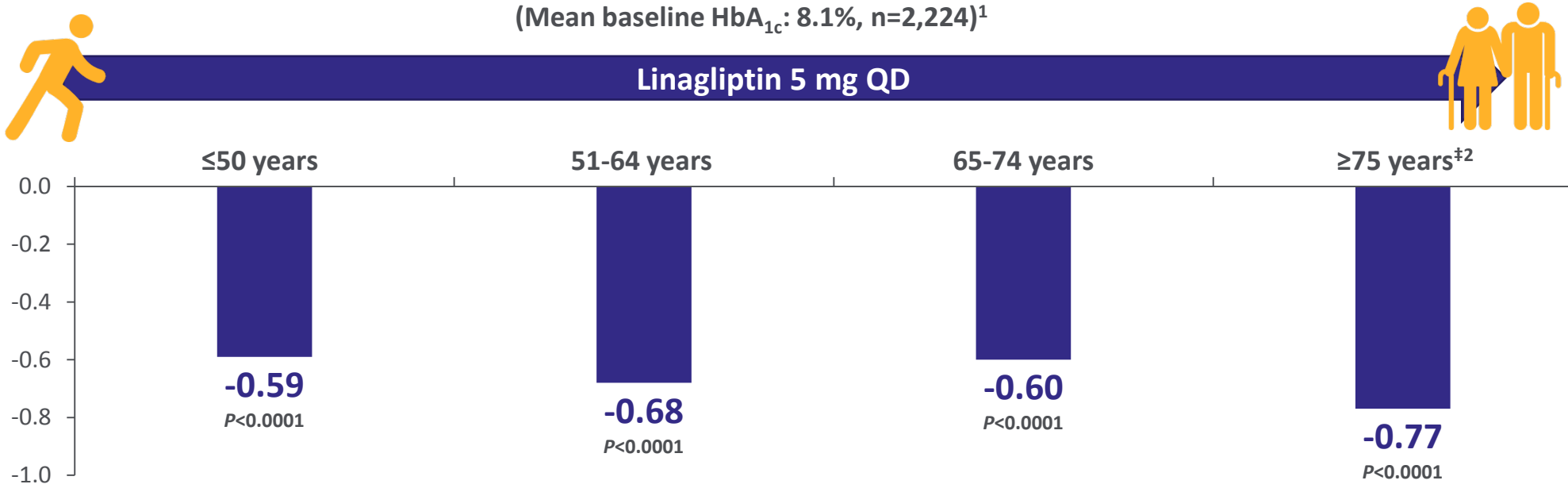
*Based on MMRM including treatment, week, week by treatment interaction, continuous baseline HbA1c and baseline HbA1c by week interaction. BL, baseline; HbA1c, glycated haemoglobin; MMRM, mixed-model repeated measures. Rosenstock J *et al. ADA 2019*

Trajenta® (linagliptin) 5mg tablets

TrajentaDuo® (linagliptin/metformin HCl)

The significantly efficacy of linagliptin was demonstrated in every age group

Adjusted mean HbA_{1c} change from baseline at 24 week by age, placebo-corrected*†
(Mean baseline HbA_{1c}: 8.1%, n=2,224)[1]



	≤50 years		51-64 years		65-74 years		≥75 years‡2	
	Lina	Pbo	Lina	Pbo	Lina	Pbo	Lina	Pbo
N	388	162	834	300	342	123	60	15
Mean baseline HbA_{1c} (%)	8.1	8.2	8.1	8.0	8.0	8.0	8.0	7.9

* Pre-specified subgroup analysis on pooled data from 3 pivotal Phase III, randomized, placebo-controlled trials: treatment in monotherapy, add-on to metformin, and add-on to metformin plus sulfonylurea. *p*-values for between-group differences (vs. placebo).
† ANCOVA-adjusted for continuous HbA_{1c}, BMI group, washout phase, treatment group, study, age group, sex, time since diagnosis of diabetes, race, and age . treatment or type 2 diabetes. treatment interactions.
‡ Linagliptin should be used with caution when treating patients aged > 80 years, as experience in this patient group is limited.

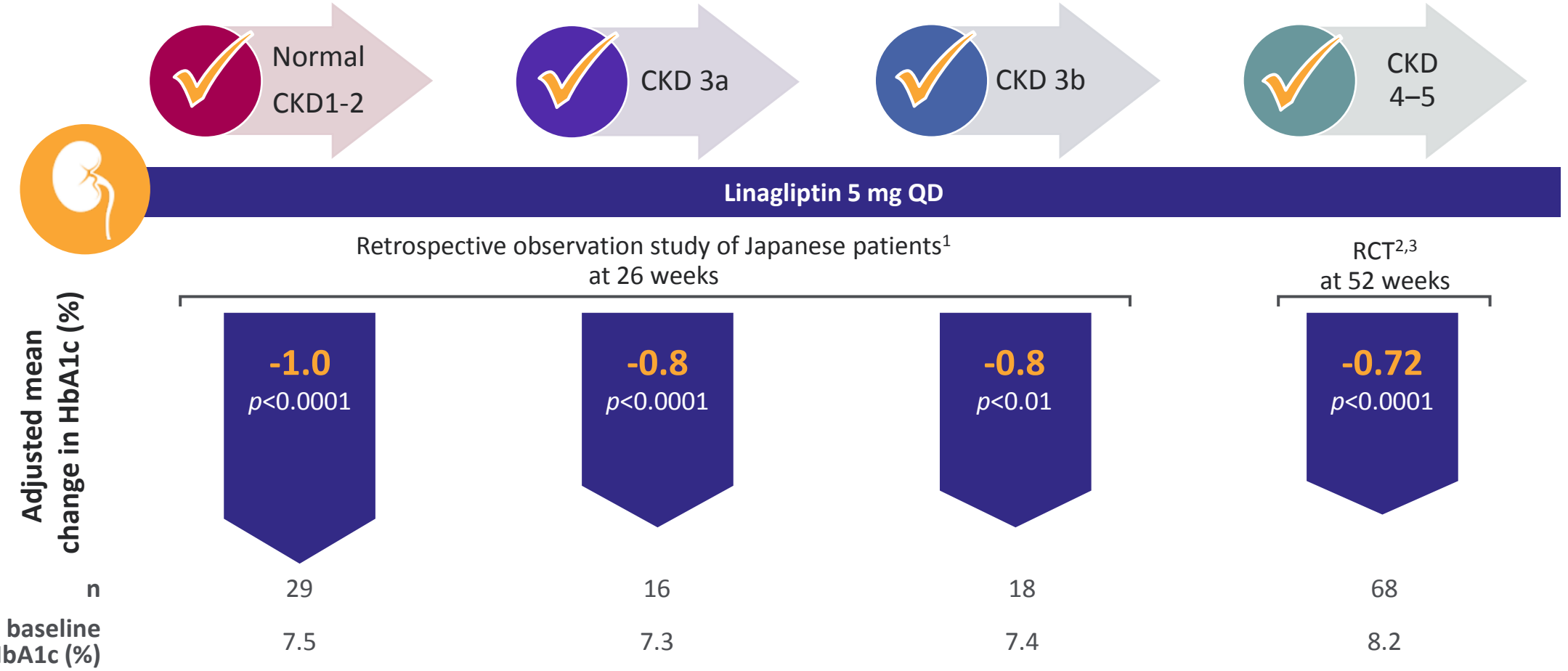
HbA_{1c}: glycated hemoglobin; Lina: linagliptin; Pbo: placebo; QD: once-daily

1. Patel S, et al. European Association for the Study of Diabetes 2011, 12-16 September 2011, Lisbon, Portugal; Poster P832; **2.** TRAJENTA® Summary of Product Characteristics. June 2017.

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

The efficacy and safety of linagliptin remain consistent across all stages of kidney function in Japanese and overall population

Adjusted mean HbA1c change from baseline versus placebo by degree of kidney function

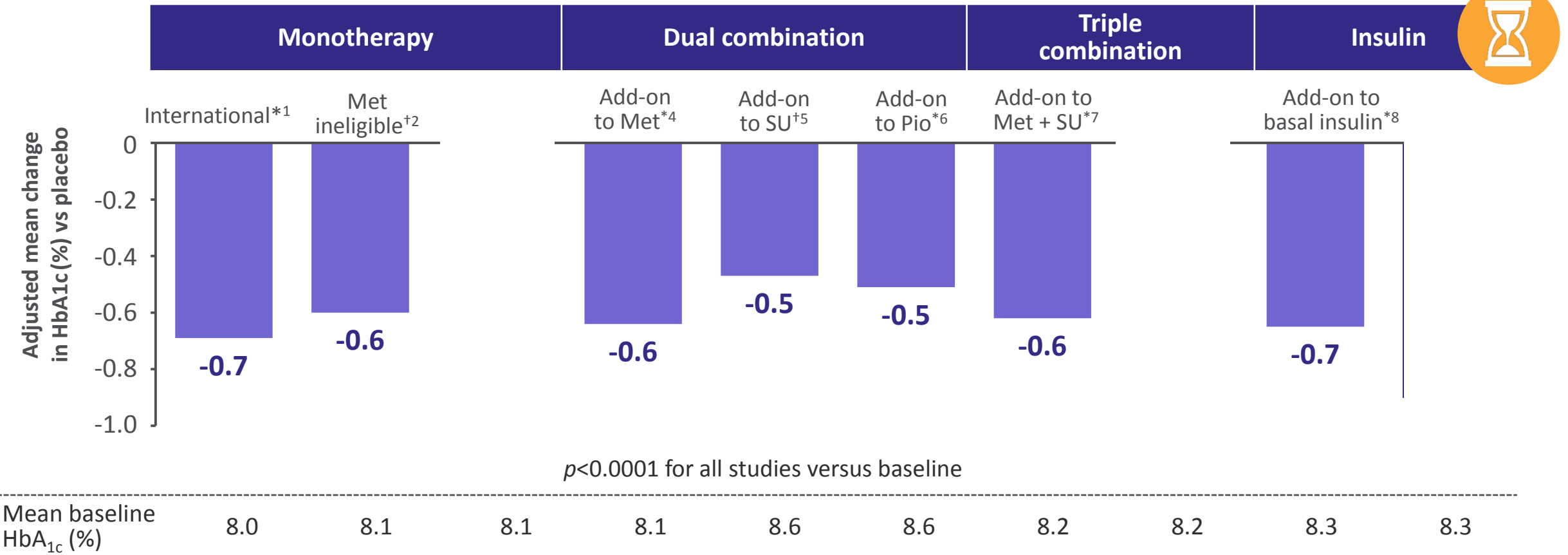


1. Ito H, et al. Expert Opin. Pharmacother. 2015:16(3); 289-296; 2. McGill JB *et al. Diabetes Care* 2013;36:237; 3. Boehringer Ingelheim and Eli Lilly. Trajenta® (linagliptin) Prescribing Information. 2017

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

Linagliptin demonstrates efficacy across different background therapy and disease duration

Adjusted mean HbA_{1c} change from baseline, placebo-corrected



p<0.0001 for all studies versus baseline

Mean baseline HbA_{1c} (%)	8.0	8.1	8.1	8.1	8.6	8.6	8.2	8.2	8.3	8.3

Treatment duration: *24 weeks. †18 weeks. ‡12 weeks

HbA1c, glycated haemoglobin; Met, metformin; Pio, pioglitazone; SU, sulphonylurea

1. Del Prato S *et al*. *Diabetes Obes Metab* 2011;13:258; 2. Barnett AH *et al*. *Diabetes Obes Metab* 2012;14:1145; 3. Kawamori R *et al*. *Diabetes Obes Metab* 2012;14:348; 4. Taskinen MR *et al*. *Diabetes Obes Metab* 2011;13:65; 5. Lewin AJ *et al*. *Clin Ther* 2012;34:1909; 6. Gomis R *et al*. *Diabetes Obes Metab* 2011;13:653; 7. Owens DR *et al*. *Diabetic Med* 2011;28:1352; 8. Yki-Järvinen H *et al*. *Diabetes Care* 2013;36:3875; 9. Diabetes Care. 2013 Dec; 36(12): 3875–3881. 10.

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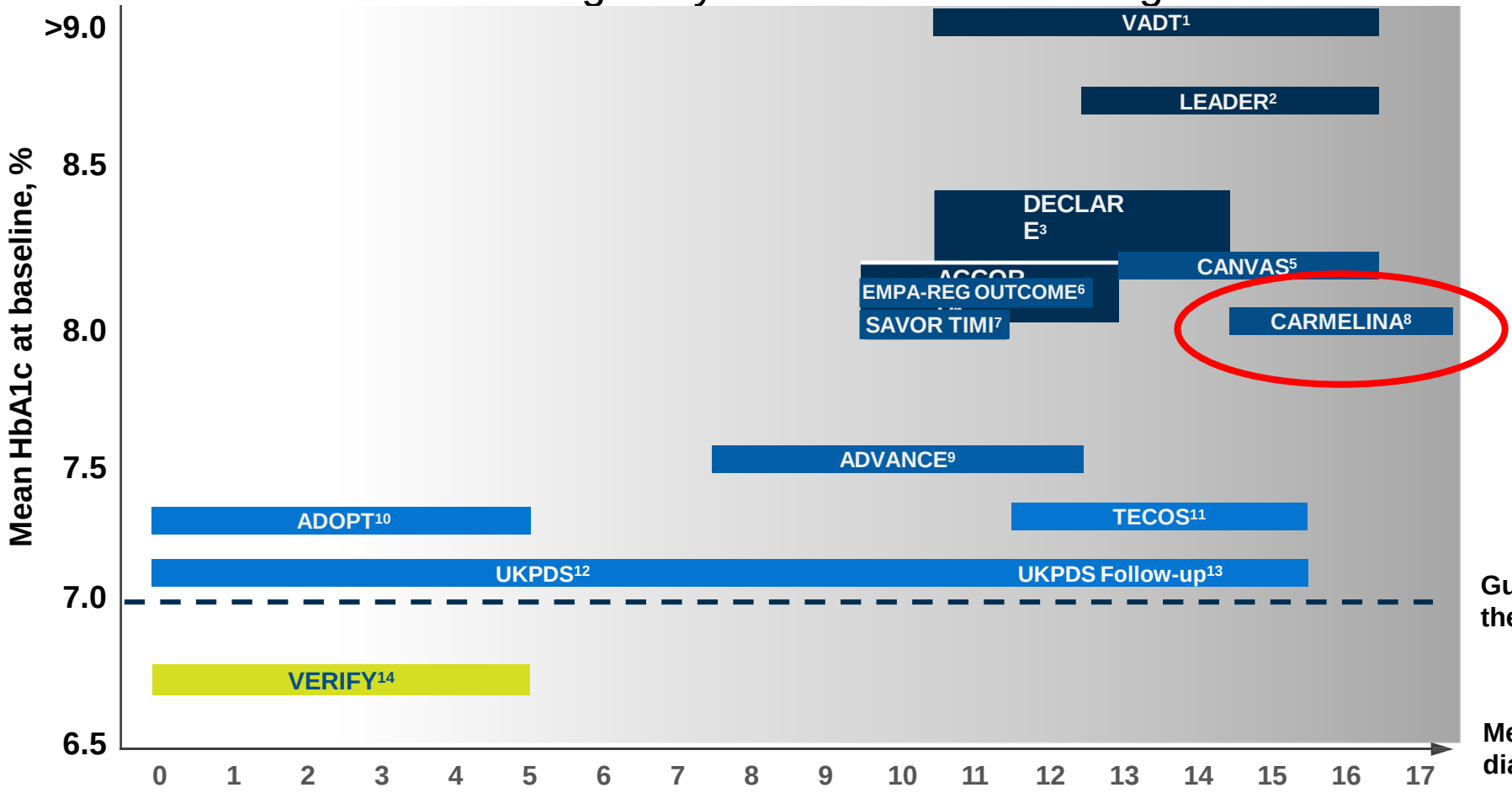
Clinical trials by diabetes progression periods

- Addressing early diabetes vs. later stage disease and



1. Duckworth W, et al. N Engl J Med. 2009;360(2):129-39. 2. Marso SP, et al. N Engl J Med 2016;375:311-22. 3. Wiviott SD, et al. N Engl J Med 2019;380:347-57. 4. ACCORD Study Group. N Engl J Med. 2008;358(24):2545-59. 5. Neal B, et al. N Engl J Med 2017;377:644-57. 6. Zinman B, et al. N Engl J Med 2015;373:2117-28. 7. Scirica BM, et al. N Engl J Med 2013;369:1317-26. 8. Rosenstock J, et al. JAMA. 2019;321(1):69-79. 9. ADVANCE Collaborative Group. N Engl J Med. 2008;358(24):2560-72. 10. Kahn SE, et al. N Engl J Med 2006;355:2427-43. 11. Green JB, et al. N Engl J Med 2015;373:232-42. 12. The UKPDS Group.Lancet. 1998;352(9131):837-53. 13. Holman RR, et al. N Engl J Med. 2008;359(15):1577-89. 14. Matthews D, et al. Diabet Med.2019;36:505-13.

More Evidence, More Confidence- CARMELINA ® & CAROLINA ®

	SAVOR-TIMI 53[1]	EXAMINE[2]	TECOS[3]	CARMELINA®[4,5]	CAROLINA®[6,7]
DPP-4 inhibitor and comparator	Saxagliptin vs placebo	Alogliptin vs placebo	Sitagliptin vs placebo	Linagliptin vs placebo	Linagliptin **vs glimepiride**
Date results published	2013	2013	2015	2018	2019
No. of patients	16,492	5380	14,671	6,979	6,033
Key inclusion criteria	Pre-existing CVD or CV risk factors	History of ACS	Pre-existing CVD	High CV risk (established CV disease and/or CKD)	Pre-existing CVD or CV risk factors
Primary endpoint	3P-MACE	3P-MACE	4P-MACE	3P-MACE	3P-MACE
Key secondary endpoint	3P-MACE plus HHF, coronary revascularisation or unstable angina	3P-MACE or urgent revascularisation due to unstable angina ≤24 hours after hospital admission	3P-MACE	**Composite renal endpoint** (renal death, ESRD or sustained decrease of ≥40% in eGFR)	4P-MACE
Median follow-up	2.1 years	18 months	3.0 years	2.2 years	6.3 years

3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HHF, hospitalisation for heart failure; NA, not available

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Green JB *et al. N Engl J Med* 2015;373:232; 4. ClinicalTrials.gov NCT01243424; 5. CARMELINA® CTP. Doc No: c02155180-06. Data on file; 6. CAROLINA® CTP. Doc No: U10-2169-05. Data on file; 7. Marx N *et al. Diab Vasc Dis Res* 2015;12:164

Trajenta® (linagliptin) 5mg tablets

TrajentaDuo® (linagliptin/metformin HCl)

Together, CARMELINA® and CAROLINA® further expand the linagliptin experience with >13,000 patients assessed in clinical trials

CARMELINA®[1]

N=6979

Patients with **established CV disease and/or CKD**

HbA_{1c} 6.5–10%

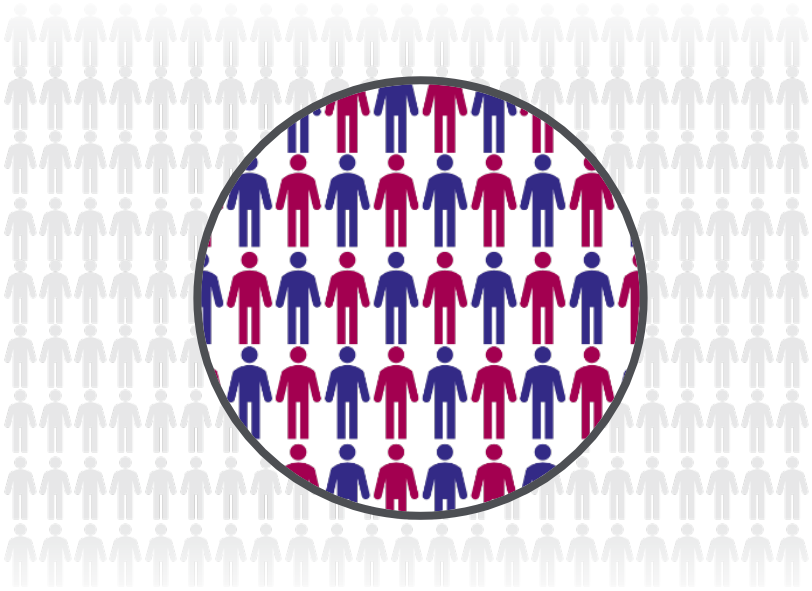
CAROLINA®[2]

N=6033

Patients **with relatively early T2D at increased CV risk**

HbA_{1c} 6.5–8.5%

A comprehensive CVOT programme demonstrating the long-term safety profile of linagliptin



for a broad range of patients

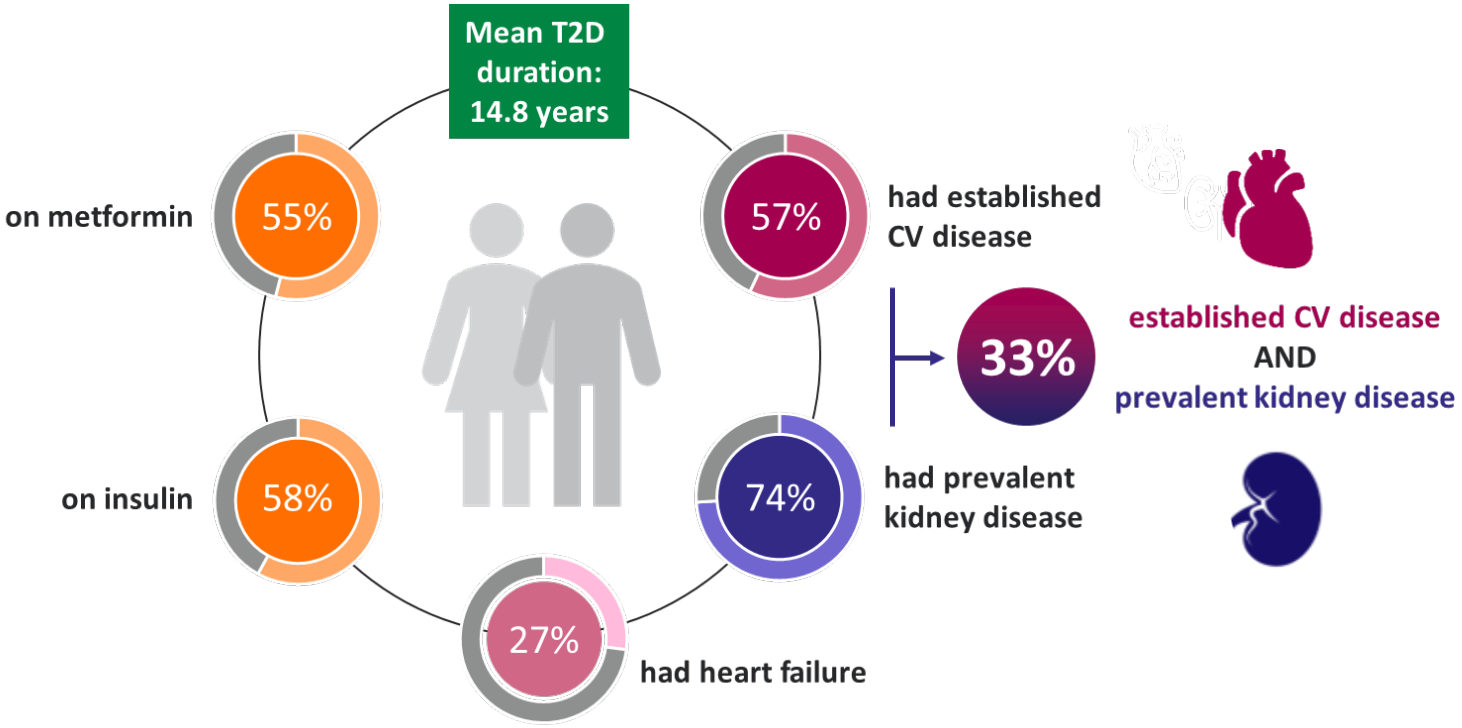
1. Rosenstock J *et al. JAMA* 2019;321:69; 2 Rosenstock J *et al. JAMA* 2019; doi:10.1001/jama.2019.13772

Trajenta® (linagliptin) 5mg tablets

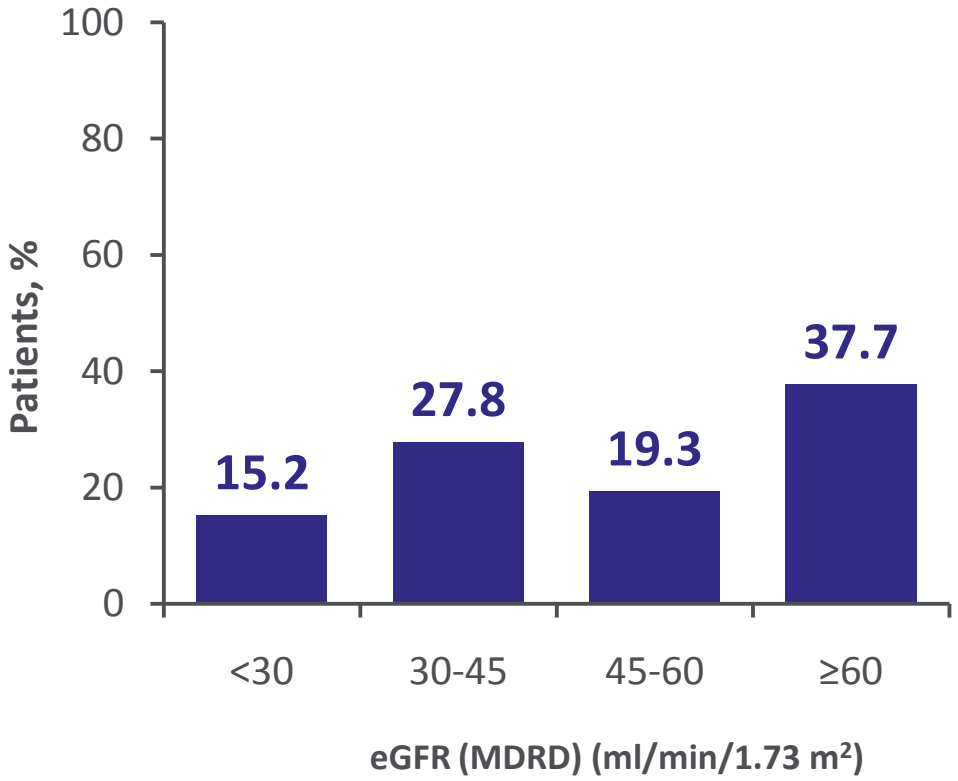
TrajentaDuo® (linagliptin/metformin HCl)

CARMELINA® trial included patients typically seen in clinical practice

Patients had established CV and/or kidney disease



Broad kidney function at baseline[1]



Rosenstock J *et al. JAMA* 2019;321:69

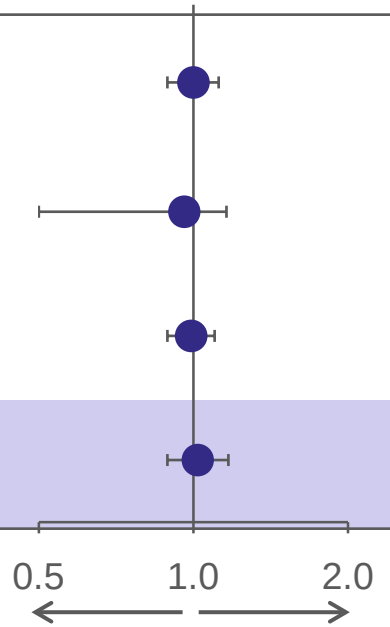
Trajenta® (linagliptin) 5mg tablets

TrajentaDuo® (linagliptin/metformin HCl)

With CARMELINA®, linagliptin shows a reassuring CV safety profile

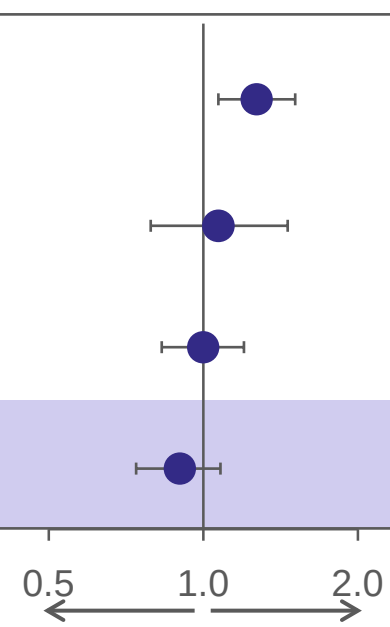
3P-MACE

	HR (95% CI)	HR (95% CI)	*p*-value
SAVOR-TIMI 53[1]	1.00 (0.89, 1.12)		0.99
EXAMINE[2,3]	0.96 (n/a, 1.16)		0.32
TECOS[4]	0.99 (0.89, 1.10)		0.84
CARMELINA®[5]	1.02 (0.89, 1.17)		0.74



Hospitalization for HF

	HR (95% CI)	HR (95% CI)	*p*-value
	1.27 (1.07, 1.51)		0.007
	1.07 (0.79, 1.46)		0.657
	1.00 (0.83, 1.20)		0.98
	0.90 (0.74, 1.08)		0.26



Direct comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

3P-MACE, 3-point major adverse CV events (CV death, non-fatal MI, non-fatal stroke); CV, cardiovascular; HF, heart failure

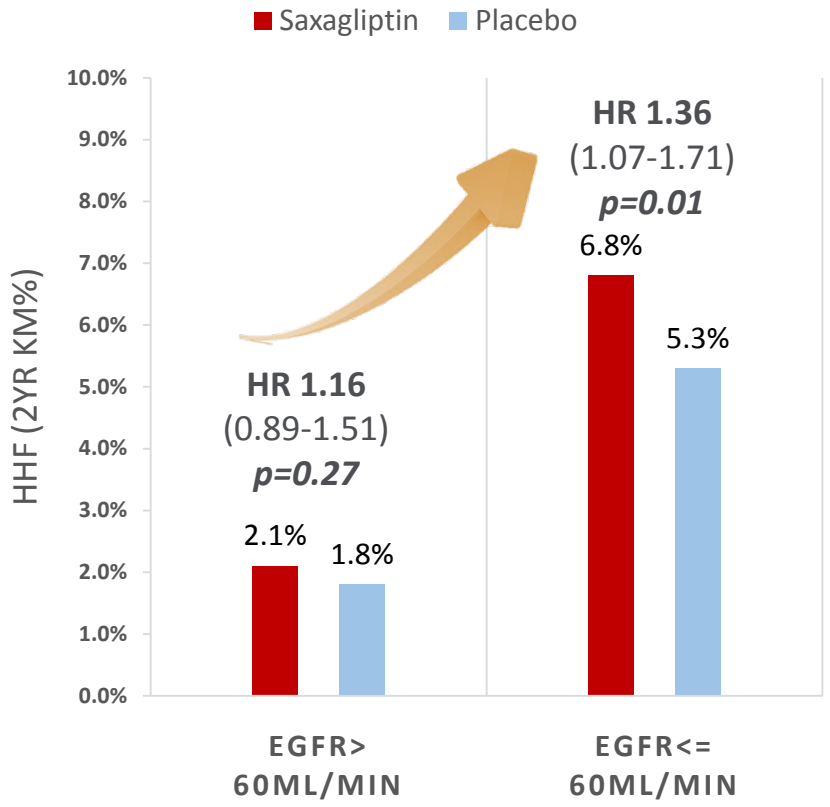
1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Zannad F *et al. Lancet* 2015;385;2067-76; 4. Green JB *et al. N Engl J Med* 2015;373:232; 5. Rosenstock *J et al. JAMA* 2018; doi: 10.1001/jama.2018.18269

Trajenta® (linagliptin) 5mg tablets

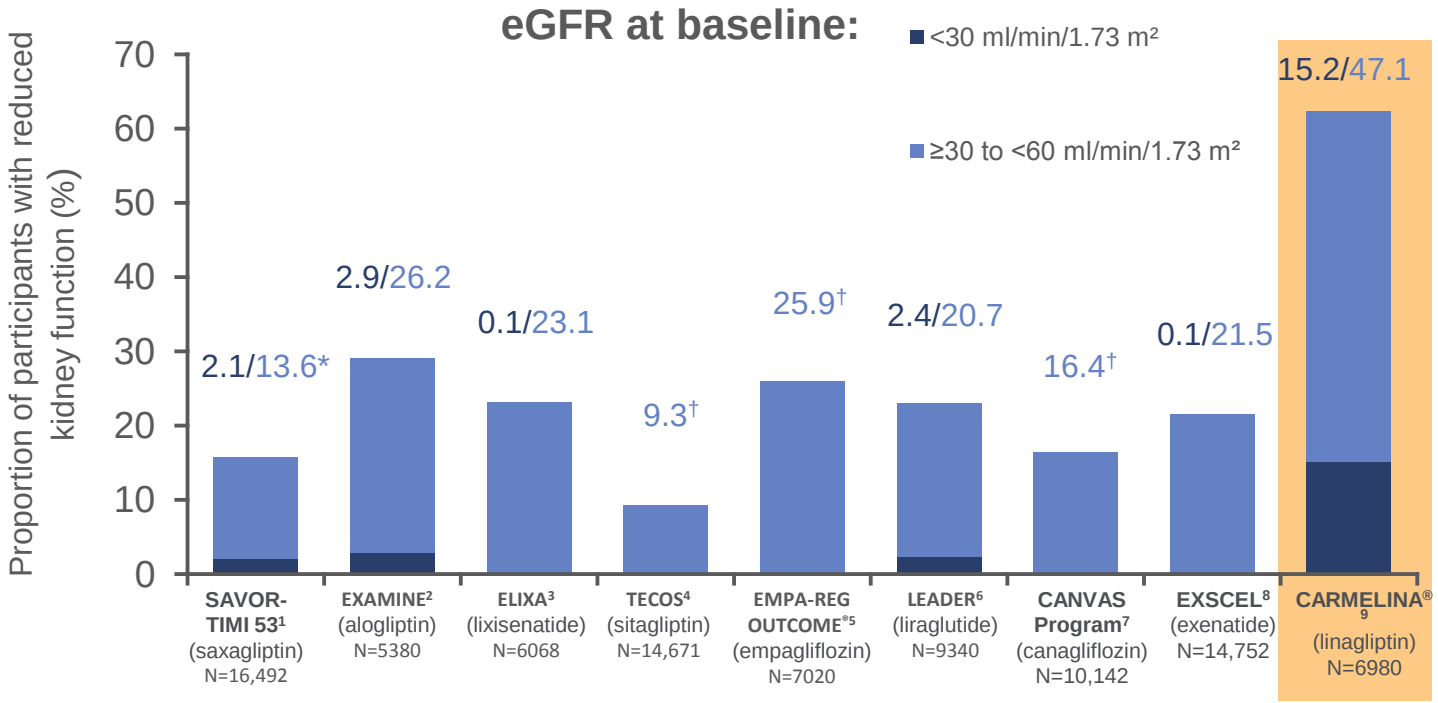
TrajentaDuo® (linagliptin/metformin HCl)

Proportion of CVOT populations with reduced kidney function at baseline (eGFR <60 ml/min/1.73 m²)

- In SAVOR study, with decrease of eGFR, ***the risk of HHF will significantly increase.***



- In CARMELINA®, 62.3% of patients had an eGFR <60 ml/min/1.73 m², compared with 9.3% to 29.1% of patients in other CVOTs[1-9]



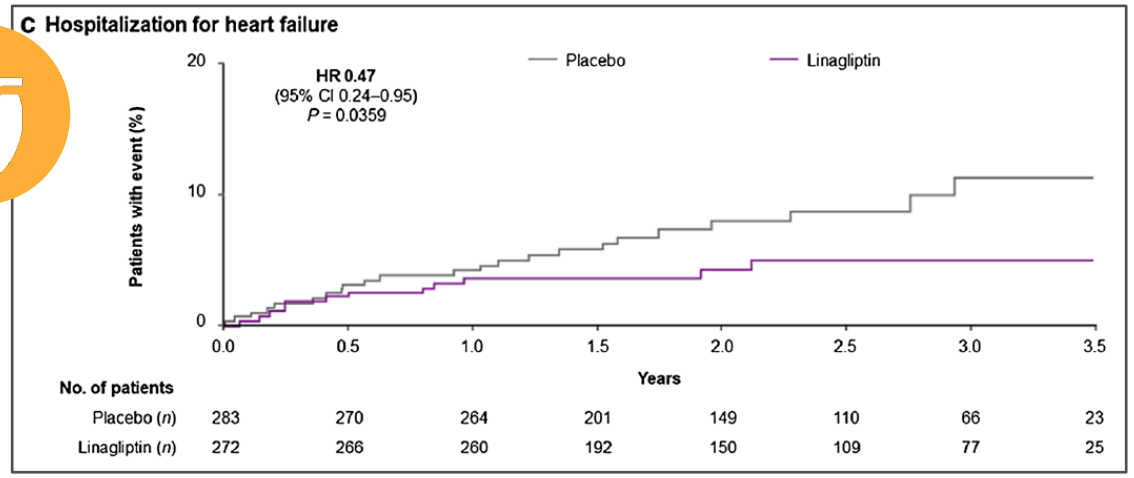
*eGFR ≥30 to <50 ml/min/1.73 m²; †Trial excluded patients with eGFR <30 ml/min/1.73 m²
CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327 (supplementary appendix); 3. Pfeffer MA *et al. N Engl J Med* 2015;373:2247 (supplementary appendix); 4. Green JB *et al. N Engl J Med* 2015;373:232 (supplementary appendix); 5. Zinman B *et al. N Engl J Med* 2015;373:2117 (supplementary appendix); 6. Marso SP *et al. N Engl J Med* 2016;375:311; 7. Neal B *et al. Diabetes Obes Metabol* 2017;19:926; 8. Holman RR *et al. N Engl J Med* 2017;377:1228

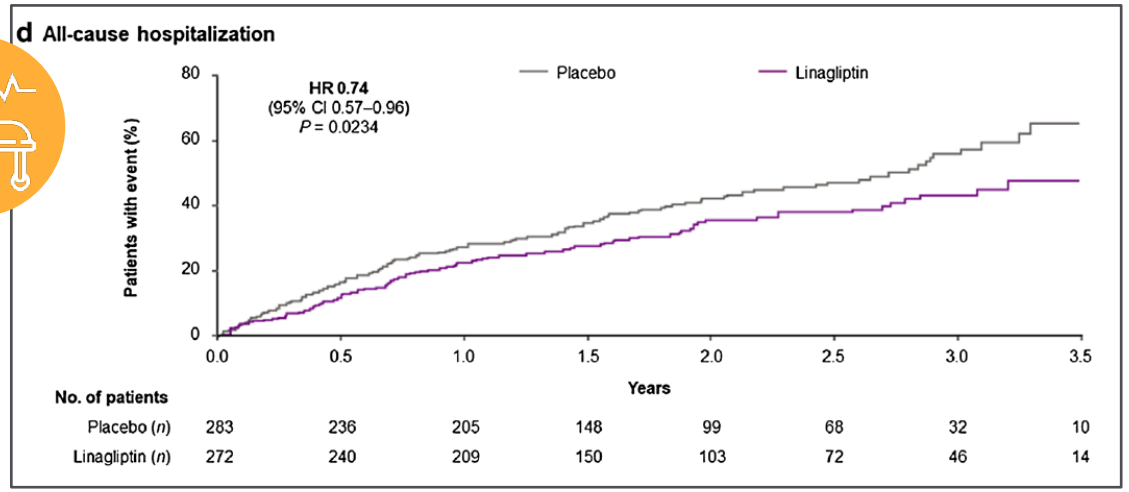
Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

CARMELINA Asian subgroup

- Time to first occurrence of hospitalisation for heart failure – Asian population (N=555)



53% risk reduction of **hospitalization for heat failure**



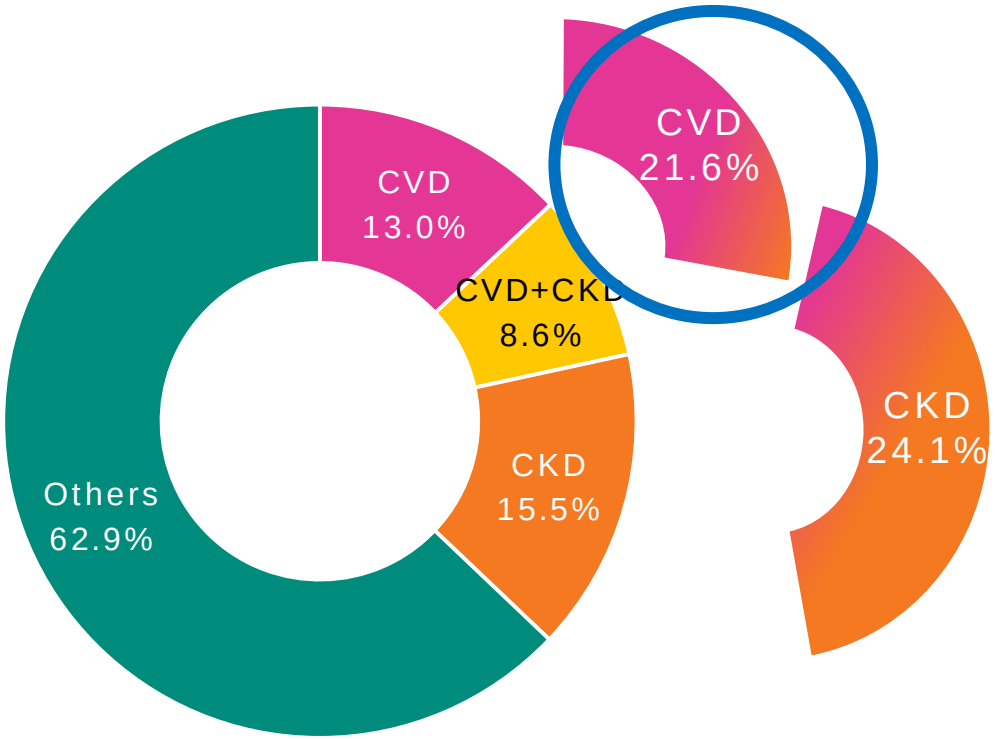
26% risk reduction of **all-cause hospitalization**

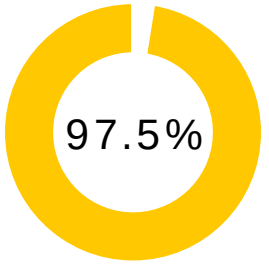
McGuire DK *et al. Circulation* 2018; doi:10.1161/CIRCULATIONAHA.118.038352

Trajenta® (linagliptin) 5mg tablets
TrajentaDuo® (linagliptin/metformin HCl)

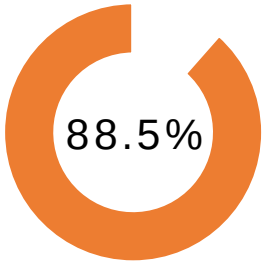
Cross-sectional—有心肾共病

A retrospective study of T2DM patients via Q-EMR from 2014 to 2015





had ≥ 1 comorbid condition



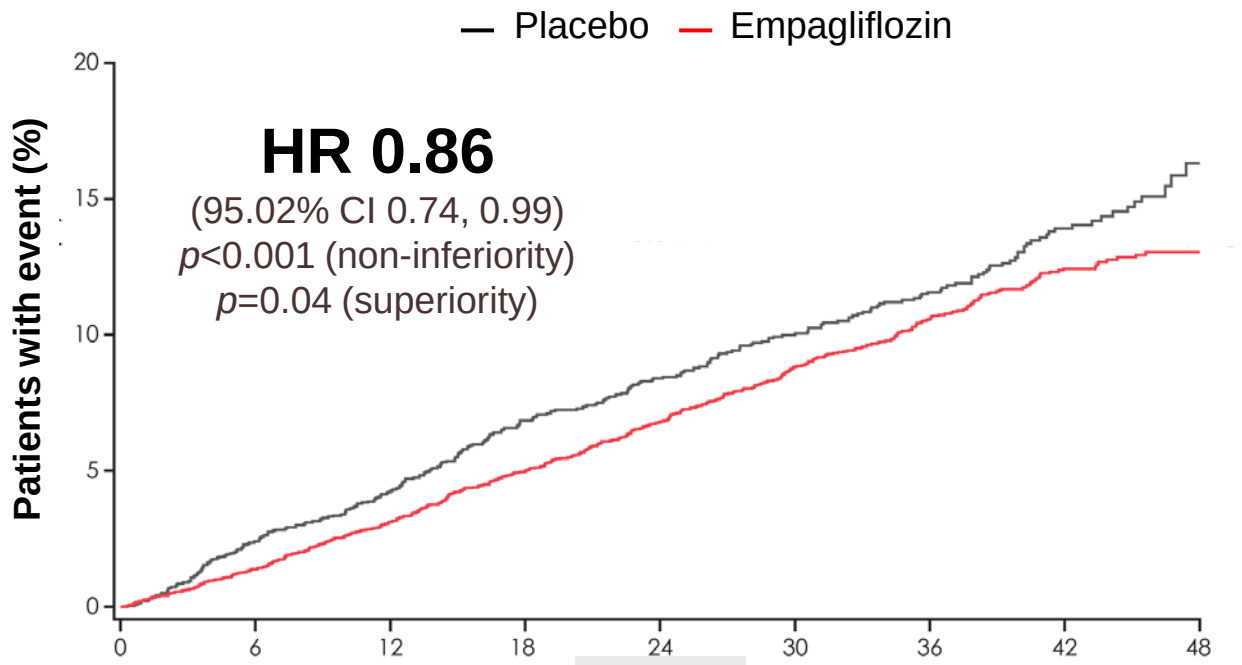
had ≥ 2 comorbid condition

Q-EMR, Quintiles Electronic Medical Record (EMR) research database

Iglay K, et al. *Curr Med Res Opin* 2016 Jul;32(7):1243-52.

2015 EMPA-REG OUTCOME
是第一個證實在ASCVD族群中，能夠降低主要心血管事件的 SGLT2i

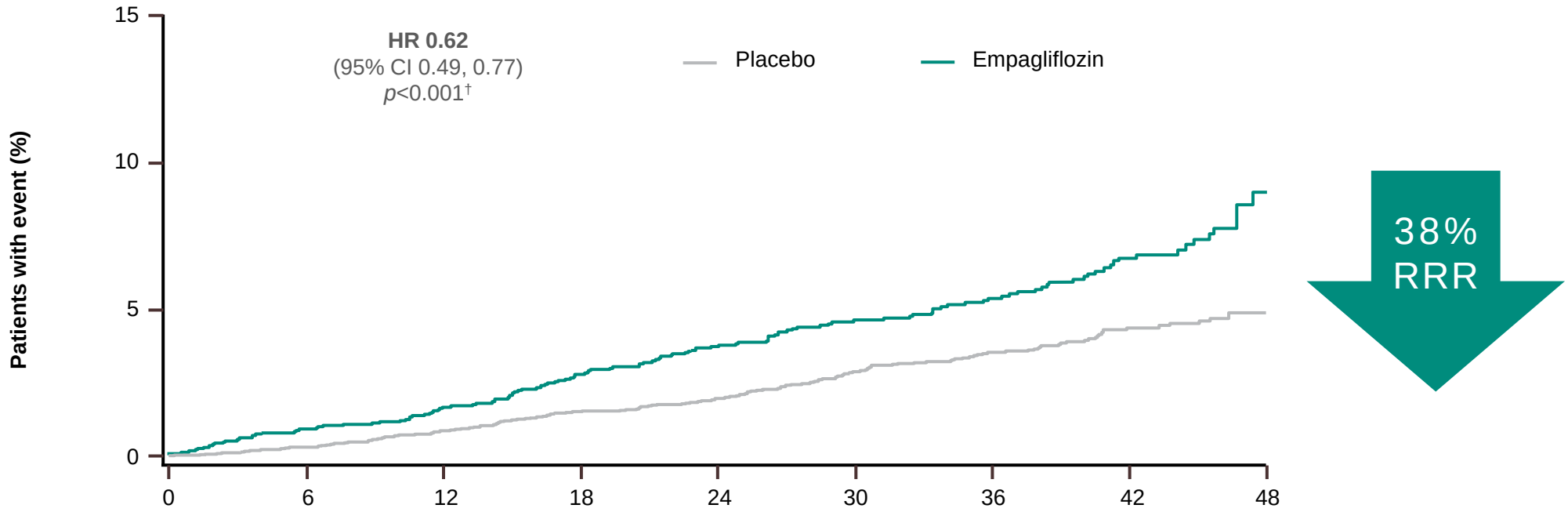
Empagliflozin demonstrated a 14% relative risk reduction in 3P-MACE on top of standard of care



No. at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

RRR for 3P-MACE: 14%; ARR for 3P-MACE: 1.6%. Absolute rates 10.5% (empagliflozin) vs 12.1% (placebo). Cumulative incidence function
3P-MACE, 3-point major adverse cardiovascular events; ARR, absolute risk reduction; CV, cardiovascular; MI, myocardial infarction; RRR, relative risk reduction
Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

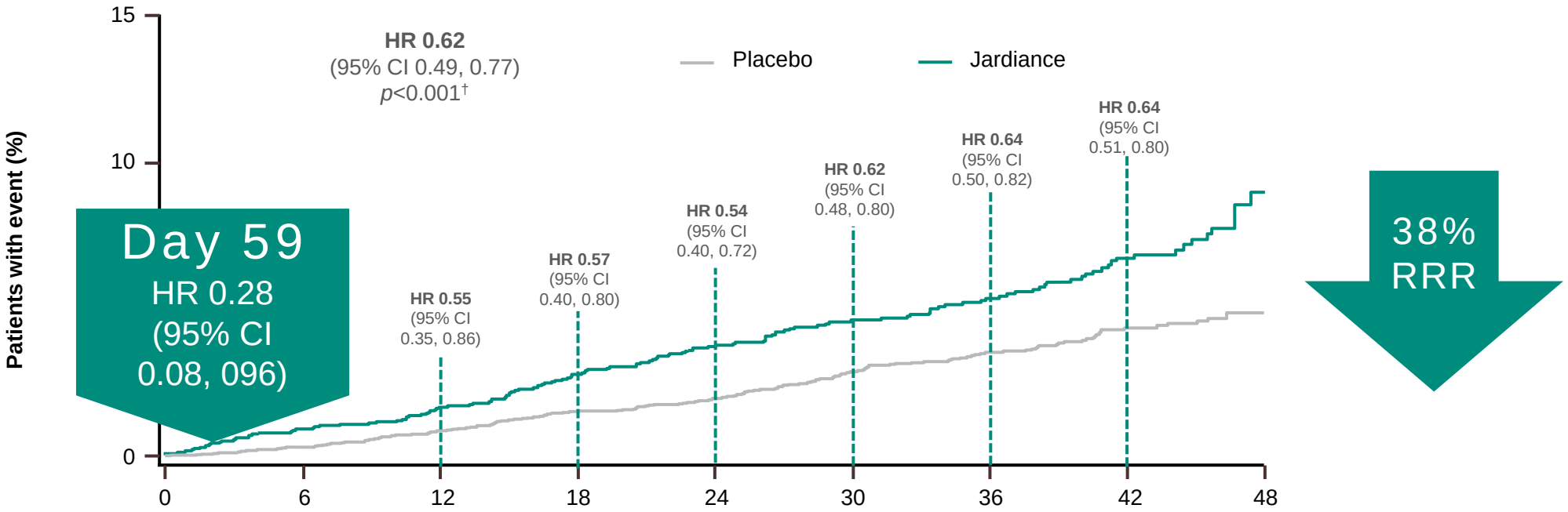
能降低38%心血管死亡風險



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

Pooled empagliflozin 10 mg and 25 mg data shown
*On top of standard of care; †Nominal *p*-value
CV, cardiovascular; RRR, relative risk reduction; T2D, type 2 diabetes
Zinman B *et al. N Engl J Med* 2015;373:2117

在試驗第 59 天就可以降低病患心血管死亡的風險

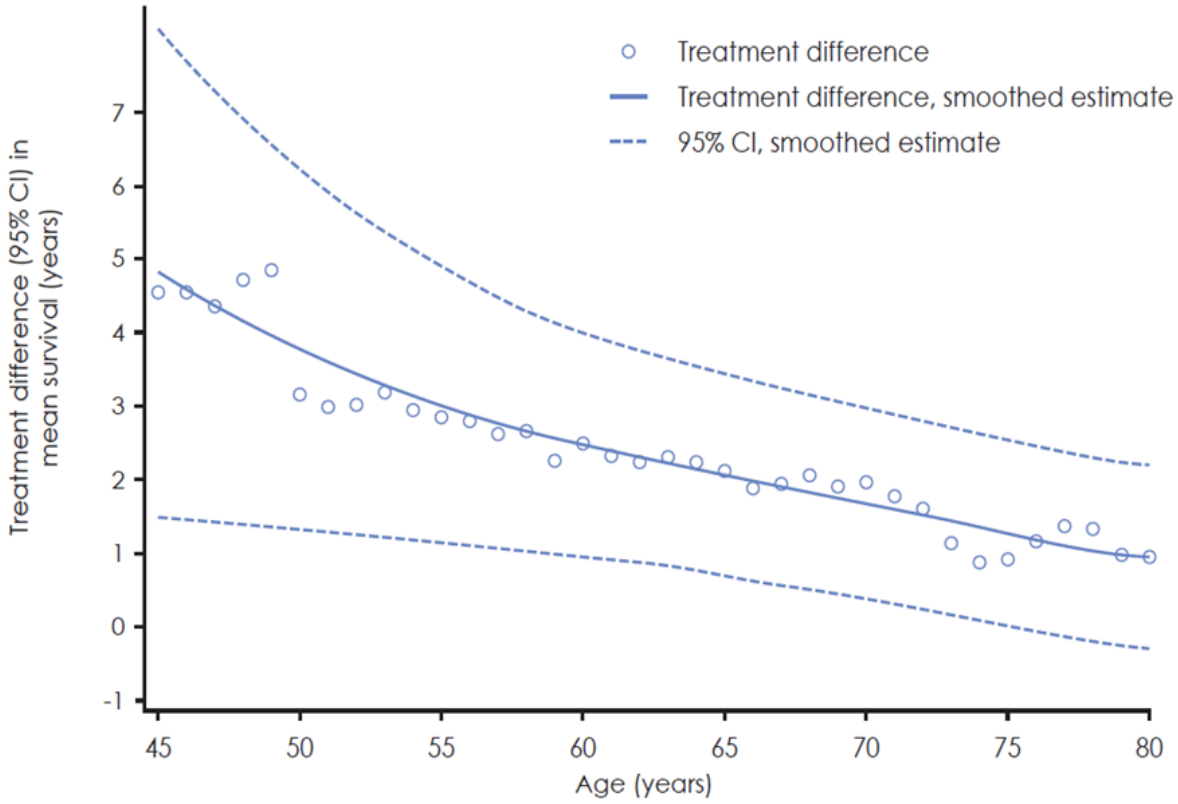


No. at risk

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

Pooled empagliflozin 10 mg and 25 mg data shown
*On top of standard of care; †Nominal *p*-value
CV, cardiovascular; RRR, relative risk reduction; T2D, type 2 diabetes
Zinman B *et al. N Engl J Med* 2015;373:2117; Fitchett D *et al*. *J Am Coll Cardiol* 2018;71:364; Verma S, et al. ADA 2020, OR-28;

降低 38% CV death 的在臨床效益將能增進病患疾病控制與預後
若 45 歲ASCVD的病人使用 Jardiance® 將能延長 4.5 年預期壽命



- Differences in estimated mean years of survival with empagliflozin vs placebo ranged from 1 to nearly 5 years.
- Estimated mean survival:

Age, years	Mean survival, years		Difference, years	*P* value
	Empagliflozin	Placebo		
45	32.1	27.6	4.5	0.007
50	28.5	25.4	3.1	0.005
60	21.8	19.2	2.5	0.001
70	14.8	12.8	2.0	0.003
80	7.7	6.7	1.0	0.13

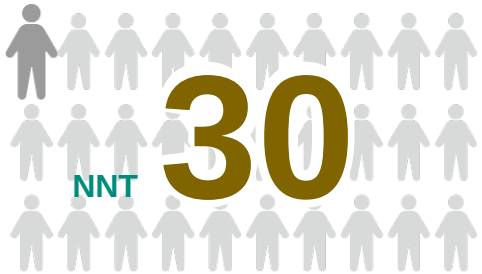
1. Claggett B te al.Circulation, 2018; 138: 1599-1601

† The estimated increased survival of 2.5 years in 60-year-old patient is based on modelling of all-cause mortality results beyond the observation period in EMPA-REG OUTCOME using the time-to-event date for patients of the respective age and assuming that beneficial effects of empagliflozin will remain consistent with long-term use

在有 Statin 和 ACEi 為標準治療的情況下
使用 Jardiance® 治療 39 位ASCVD病患就能預防一個病患死亡
(平均追蹤3.1年)

4S[1]

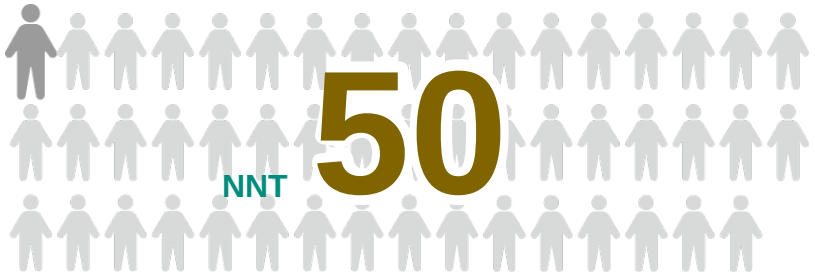
Simvastatin for 5.4 years



In high CV risk
5% diabetes,
26% hypertension

HOPE[2]

Ramipril for 5 years

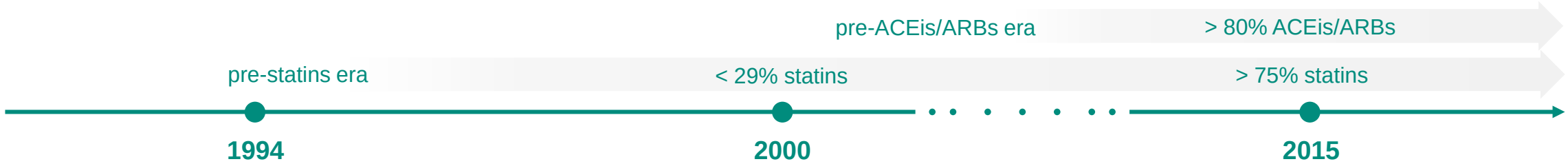


In high CV risk
38% diabetes,
46% hypertension

EMPA-REG OUTCOME®[3]

Empagliflozin for 3.1 years

T2D with established
CV disease (CAD, PAD, MI or stroke)
on top of standard of care

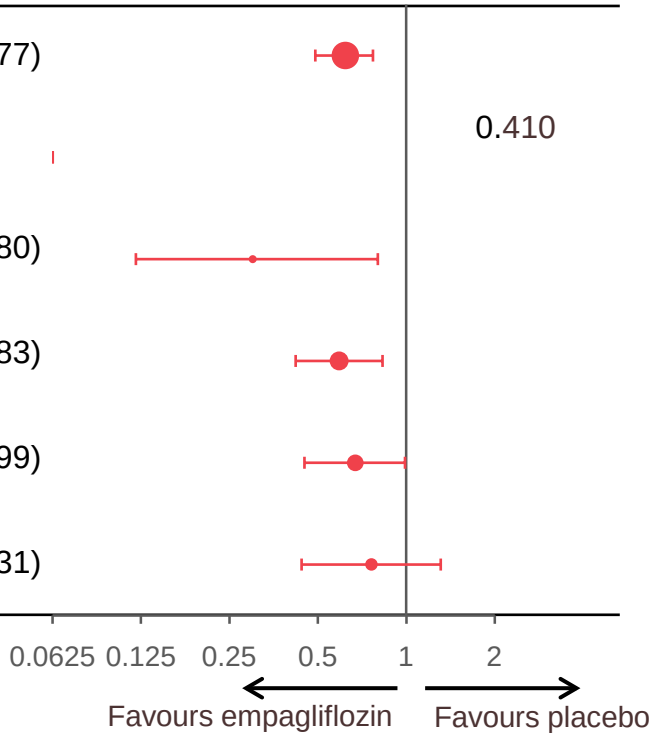


ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, cardiovascular artery disease; MI, myocardial infarction; NNT, number needed to treat; PAD peripheral artery disease.

1. 4S group. Lancet. 1994;344:1383-89. 2. HOPE investigators. N Engl J Med. 2000;342:145-53. 3. Zinman B et al. N Engl J Med. 2015;373:2117-28.

不論病人 baseline HbA1c 高或是低
使用 Jardiance® 都能降低心血管死亡風險

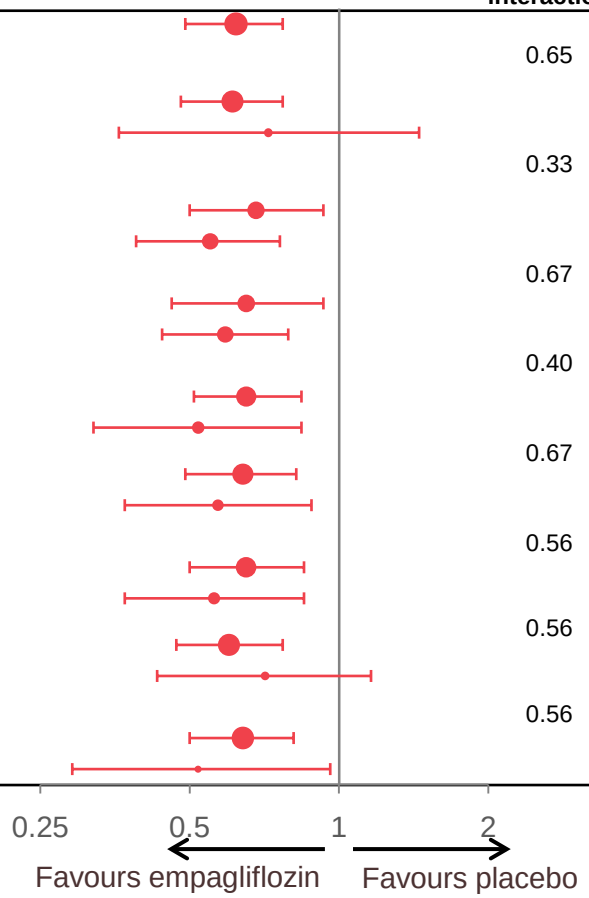
	Empagliflozin	Placebo	HR (95% CI)	*p*-value for interaction
	n with event/N analysed (%)			
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
Baseline HbA1c, %				0.410
<7.0	7/297 (2.4)	10/127 (7.9)	0.30 (0.12, 0.80)	
7.0 to <8.0	75/2042 (3.7)	63/1029 (6.1)	0.59 (0.42, 0.83)	
8.0 to <9.0	56/1534 (3.7)	43/795 (5.4)	0.67 (0.45, 0.99)	
≥9.0	34/812 (4.2)	21/382 (5.5)	0.76 (0.44, 1.31)	



Post hoc analysis. Cox regression analysis in patients treated with ≥1 dose of study drug; *p*-values relate to tests of the homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction), with no adjustment for multiple tests
CV, cardiovascular; HbA1c, glycated haemoglobin
Inzucchi S *et al. Circulation* 2018;138:1904

不論病人 baseline 的心血管疾病
使用 Jardiance® 都能降低心血管死亡風險

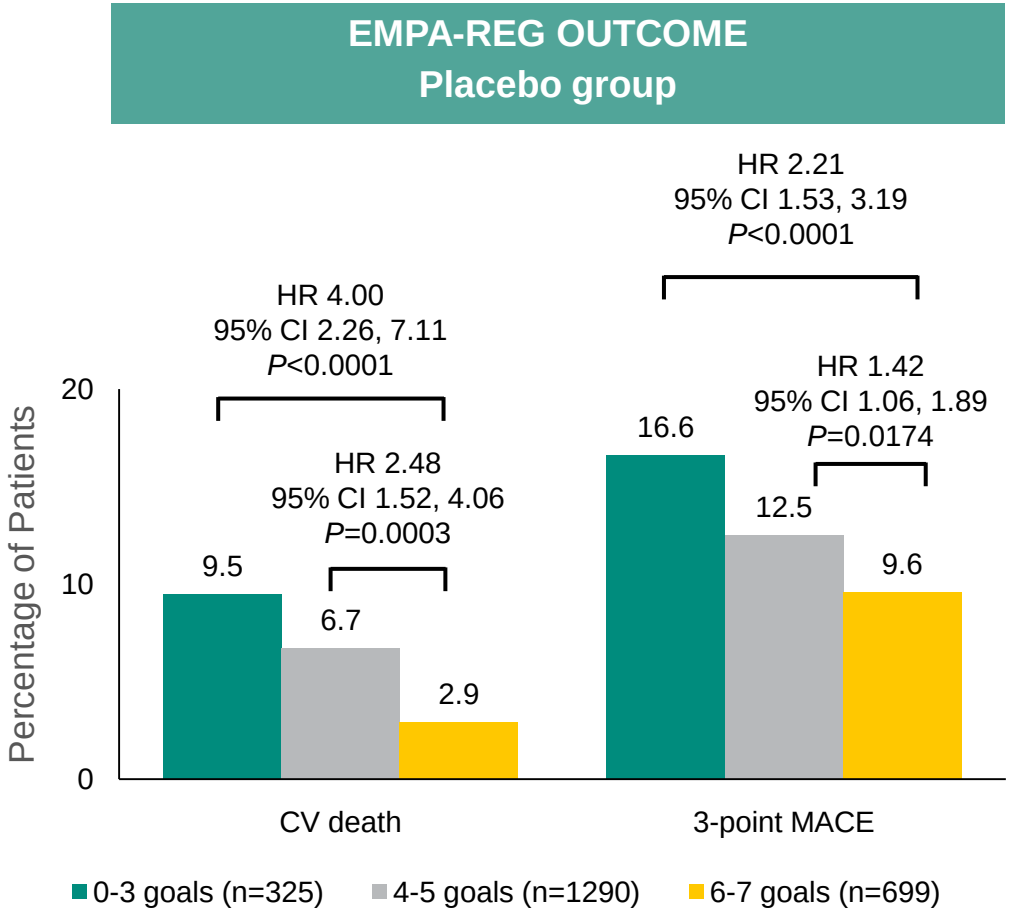
	Empagliflozin	Placebo	HR (95% CI)	*p*-value for interaction
	n with event/N analysed (%)			
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
Single vessel coronary artery disease				0.65
No	152/4189 (3.6)	124/2094 (5.9)	0.61 (0.48, 0.77)	
Yes	20/498 (4.0)	13/238 (5.5)	0.72 (0.36, 1.45)	
Multi-vessel coronary artery disease				0.33
No	101/2508 (4.0)	71/1233 (5.8)	0.68 (0.50, 0.93)	
Yes	71/2179 (3.3)	66/1100 (6.0)	0.55 (0.39, 0.76)	
History of MI				0.67
No	71/2497 (2.8)	55/1250 (4.4)	0.65 (0.46, 0.93)	
Yes	101/2190 (4.6)	82/1083 (7.6)	0.59 (0.44, 0.79)	
History of CABG				0.40
No	137/3512 (3.9)	105/1770 (5.9)	0.65 (0.51, 0.84)	
Yes	35/1175 (3.0)	32/563 (5.7)	0.52 (0.32, 0.84)	
Peripheral artery disease				0.67
No	128/3704 (3.5)	101/1853 (5.5)	0.64 (0.49, 0.82)	
Yes	44/982 (4.5)	36/479 (7.5)	0.57 (0.37, 0.88)	
History of stroke				0.56
No	125/3603 (3.5)	93/1779 (5.2)	0.65 (0.50, 0.85)	
Yes	47/1084 (4.3)	44/553 (8.0)	0.56 (0.37, 0.85)	
Heart failure*				0.56
No	134/4225 (3.2)	110/2089 (5.3)	0.60 (0.47, 0.77)	
Yes	38/462 (8.2)	27/244 (11.1)	0.71 (0.43, 1.16)	
History of atrial fibrillation†				0.56
No	151/4440 (3.4)	116/2191 (5.3)	0.64 (0.50, 0.81)	
Yes	21/247 (8.5)	21/142 (14.8)	0.52 (0.29, 0.96)	



Cox regression analysis in patients treated with ≥1 dose of study drug; p-values for interaction of subgroup by treatment are presented
*Based on narrow standardised MedDRA query 'cardiac failure'; †Based on one MedDRA preferred term
CABG, coronary artery bypass graft; CV, cardiovascular; MI, myocardial infarction
Fitchett D *et al. J Am Coll Cardiol* 2018;71:364; Zinman B *et al. AHA* 2016; poster S2044

心血管危險因子的控制與病患發生主要心血管事件與死亡率息息相關

- Patients were categorised by baseline attainment of the following CV risk factor **goals**:
  1. HbA1c <7.5%
  2. Normoalbuminuria
  3. LDL-C <100 mg/dl or statin use
  4. Aspirin use
  5. SBP <140 mmHg and DBP <90 mmHg
  6. Non-smoking status
  7. ACE inhibitor/ARB use



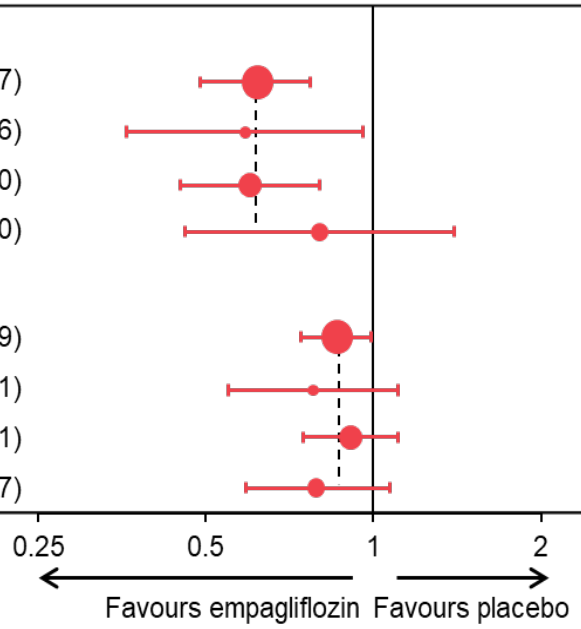
Cox regression analysis in patients treated with ≥1 dose of study drug with terms for age, sex, BMI, HbA1c, eGFR, region, CV risk factors goal attainment. *Excludes fatal stroke
3-point MACE, CV death, non-fatal myocardial infarction, or non-fatal stroke; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; MACE, major adverse CV events

Source: Inzucchi S, *et al. J Clin Endocrinol Metab* 2020; Jun 2. doi: 10.1210/clinem/dgaa321. Online ahead of print

EMPA-REG OUTCOME®

不論病人達成幾項心血管風險控制目標 使用Jardiance® 皆能降低心血管事件

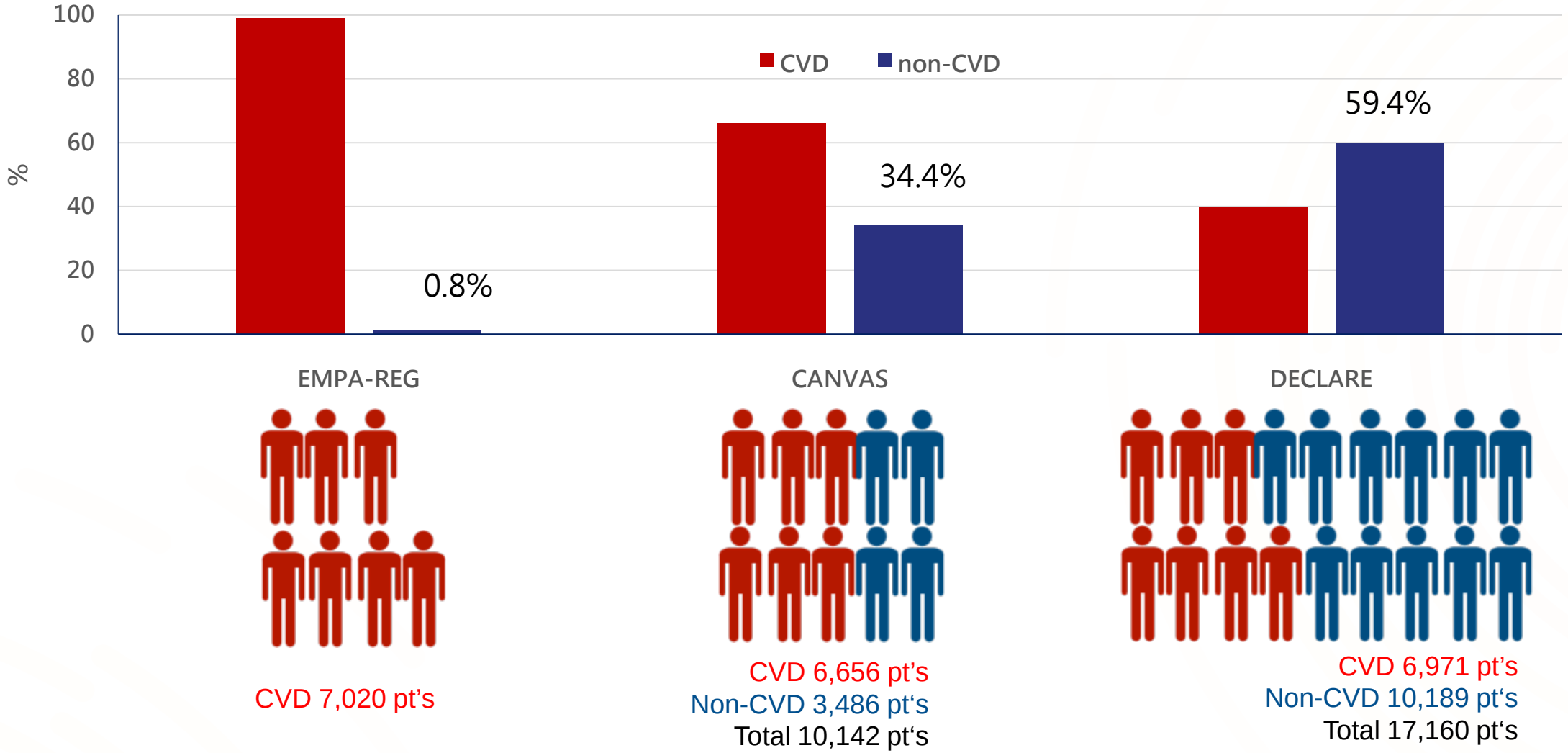
	Empagliflozin		Placebo		Hazard ratio (95% CI)	Interaction *p*-value*
	n event/N (%)	Rate per 1000 patient-years	n event/N (%)	Rate per 1000 patient-years		
CV death						
All patients	172/4687 (3.7)	12.4	137/2333 (5.9)	20.2	0.62 (0.49, 0.77)	0.6319
0-3 goals attained	34/559 (6.1)	21.1	31/325 (9.5)	33.8	0.59 (0.36, 0.96)	
4-5 goals attained	103/2605 (4.0)	13.5	86/1290 (6.7)	23.2	0.60 (0.45, 0.80)	
6-7 goals attained	34/1457 (2.3)	7.8	20/699 (2.9)	9.5	0.80 (0.46, 1.40)	
3-point MACE						
All patients	490/4687 (10.5)	37.4	282/2333 (12.1)	43.9	0.86 (0.74, 0.99)	0.6301
0-3 goals attained	77/559 (13.8)	51.2	54/325 (16.6)	62.7	0.78 (0.55, 1.11)	
4-5 goals attained	294/2605 (11.3)	40.7	161/1290 (12.5)	45.9	0.91 (0.75, 1.11)	
6-7 goals attained	113/1457 (7.8)	27.0	67/699 (9.6)	33.4	0.79 (0.59, 1.07)	



Cox regression analysis in patients treated with ≥1 dose of study drug with terms for age, sex, body mass index, HbA1c, eGFR, region, treatment, CV risk factors goal attainment, and treatment by CV risk factors goal attainment interaction; 85 patients (66 empagliflozin, 19 placebo) were missing CV risk factors goal attainment data at baseline; *p*-value relates to test of homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction) without adjustment for multiple testing. *Excludes fatal stroke. 3-point MACE, CV death, non-fatal myocardial infarction, or non-fatal stroke; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure

Source: Inzucchi S, *et al. J Clin Endocrinol Metab* 2020; Jun 2. doi: 10.1210/clinem/dgaa321. Online ahead of print

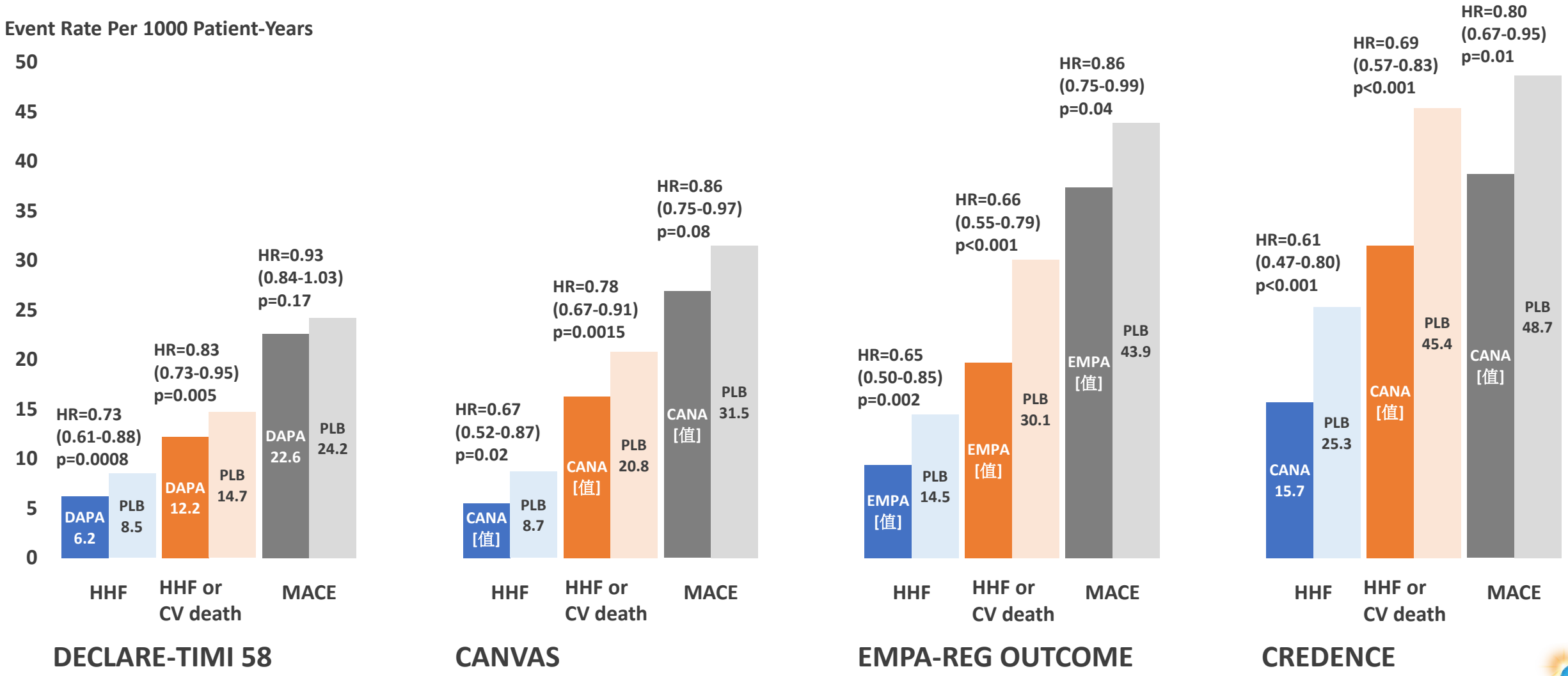
CVD and Non-CVD proportion in 3 CVOTs of SGLT2i



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.

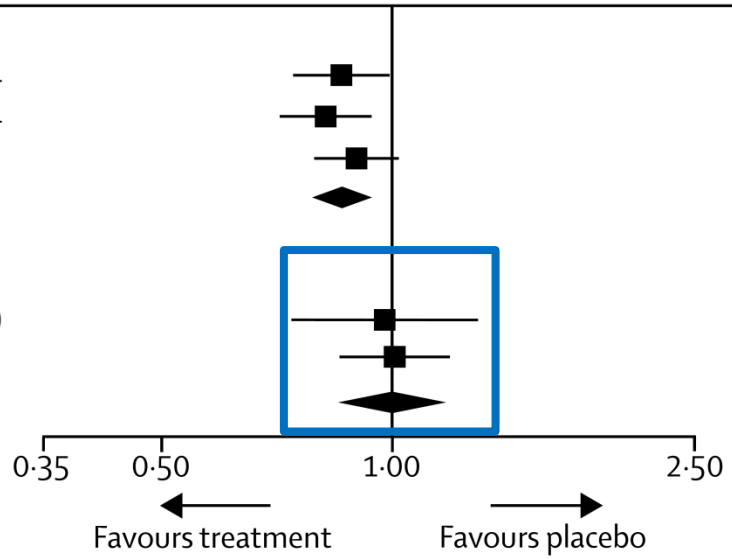
Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) event rates per 1000 patients in SGLT2i trials



Kluger et al. Cardiovasc Diabetol (2019) 18:99

3P MACE: CV death, non fatal MI, non fatal stroke

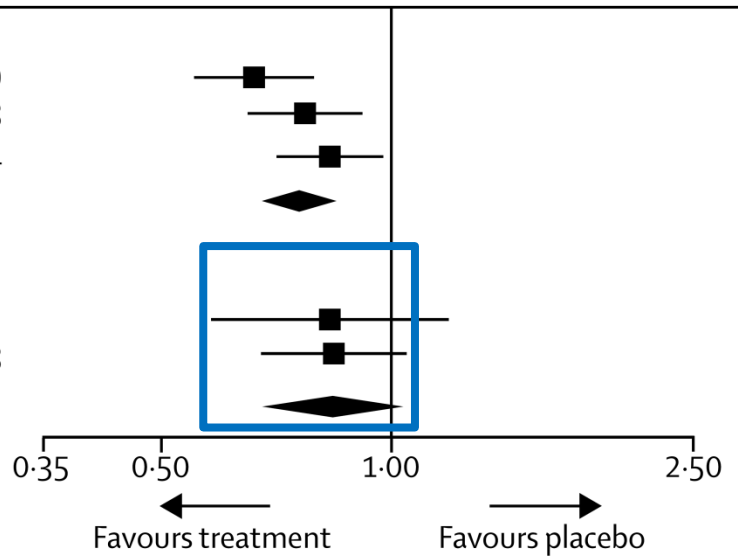
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**



DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Hospitalization for heart failure and cardiovascular death

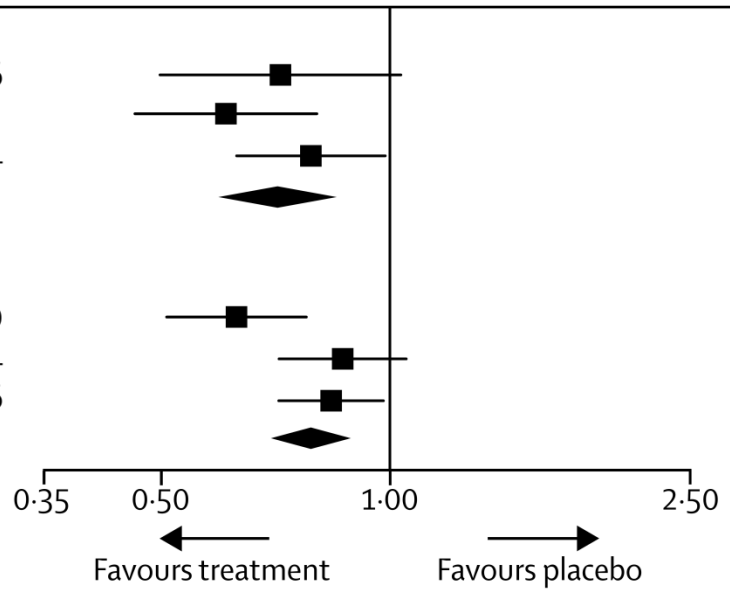
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**



DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Hospitalization for heart failure and cardiovascular death

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803/1461	658/1461	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852/1724	872/1724	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225/6314	2089/6314	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730/15 436	7706/15 436	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

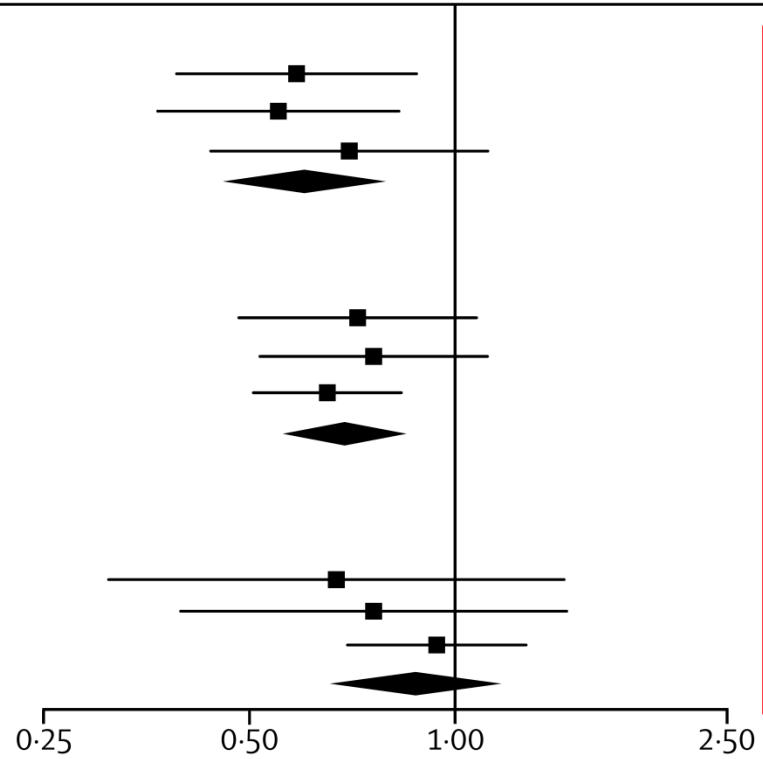


DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Hospitalization for heart failure

B

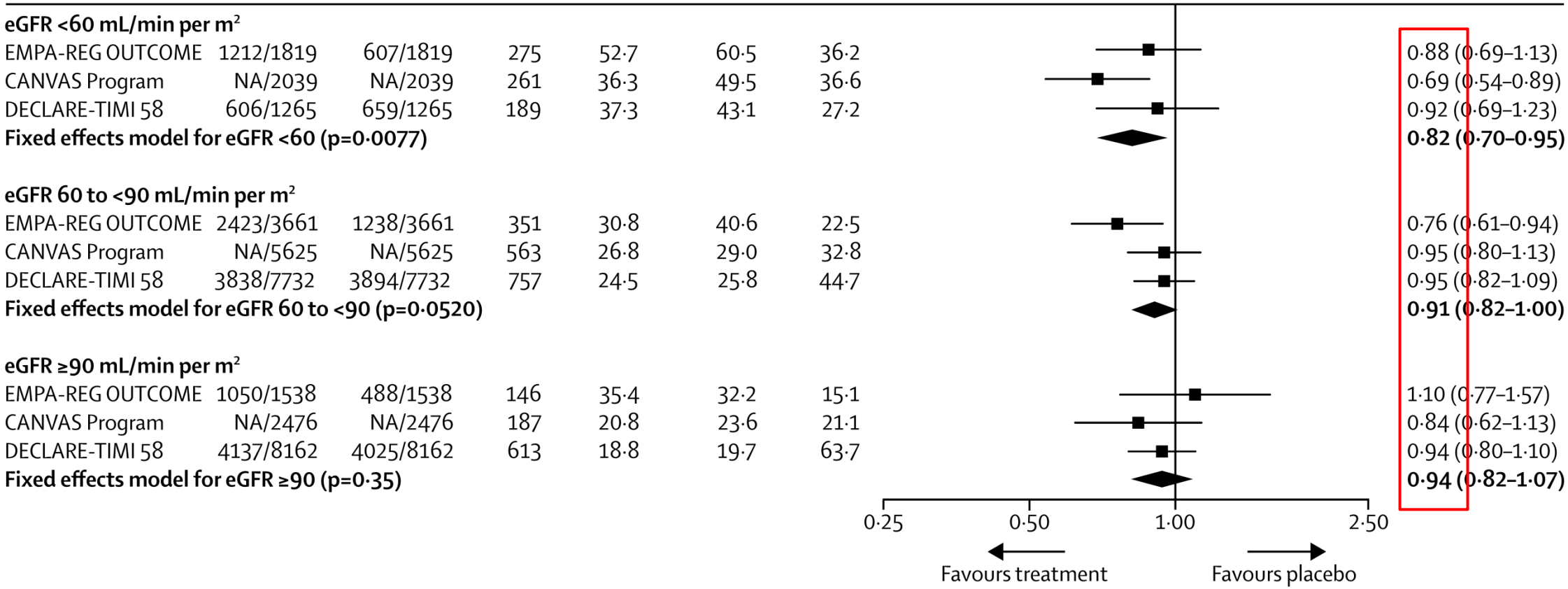
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212/1819	607/1819	94	14·9	25·8	36·5	0·59 (0·39–0·88)
CANVAS Program	NA/2039	NA/2039	98	11·6	21·3	36·1	0·55 (0·37–0·83)
DECLARE-TIMI 58	606/1265	659/1265	77	12·3	19·3	27·4	0·70 (0·44–1·12)
Fixed effects model for eGFR <60 (p<0·0001)							**0·60 (0·47–0·77)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423/3661	1238/3661	100	8·4	11·7	21·3	0·72 (0·48–1·07)
CANVAS Program	NA/5625	NA/5625	108	4·6	6·1	23·4	0·76 (0·52–1·12)
DECLARE-TIMI 58	3838/7732	3894/7732	251	6·5	9·9	55·2	0·65 (0·51–0·84)
Fixed effects model for eGFR 60 to <90 (p<0·0001)							**0·69 (0·57–0·83)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050/1538	488/1538	27	5·4	7·9	11·3	0·67 (0·31–1·44)
CANVAS Program	NA/2476	NA/2476	37	3·7	5·1	15·7	0·76 (0·40–1·47)
DECLARE-TIMI 58	4137/8162	4025/8162	170	5·1	5·4	73·0	0·94 (0·69–1·26)
Fixed effects model for eGFR ≥90 (p=0·31)							**0·88 (0·68–1·13)**



DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Major adverse cardiovascular events

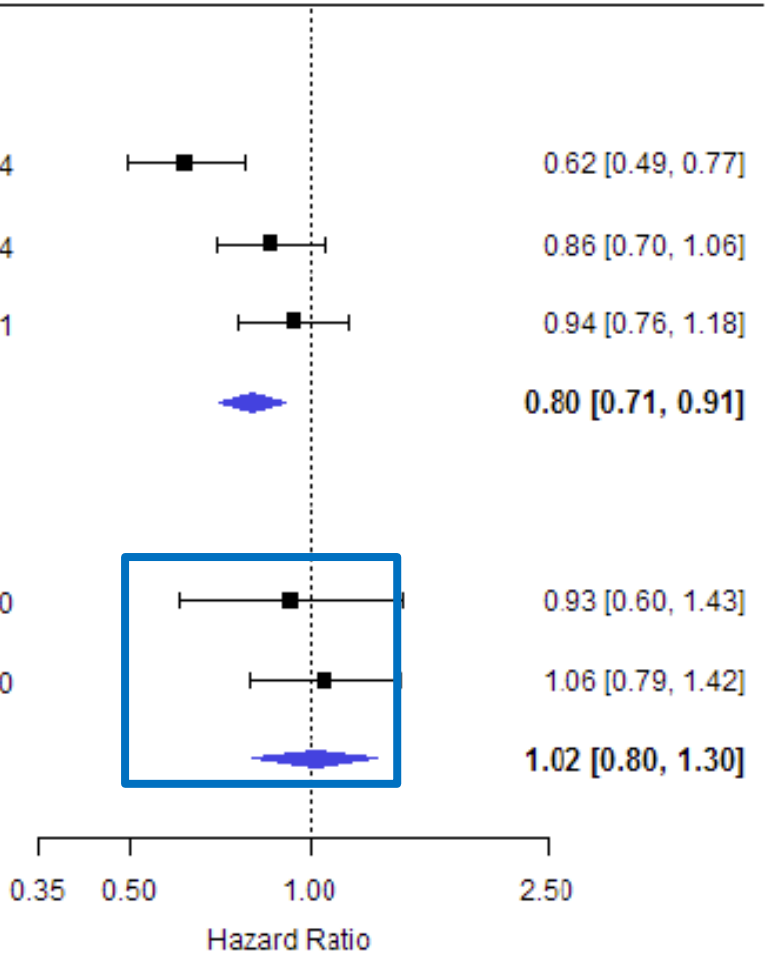
C



DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Figure S7: Treatment effect on cardiovascular death stratified by presence or absence of established atherosclerotic cardiovascular disease

CVD	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
Atherosclerotic Cardiovascular Disease:						
EMPA-REG OUTCOME	7020	309	12.4	20.2	32.4	0.62 [0.49, 0.77]
CANVAS Program	6656	362	14.8	16.8	34.4	0.86 [0.70, 1.06]
DECLARE-TIMI 58	6974	316	10.9	11.6	33.1	0.94 [0.76, 1.18]
FE Model for ASCVD (P-value = 0.0005)						**0.80 [0.71, 0.91]**
Multiple Risk Factor:						
CANVAS Program	3486	91	6.5	6.2	39.0	0.93 [0.60, 1.43]
DECLARE-TIMI 58	10186	178	4.4	4.1	61.0	1.06 [0.79, 1.42]
FE Model for MRF (P-value = 0.89)						**1.02 [0.80, 1.30]**

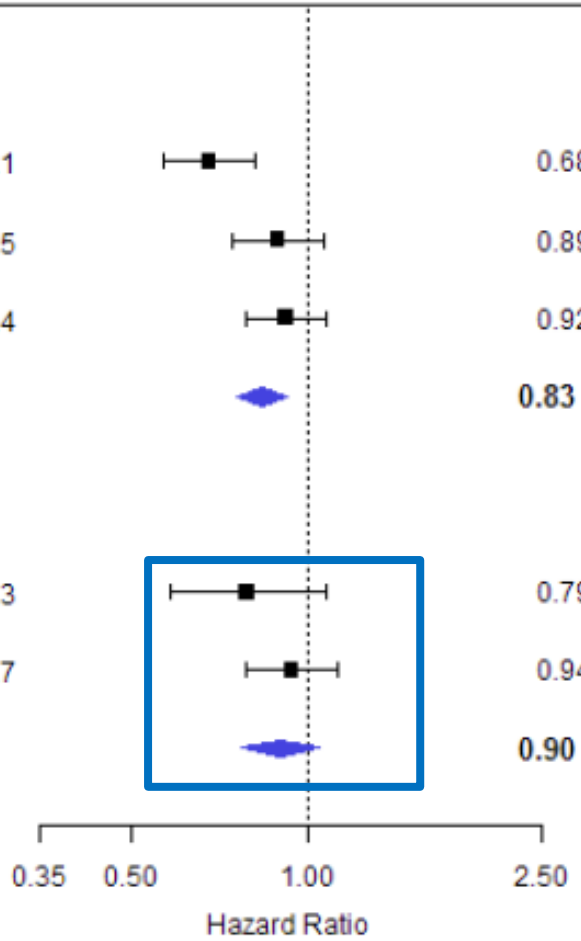


EM-TW-100289_201904

Figure S15: Treatment effect on all-cause mortality stratified by presence or absence of atherosclerotic cardiovascular disease

ACM
(all cause mortality)

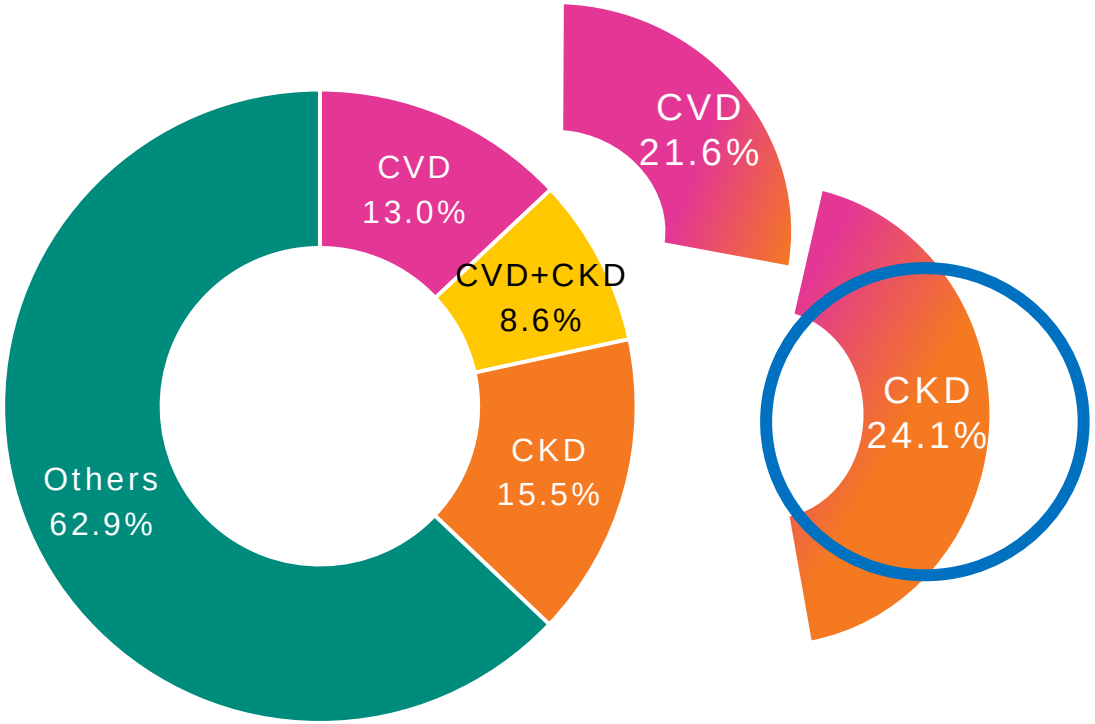
	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
Atherosclerotic Cardiovascular Disease:						
EMPA-REG OUTCOME	7020	463	19.4	28.6	32.1	0.68 [0.57, 0.82]
CANVAS Program	6656	509	21.1	23.1	32.5	0.89 [0.75, 1.07]
DECLARE-TIMI 58	6974	626	21.3	23.2	35.4	0.92 [0.79, 1.08]
FE Model for ASCVD (P-value = 0.0003)						**0.83 [0.75, 0.92]**
Multiple Risk Factor:						
CANVAS Program	3486	172	11.2	13.4	37.3	0.79 [0.58, 1.07]
DECLARE-TIMI 58	10186	473	11.0	11.7	62.7	0.94 [0.78, 1.12]
FE Model for MRF (P-value = 0.18)						**0.90 [0.77, 1.05]**

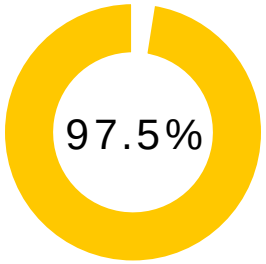


EM-TW-100289_201904

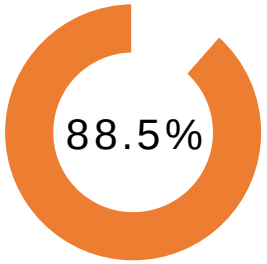
Cross-sectional—有心肾共病

A retrospective study of T2DM patients via Q-EMR from 2014 to 2015



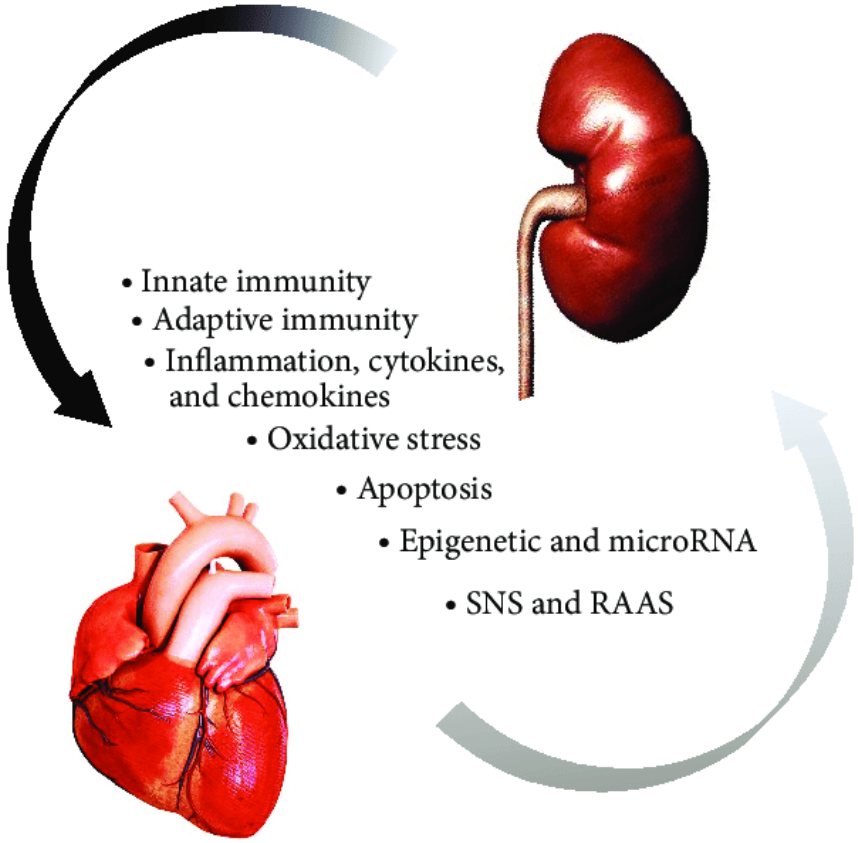


had ≥ 1 comorbid condition

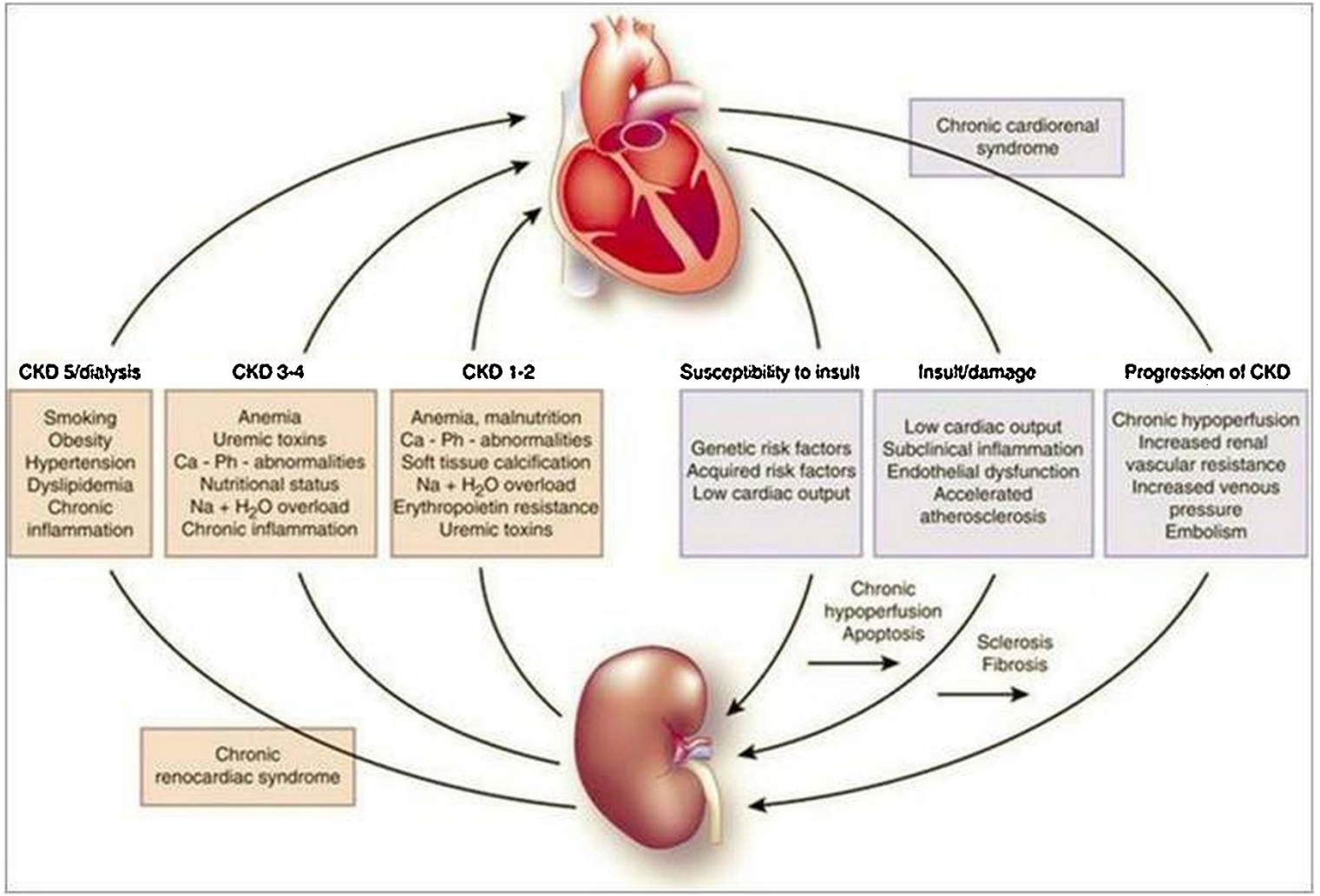


had ≥ 2 comorbid condition

Q-EMR, Quintiles Electronic Medical Record (EMR) research database
Iglay K, et al. *Curr Med Res Opin* 2016 Jul;32(7):1243-52.


• Innate immunity
• Adaptive immunity
• Inflammation, cytokines, and chemokines
• Oxidative stress
• Apoptosis
• Epigenetic and microRNA
• SNS and RAAS


心火
腎水
心腎不交



Indian Heart Journal 69 (2017) 255–265 .

eGFR and albuminuria categories indicate CKD prognosis

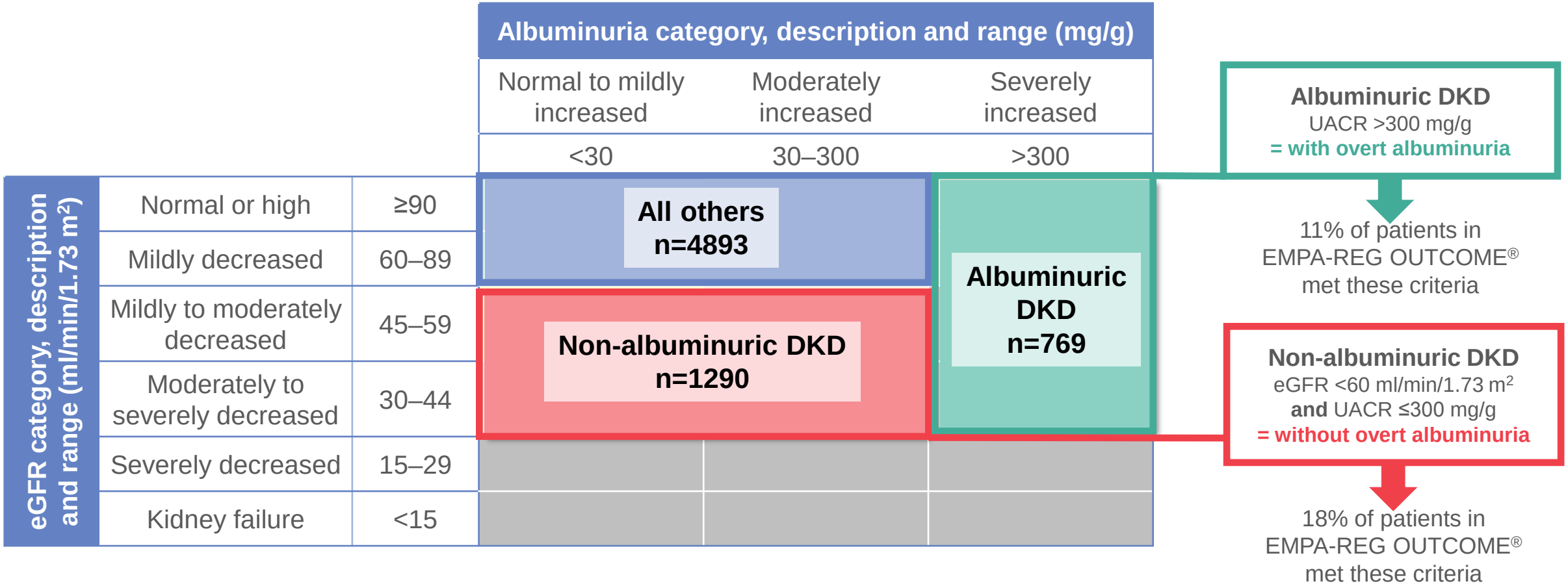
GFR categories, description and range (ml/min/1.73 m^2)				Albuminuria stages, description and range (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30–300	>300
	G1	Normal or high	≥90			
	G2	Mild decrease	60–89			
	G3a	Mild–moderate decrease	45–59			
	G3b	Moderate–severe decrease	30–44			
	G4	Severe decrease	15–29			
	G5	Kidney failure	<15			

Green: low CKD risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

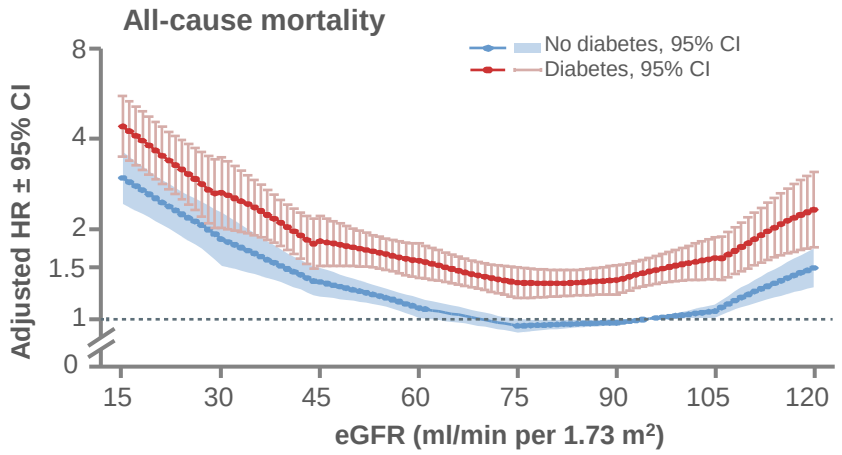
Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3:1

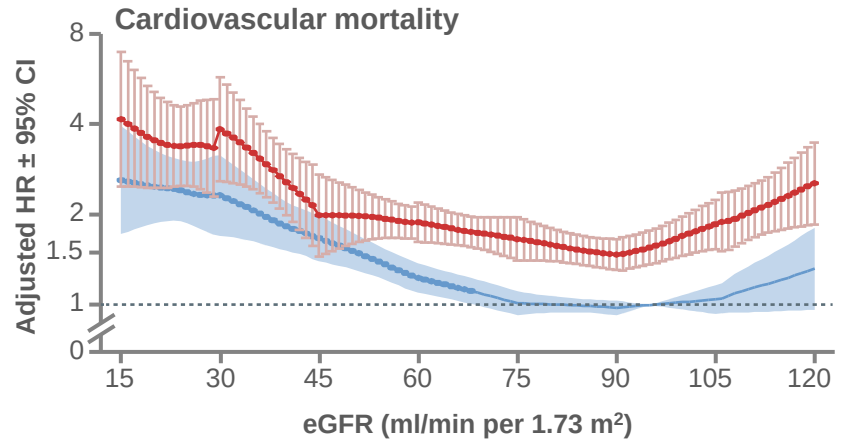
EMPA-REG OUTCOME®: Exploratory analysis
Different clinical phenotypes of DKD vs all others



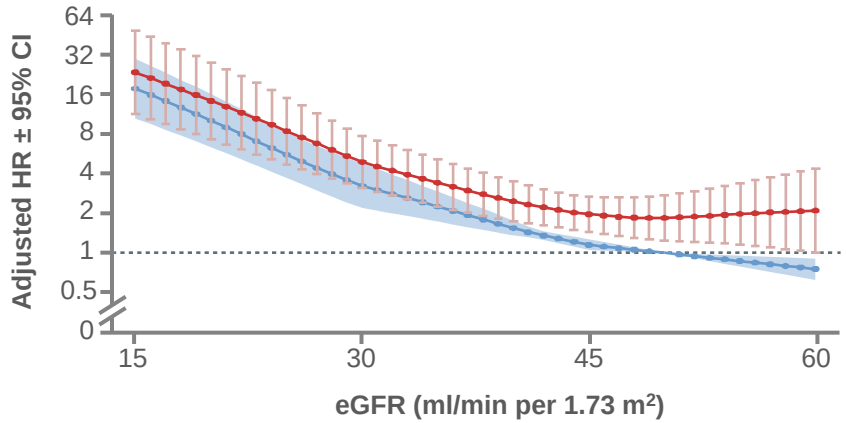
Declining eGFR is associated with mortality and ESRD in diabetes

Mortality and eGFR





ESRD and eGFR



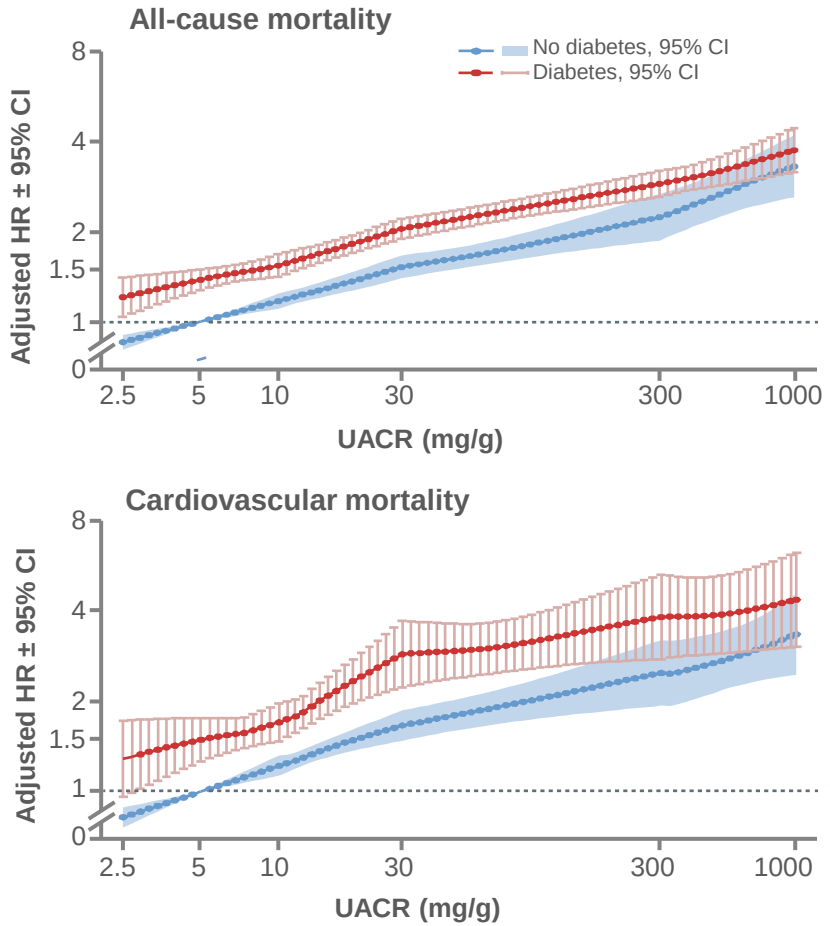
HRs adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index and albuminuria

Includes data from participants with type 1 and type 2 diabetes

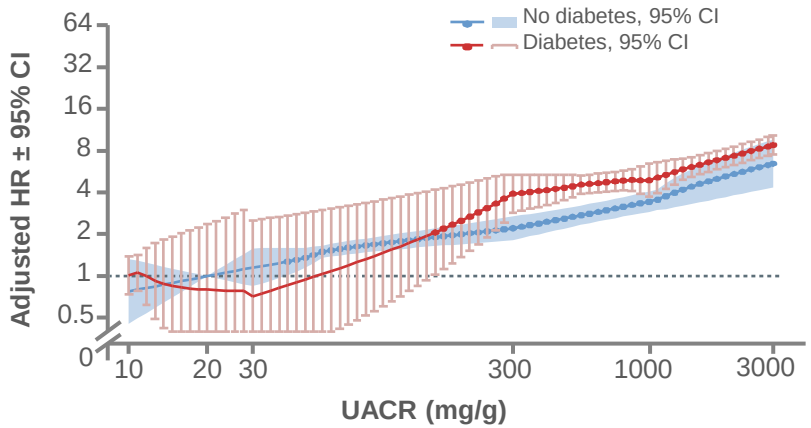
eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio. Fox CS *et al*. *Lancet* 2012;380:1662

Increasing UACR is associated with mortality and ESRD in diabetes

Mortality and UACR



ESRD and UACR



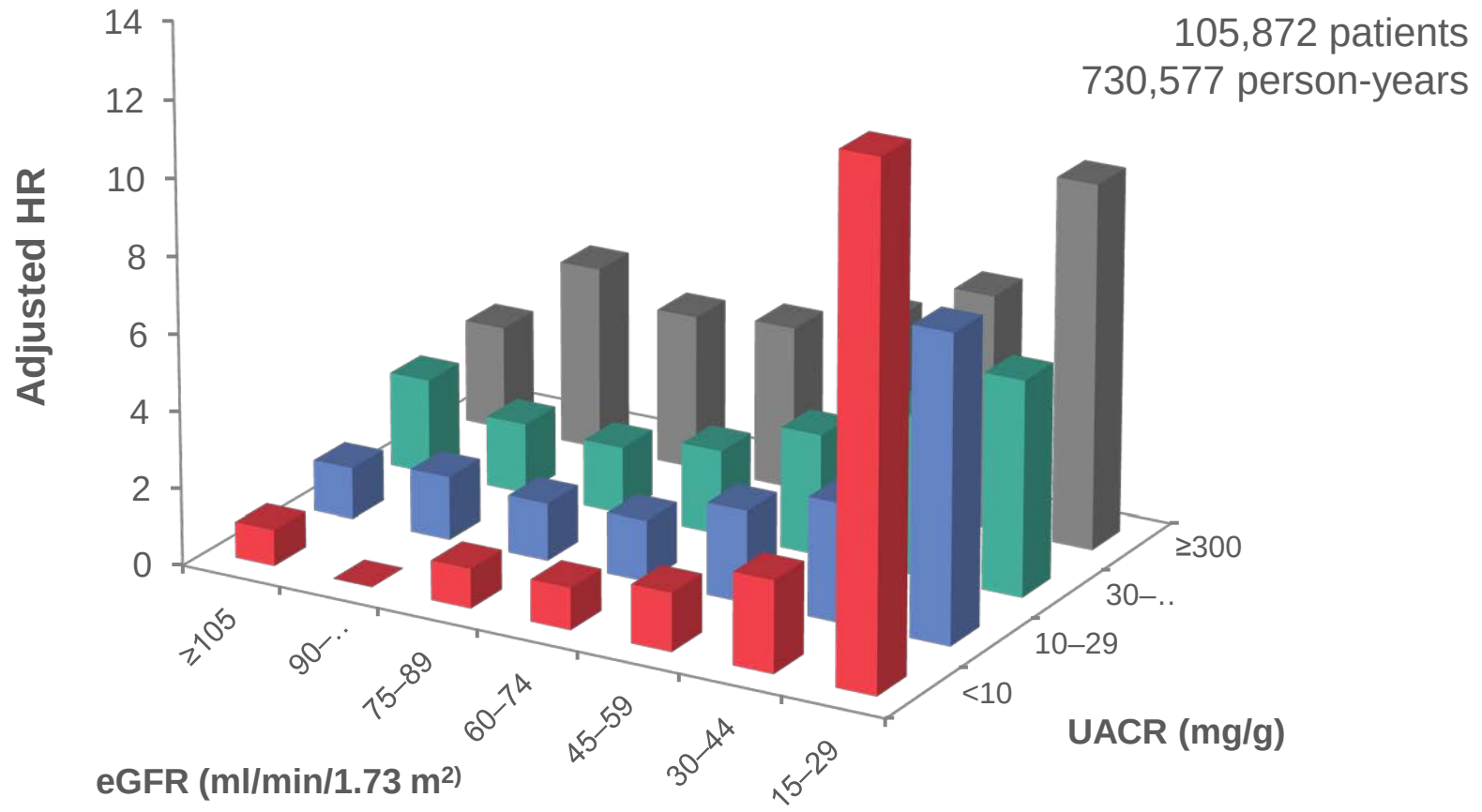
HRs adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body-mass index and albuminuria

Includes data from participants with type 1 and type 2 diabetes

ESRD, end-stage renal disease; HR, hazard ratio; UACR, urine albumin-to-creatine ratio. Fox CS *et al*. *Lancet* 2012;380:1662

Risk of CV death increases as renal function declines

CV death



Low eGFR and high UACR are independent predictors of CV mortality

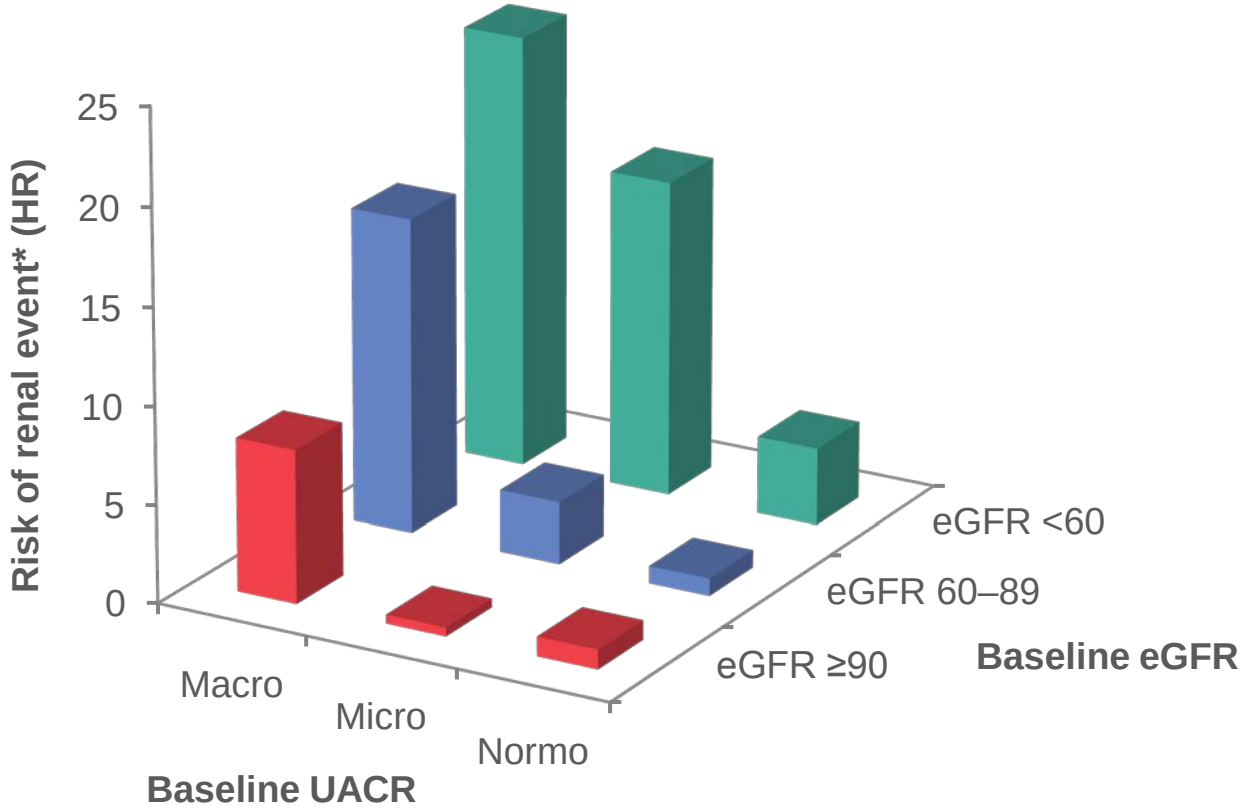
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, urine albumin-to-creatinine ratio
Matsushita K *et al. Lancet* 2010;375:2073

Risk of renal events* increases as renal function declines

Renal events

10,640 patients with available data

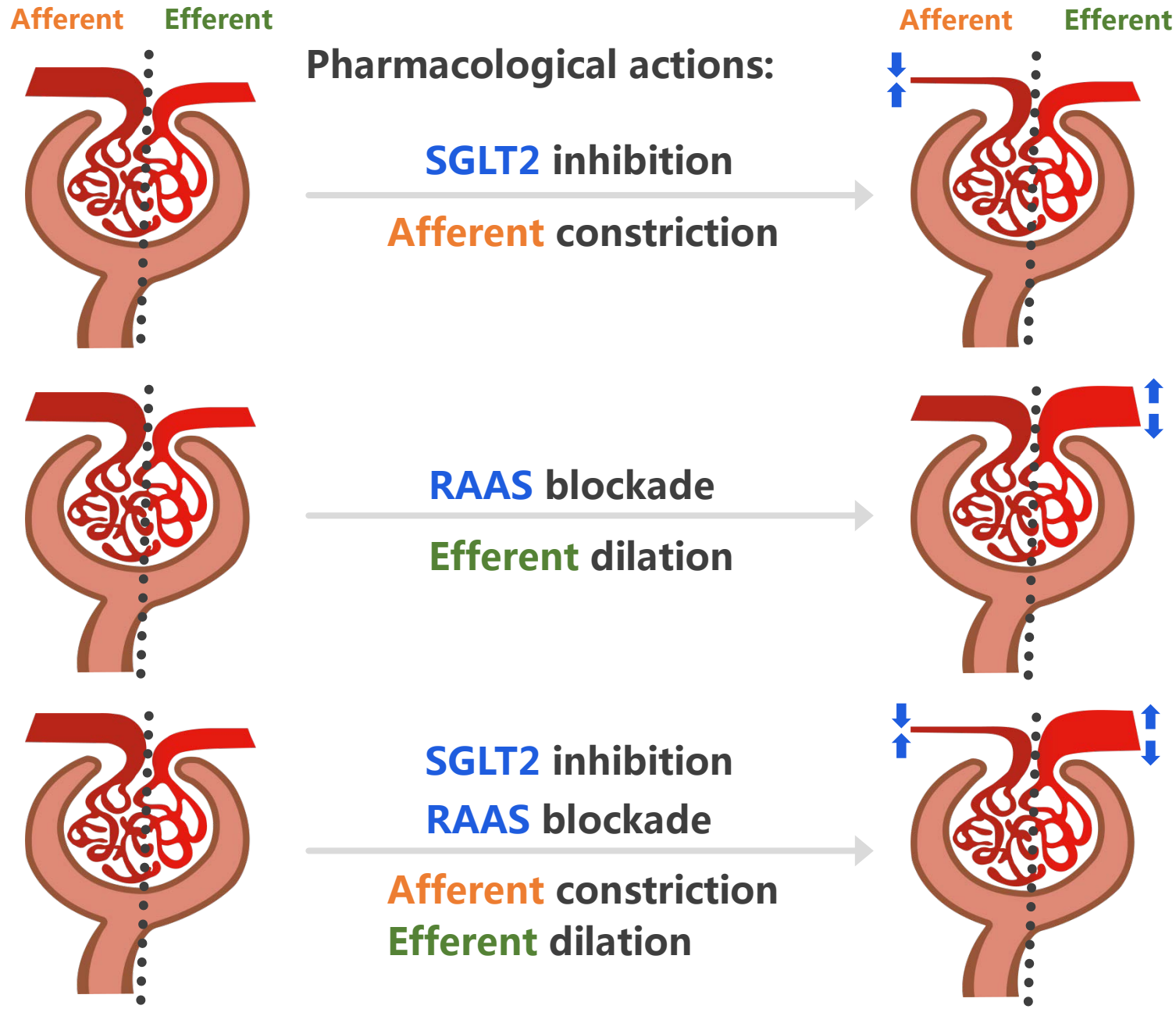
Average follow-up 4.3 years



*Renal events defined as: death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >200 µmol/l eGFR in ml/min/1.73 m^2

eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, urine albumin-to-creatinine ratio

Ninomiya T *et al. J Am Soc Nephrol* 2009;20:1813

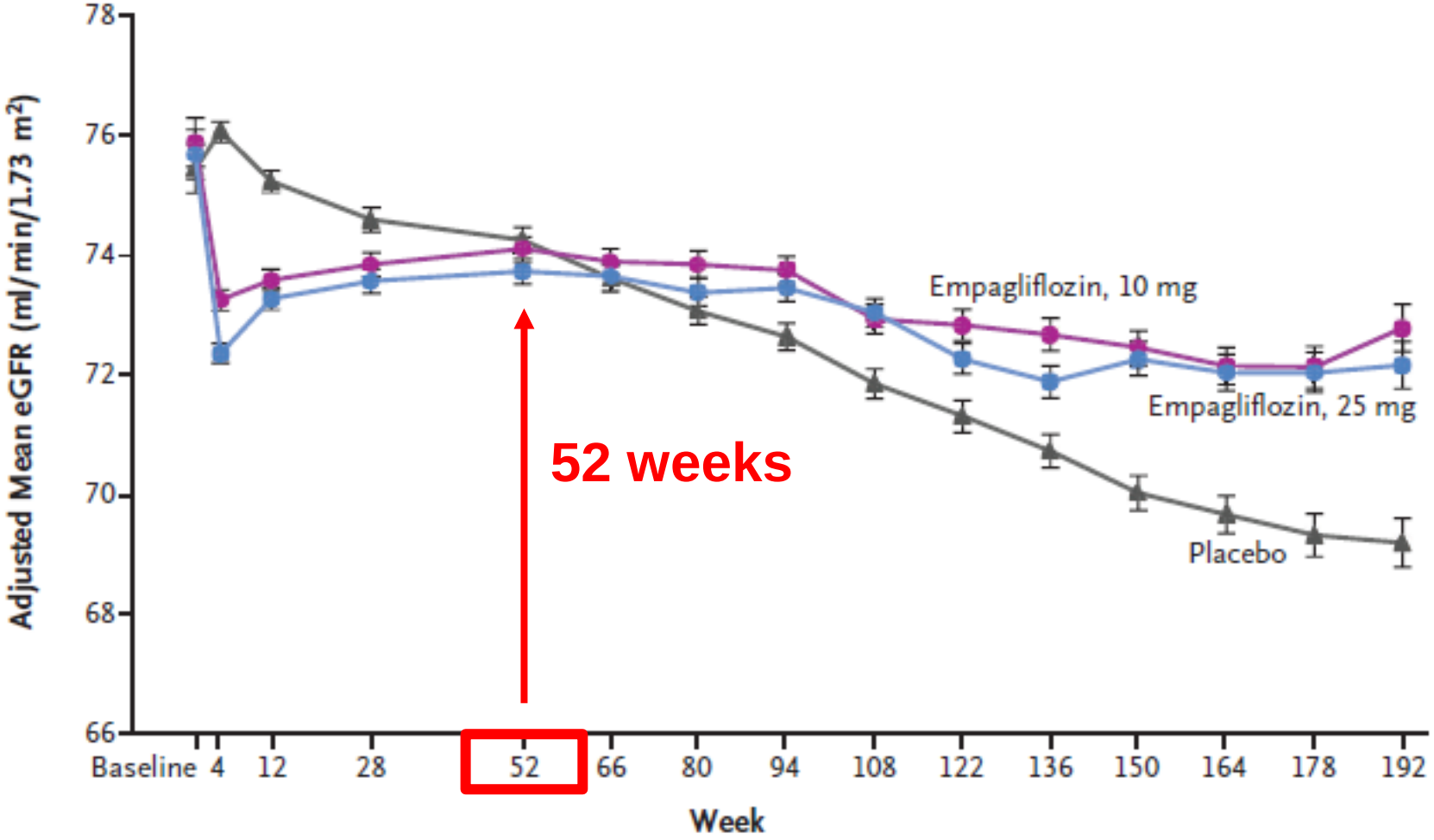


26. Diabetologia (2014) 57:2599–2602; 27. Circulation. 2014 Feb 4;129(5):587-97. Weber M et al. AHA 2013, Poster 2095

eGFR

Empa

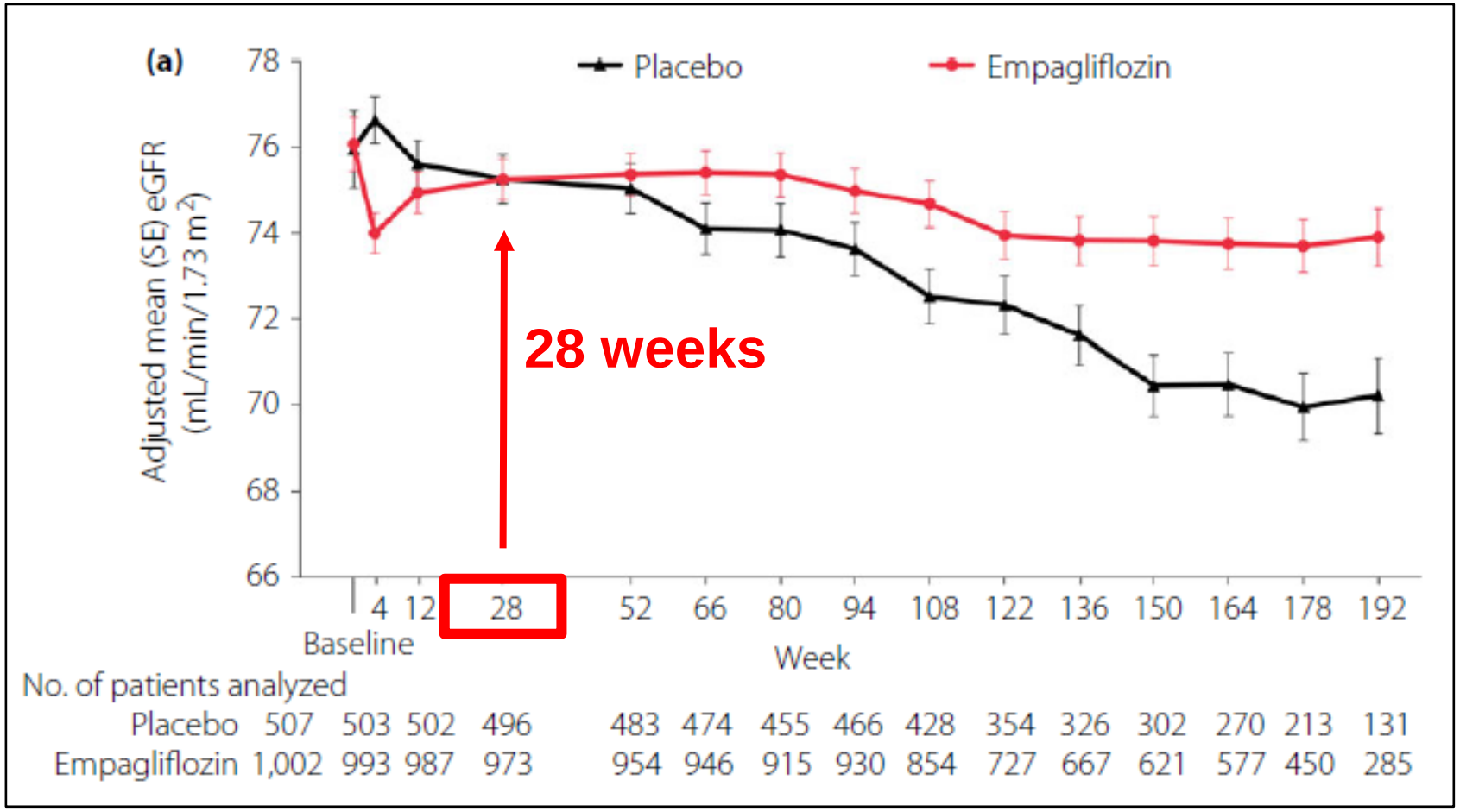
EMPA-REG OUTCOME: eGFR slope



EMPA REG renal OUTCOME

eGFR Empa

EMPA-REG OUTCOME Asian group: eGFR slope

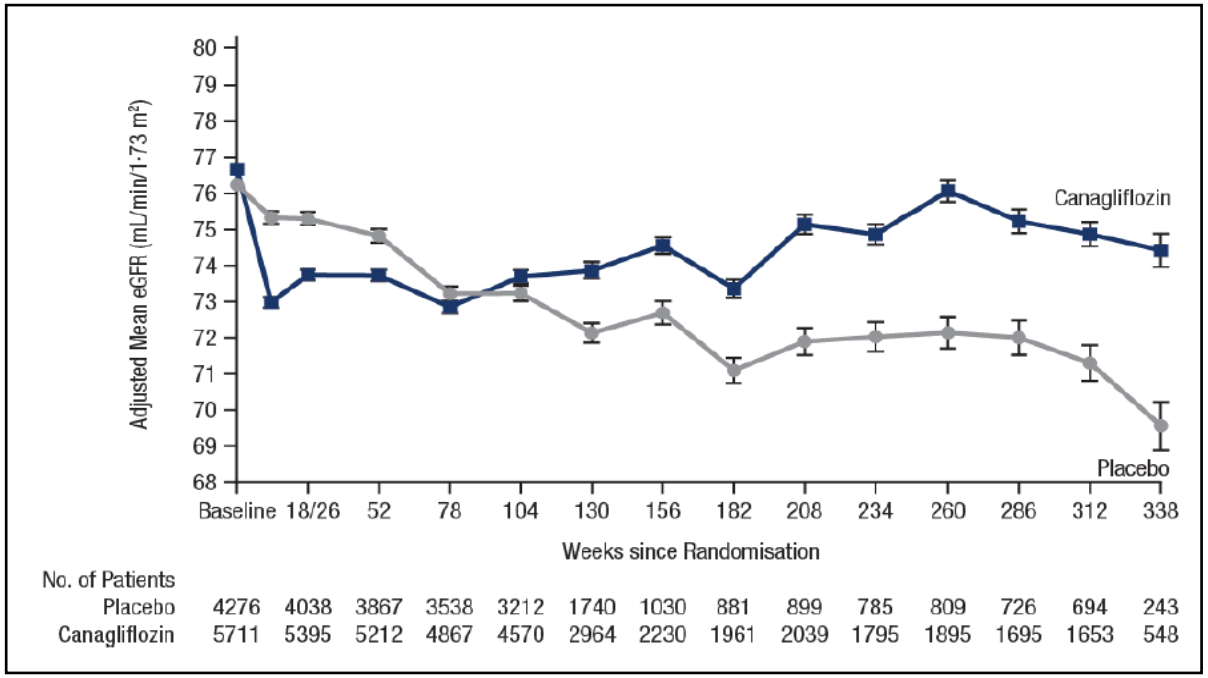


J Diabetes Investig 2018 doi: 10.1111/jdi.12971

The decline in the estimated GFR was slower in the canagliflozin group than in the placebo group

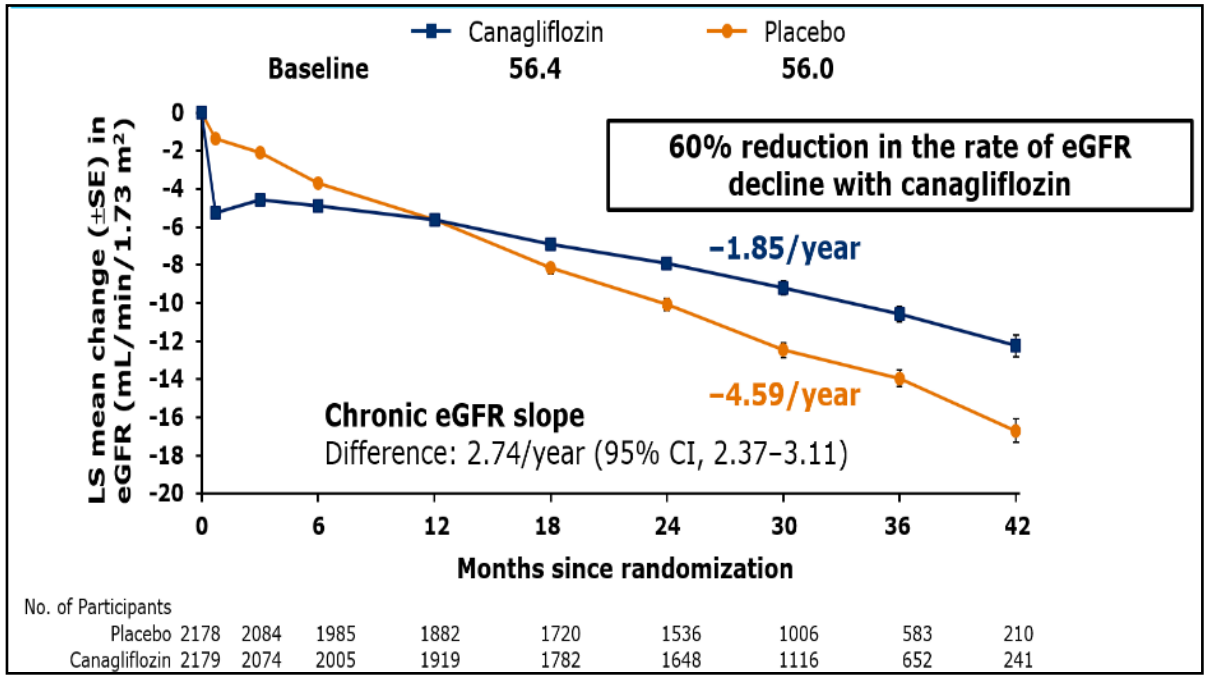
N Engl J Med 2017; 377:644-657 ; Lancet Diabetes Endocrinol . 2018 Sep;6(9):691-704. ; N Engl J Med 2019; 380:2295-2306

Secondary renal outcomes of the CANVAS/CANVAS R study



Mean eGFR 76 ml/min
Mean ACR 12mg/gCr

CREDENCE study

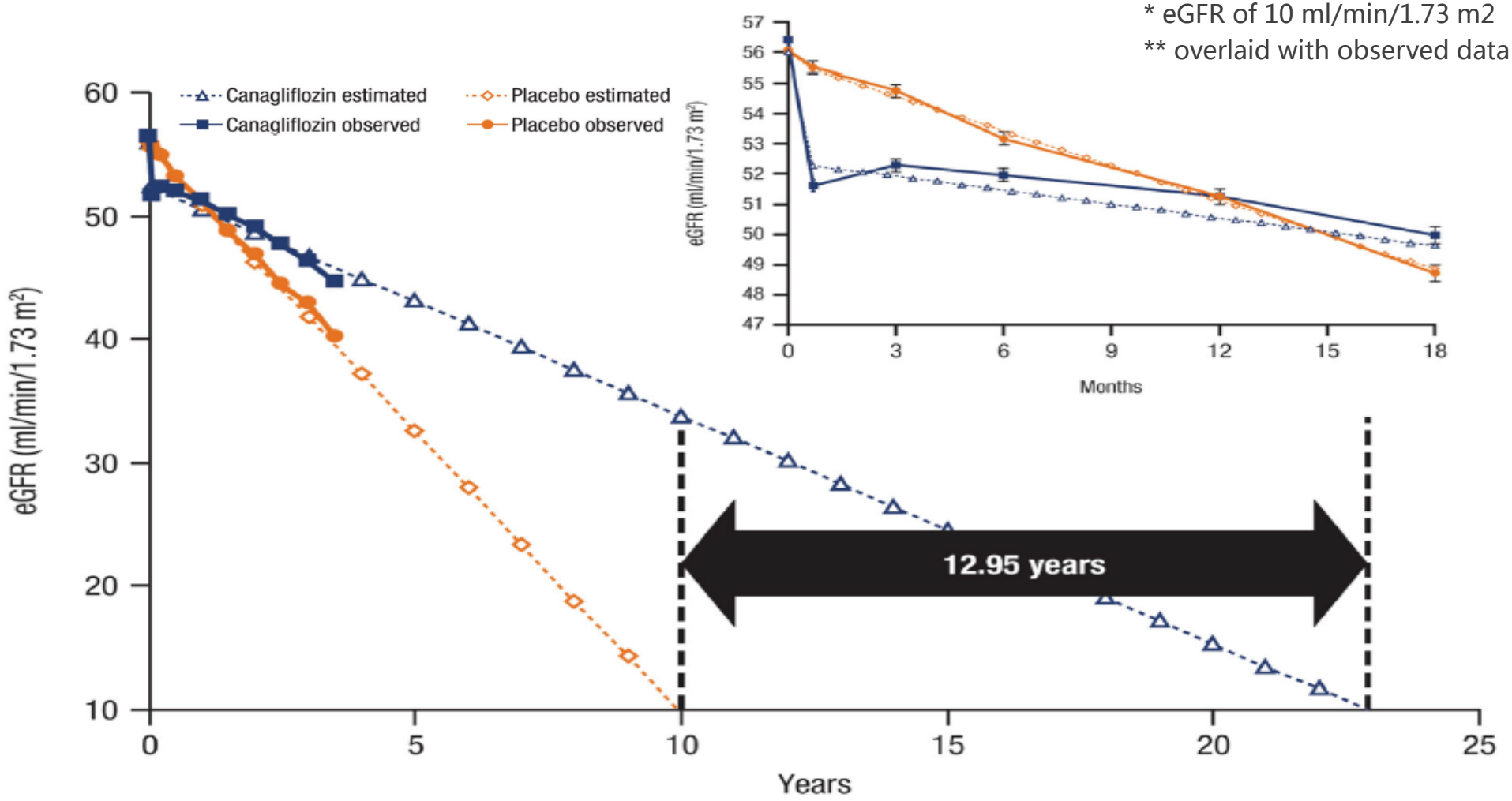


Mean eGFR 56 ml/min
Mean ACR 923 mg/gCr

Estimated eGFR values used to project the delay in time to dialysis* by treatment in the CREDENCE trial**

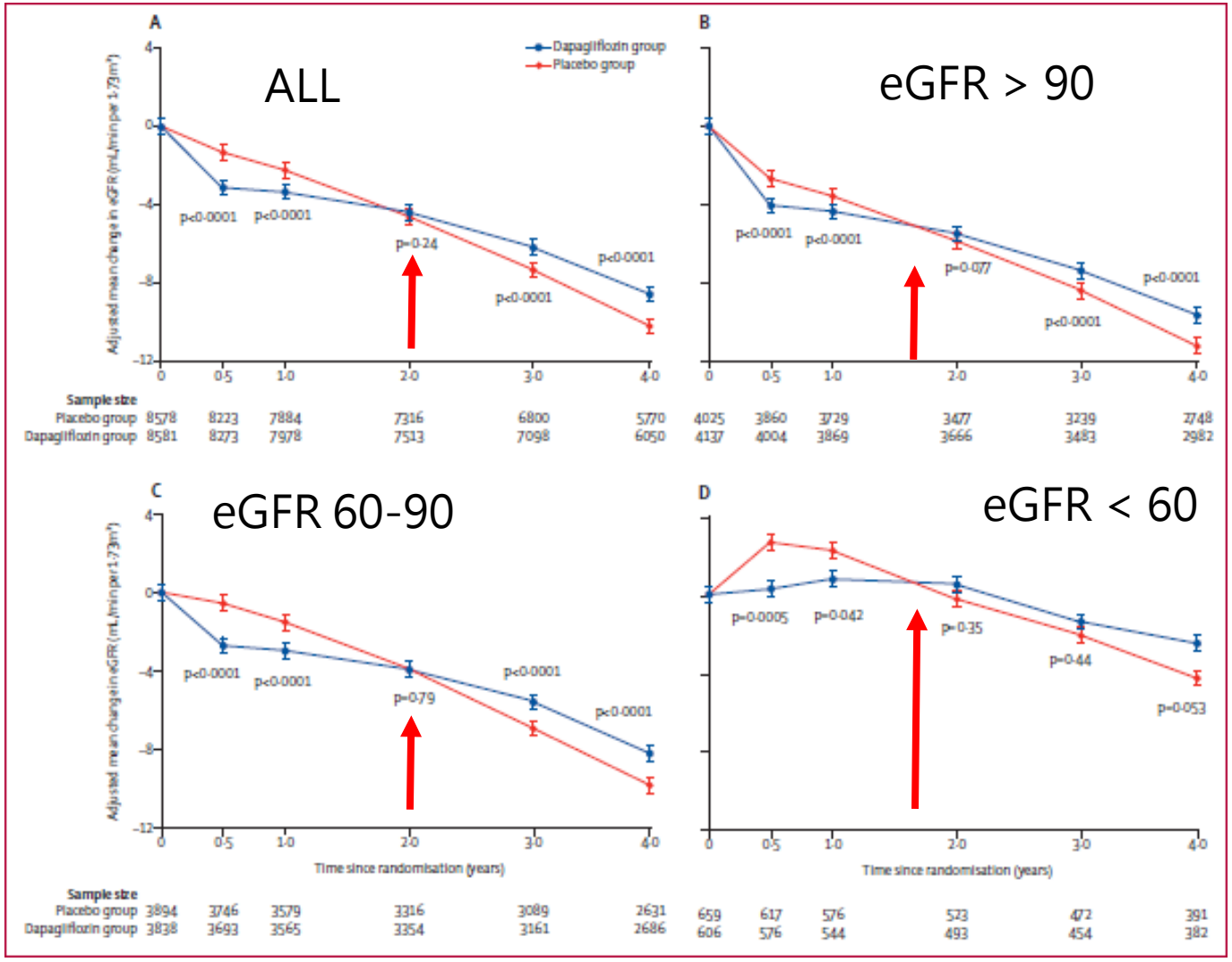
Diabetes Ther. 2020 Dec 18. doi: 10.1007/s13300-020-00953-4. Online ahead of print

* eGFR of 10 ml/min/1.73 m2
** overlaid with observed data



CAN-20201228

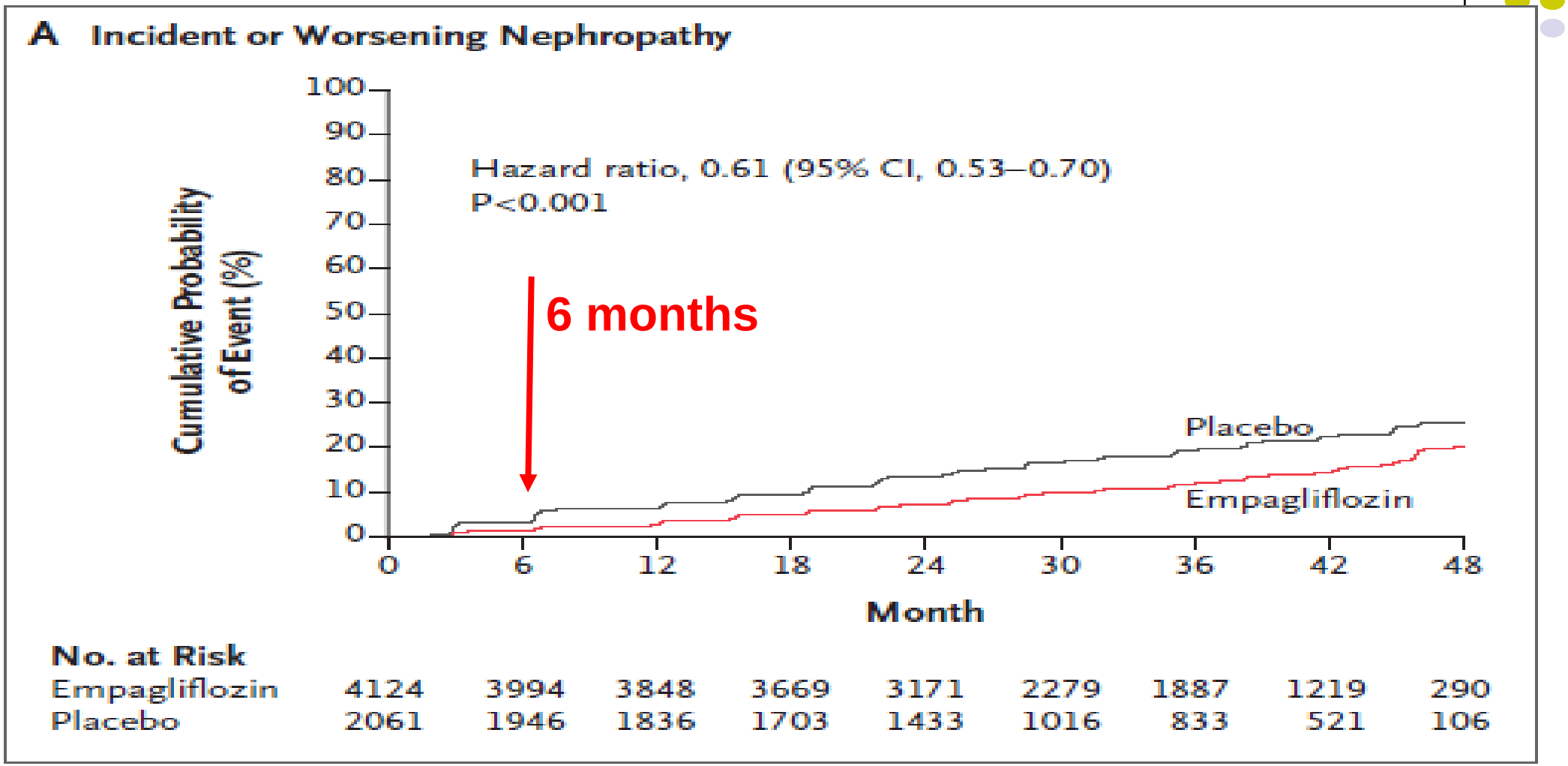
DECLARE: 病患 eGFR 兩年黃金交叉



DECLARE – CKD sub group analysis

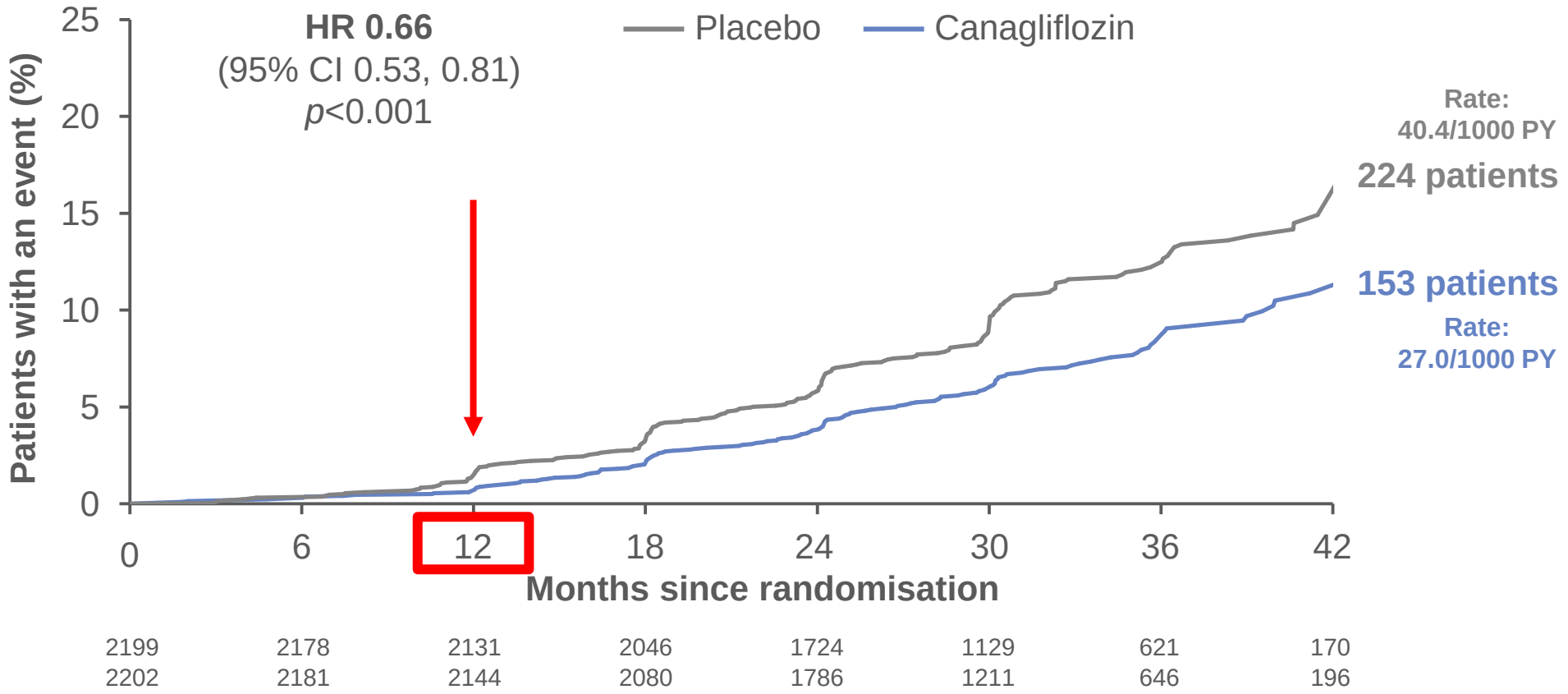
Renal OUTCOME Empa

EMPA-REG OUTCOME



CREDENCE 一年觀察到差異

CREDENCE:
composite of ESKD, doubling of serum creatinine or death from kidney causes

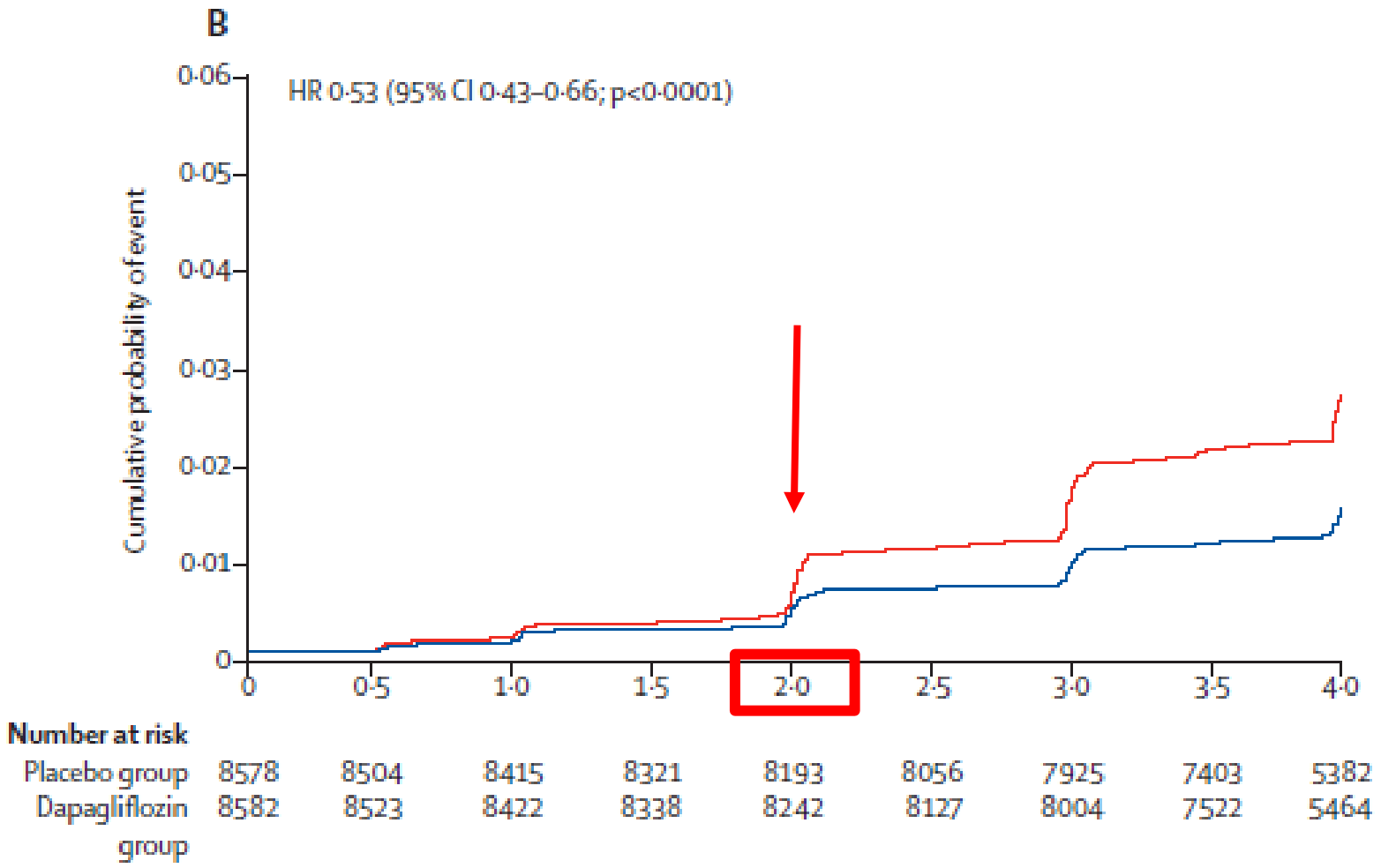


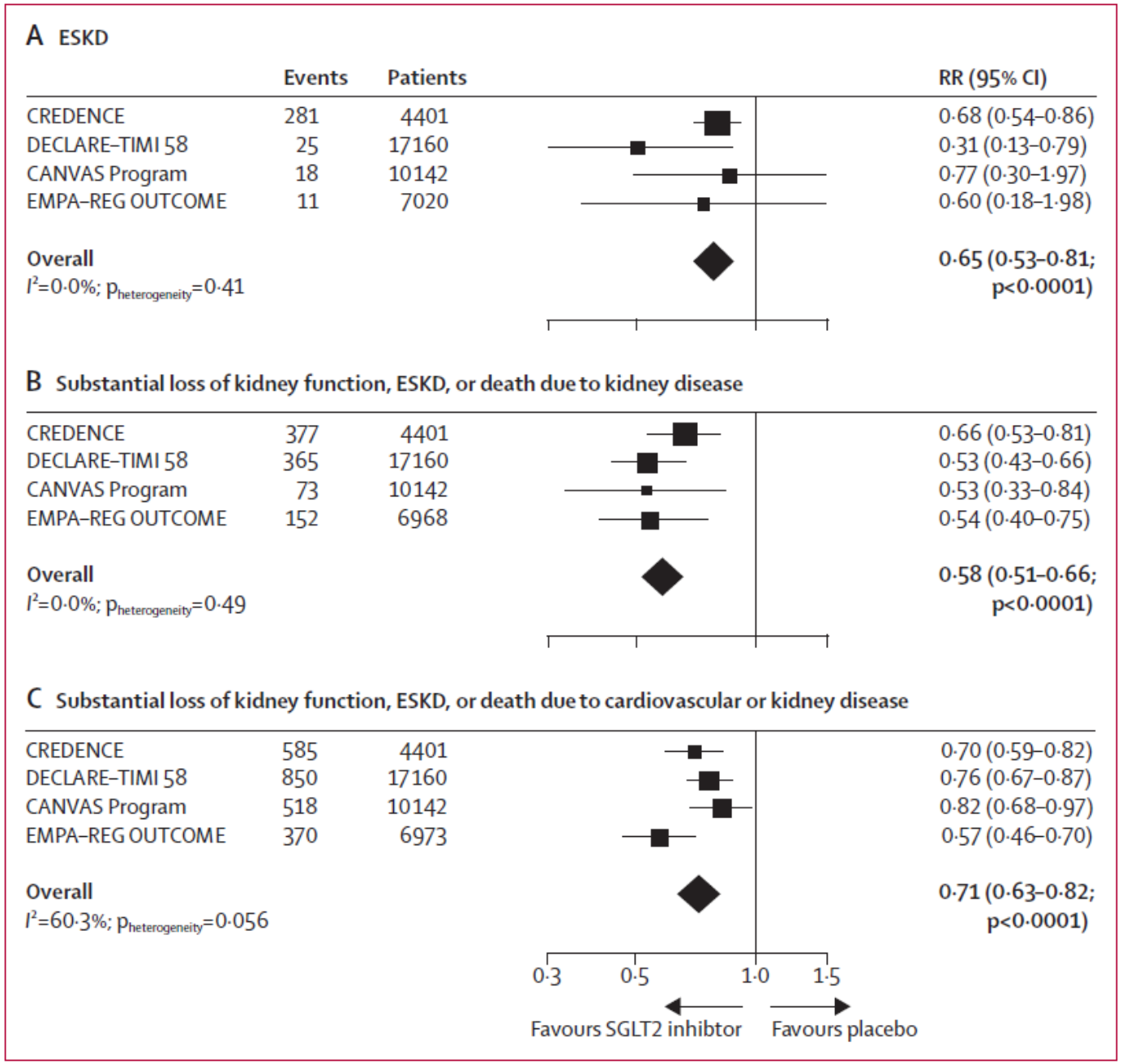
No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

*Composite of ESKD (RRT or sustained eGFR <15 ml/min/1.73 m^2), doubling of serum creatinine or death from kidney causes
eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PY, patient-years; RRR, relative risk reduction; RRT, renal replacement therapy
Perkovic V *et al. N Engl J Med* 2019; doi: 10.1056/NEJMoa1811744

Renal OUTCOME Dapa

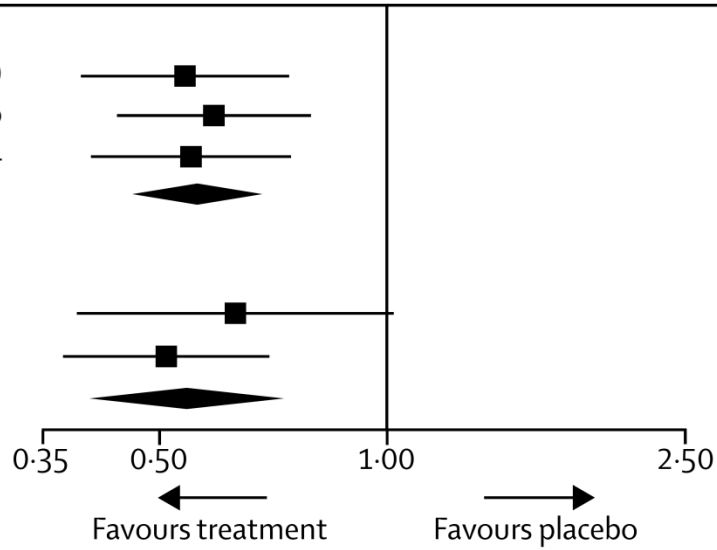
DECLARE CKD Renal outcome: 兩年看出差異




A ESKD
Events
Patients
RR (95% CI)
CREDENCE 281 4401 0·68 (0·54–0·86)
DECLARE–TIMI 58 25 17160 0·31 (0·13–0·79)
CANVAS Program 18 10142 0·77 (0·30–1·97)
EMPA–REG OUTCOME 11 7020 0·60 (0·18–1·98)
Overall
I^2=0·0%; $p_{heterogeneity}$=0·41
0·65 (0·53–0·81; p<0·0001)
B Substantial loss of kidney function, ESKD, or death due to kidney disease
CREDENCE 377 4401 0·66 (0·53–0·81)
DECLARE–TIMI 58 365 17160 0·53 (0·43–0·66)
CANVAS Program 73 10142 0·53 (0·33–0·84)
EMPA–REG OUTCOME 152 6968 0·54 (0·40–0·75)
Overall
I^2=0·0%; $p_{heterogeneity}$=0·49
0·58 (0·51–0·66; p<0·0001)
C Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease
CREDENCE 585 4401 0·70 (0·59–0·82)
DECLARE–TIMI 58 850 17160 0·76 (0·67–0·87)
CANVAS Program 518 10142 0·82 (0·68–0·97)
EMPA–REG OUTCOME 370 6973 0·57 (0·46–0·70)
Overall
I^2=60·3%; $p_{heterogeneity}$=0·056
0·71 (0·63–0·82; p<0·0001)
0·3
0·5
1·0
1·5
Favours SGLT2 inhibtor
Favours placebo

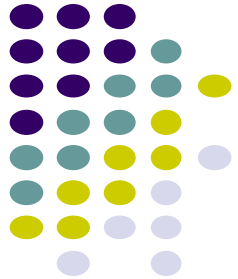
Composite of renal worsening, end-stage renal disease, or renal death

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**



DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Composite of worsening of renal function, end-stage renal disease, or renal death



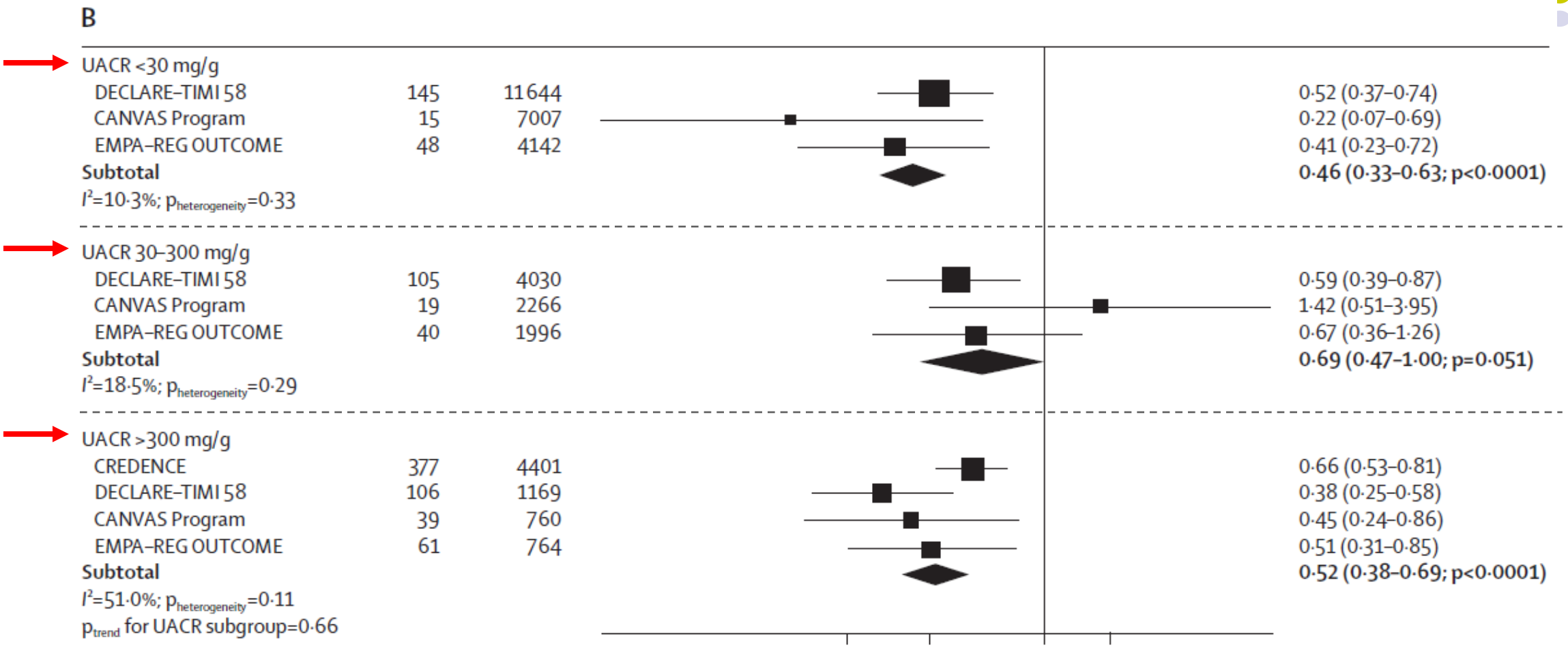
A

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		Interaction *P* value = 0.0258	
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196/1801	605/1801	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA/2039	NA/2039	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606/1265	659/1265	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406/3638	1232/3638	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA/5625	NA/5625	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838/7732	3894/7732	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043/1529	486/1529	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA/2476	NA/2476	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137/8162	4025/8162	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**

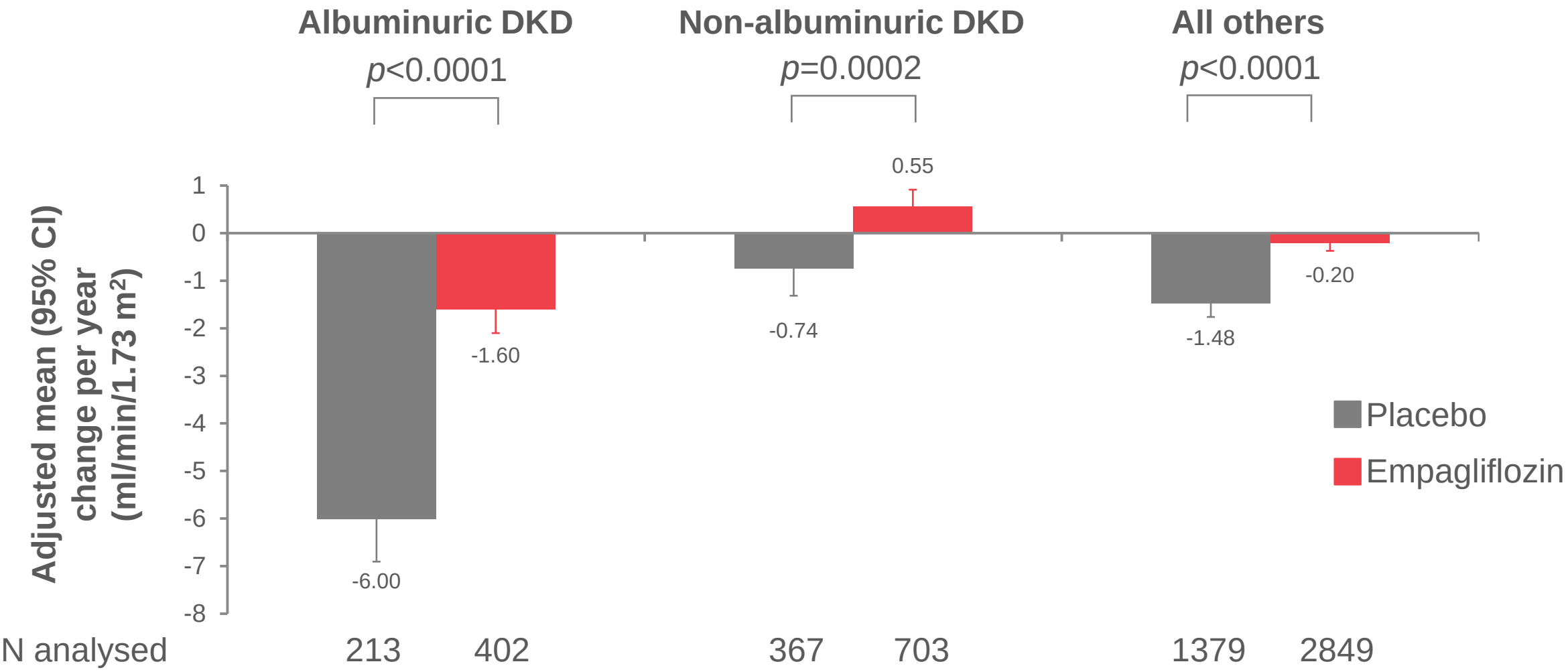
Interaction
P value = 0.0258

DOI:https://doi.org/10.1016/S0140-6736(18)32590-X.

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by UACR

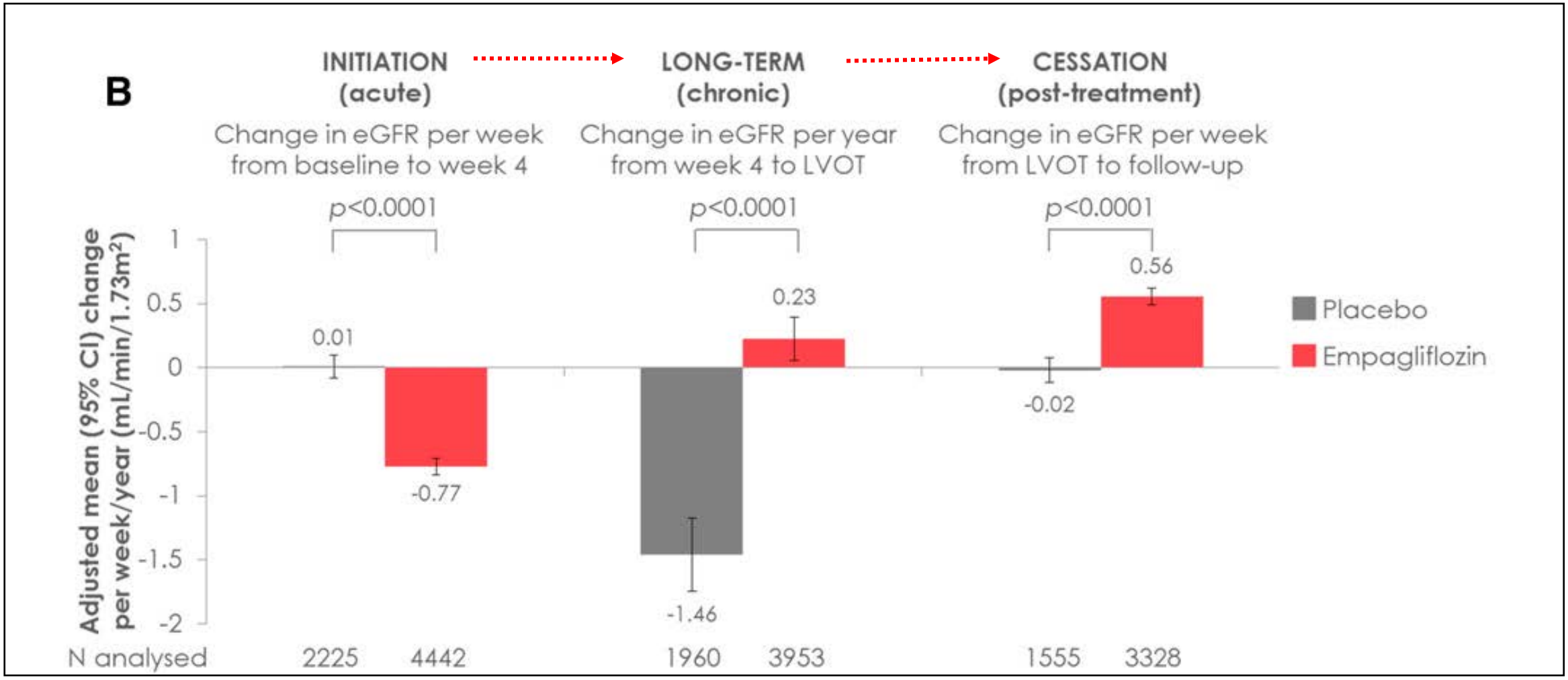


Change in eGFR per year during a pre-specified study period of chronic maintenance treatment (week 4 until last week on-treatment)

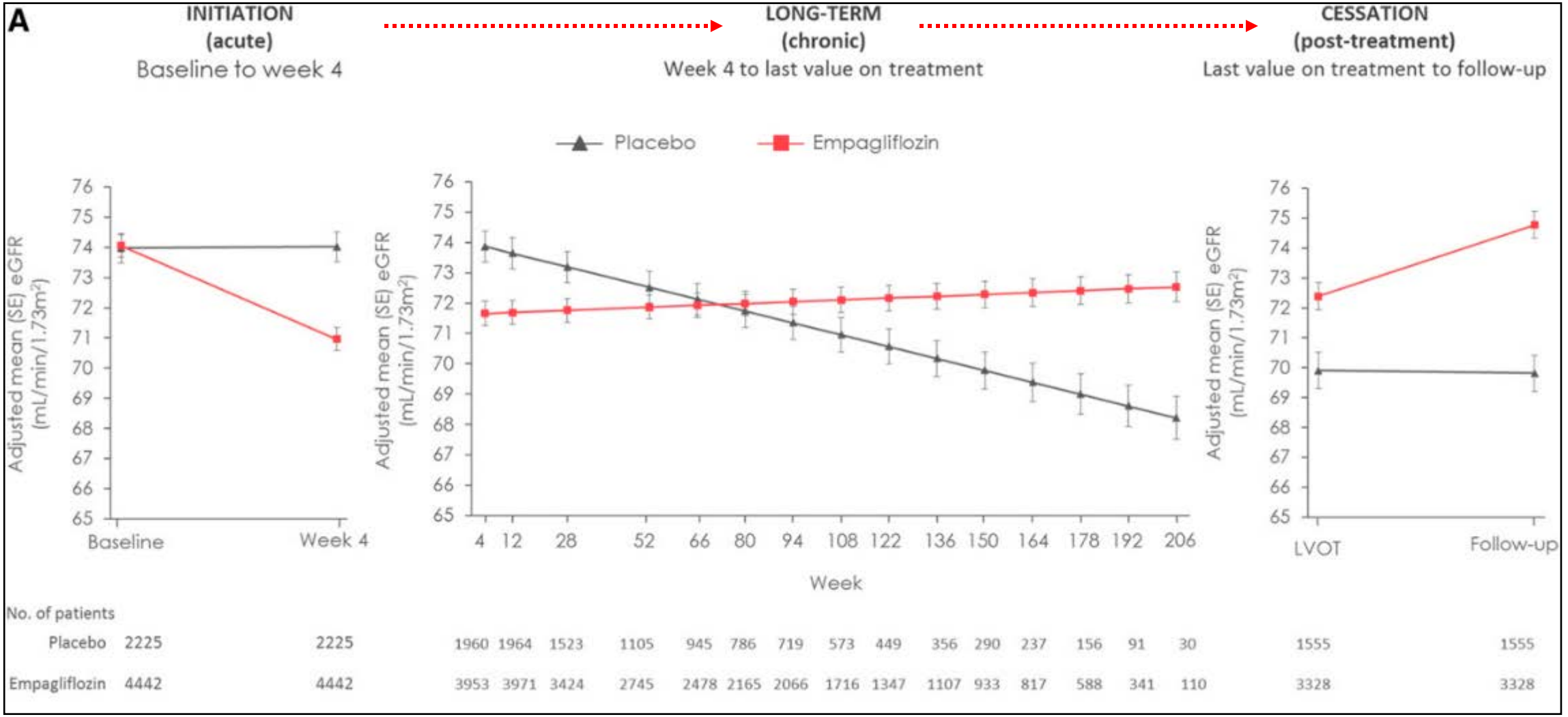


Adjusted mean eGFR slopes across selected subgroups are shown based on baseline characteristics (albuminuric DKD, non-albuminuric DKD, 'all others'). All patients treated with ≥1 dose of study drug. Adjusted mean slopes represent the average change in eGFR per year assessed using a random intercept, random coefficient model as reported previously. DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; SE, standard error.

Change in eGFR per week or year during prespecified study periods



Adjusted mean eGFR over prespecified study periods



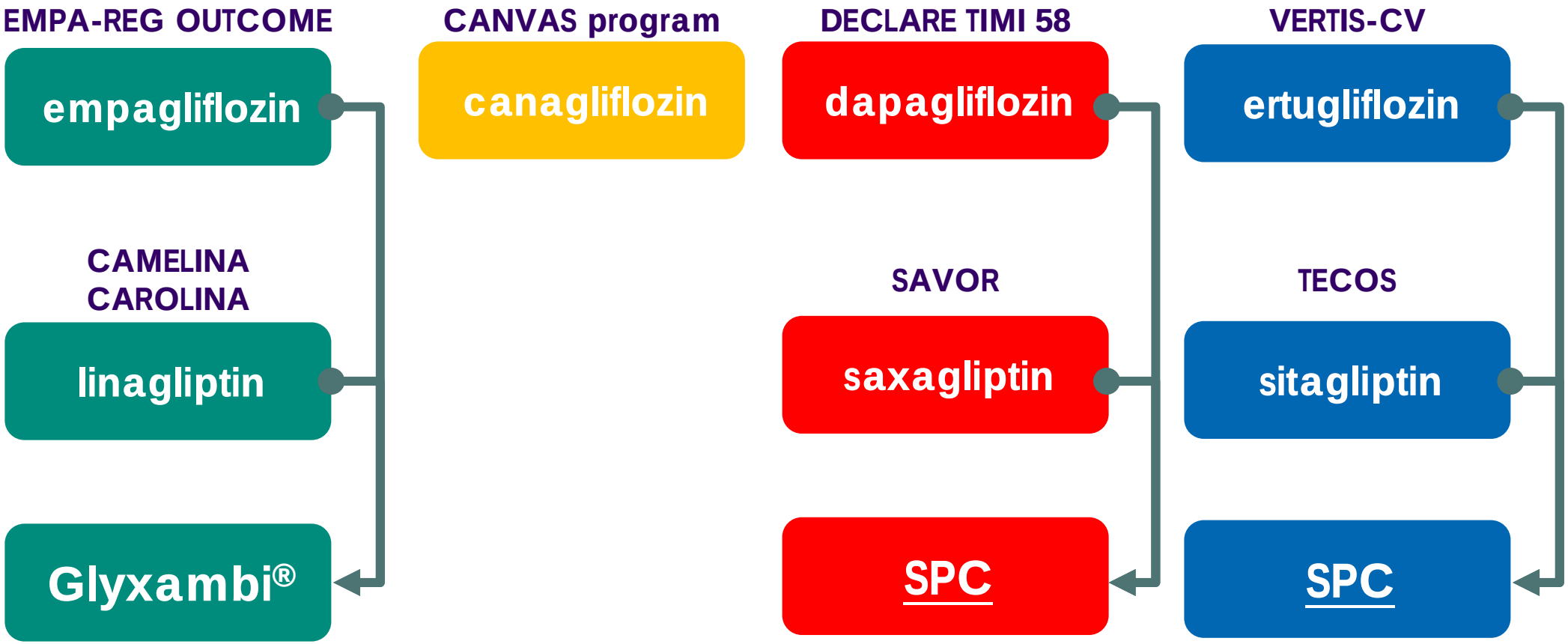
Combination therapy

目前台灣上市的 SGLT2i and DPP4i

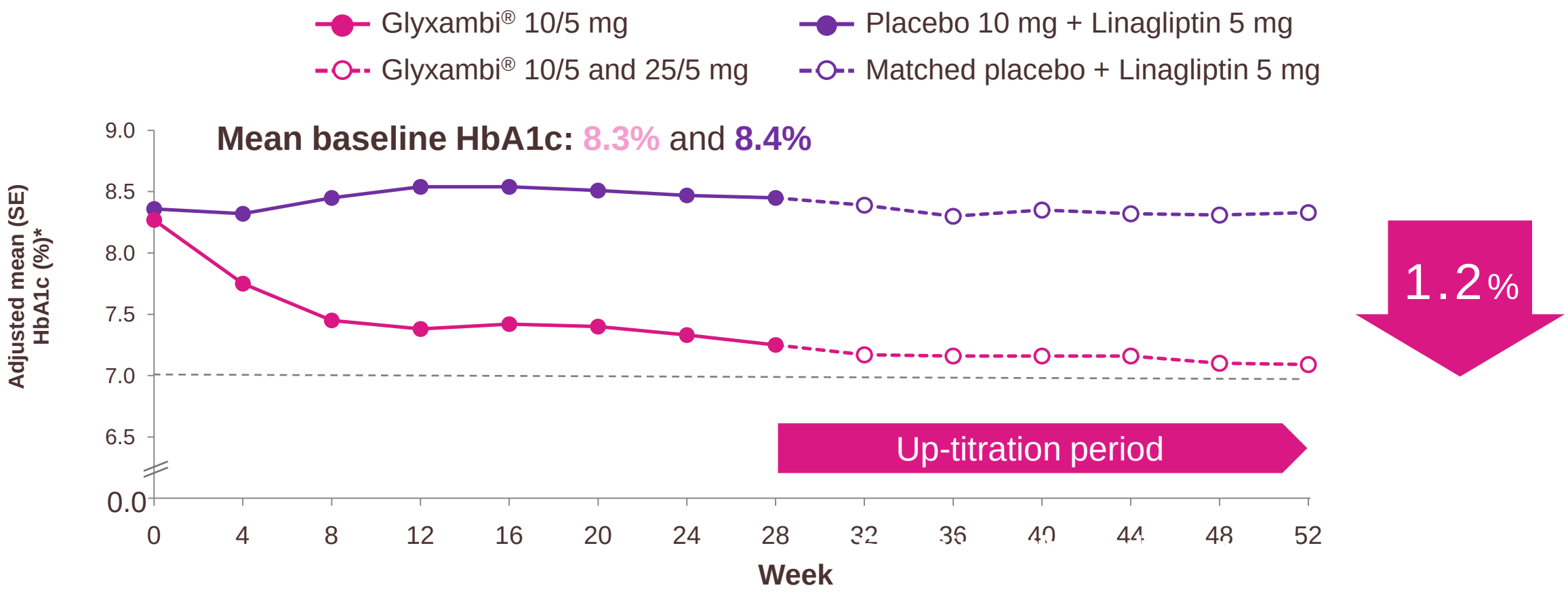
	2015 EMPA-REG OUTCOME	2017 CANVAS program	2019 DECLARE TIMI 58	2020 VERTIS-CV
SGLT2i	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin
	empagliflozin + metformin		Dapagliflozin + Metformin	
DPP4i	linagliptin		saxagliptin	Sitagliptin
	linagliptin + metformin		saxagliptin + Metformin	Sitagliptin + Metformin
	CAMELINA CAROLINA		SAVOR	TECOS

根據健保給付規範
目前只給付 SGLT2i 與 DPP4i 之複方用藥

Metformin



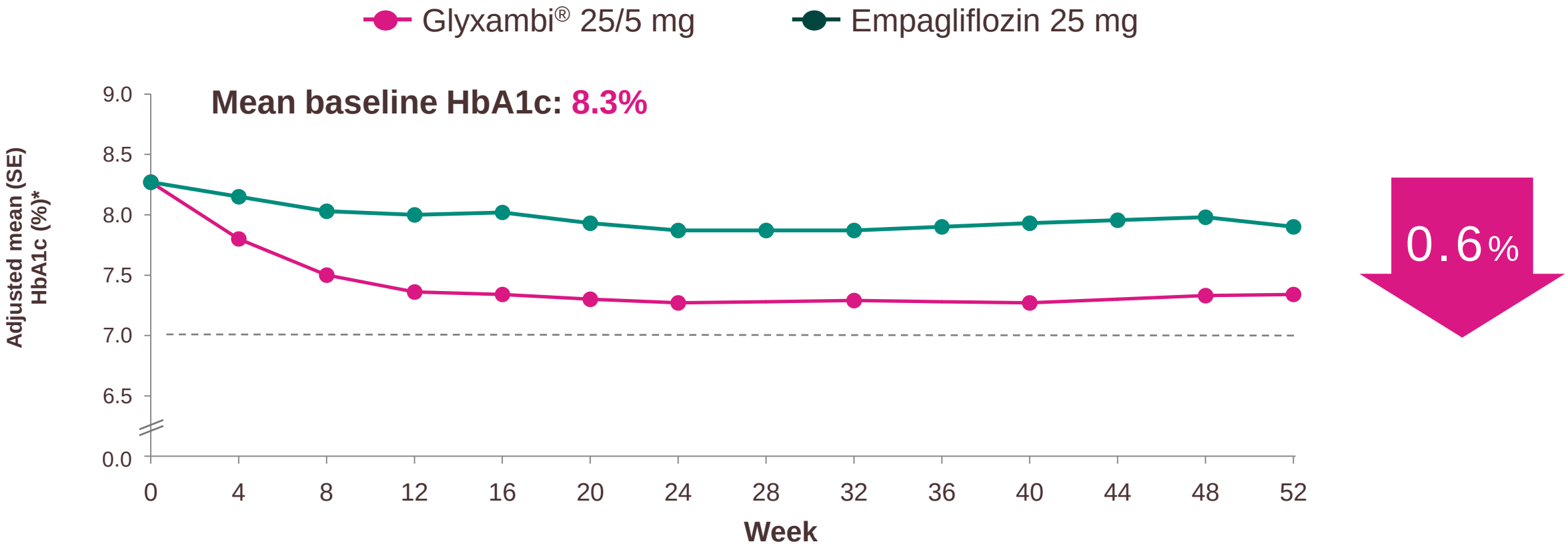
Combination 在 DPP4-i 後提供額外 1.2% A1C 降幅



FDC, fixed-dose combination

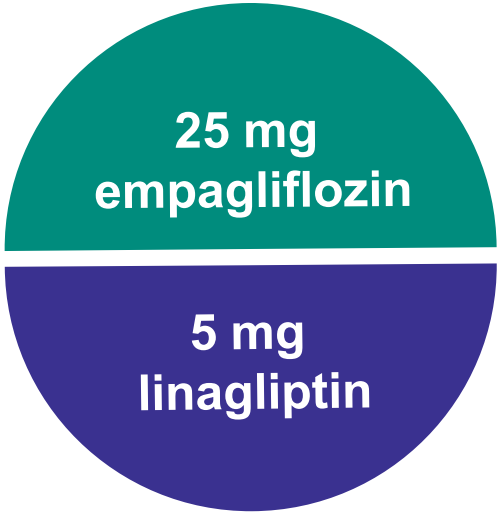
Kawamori R *et al. Diabetes Obes Metab* 2018;20:2200

Combination 在SGLT2-i後提供額外 0.6% A1C 降幅



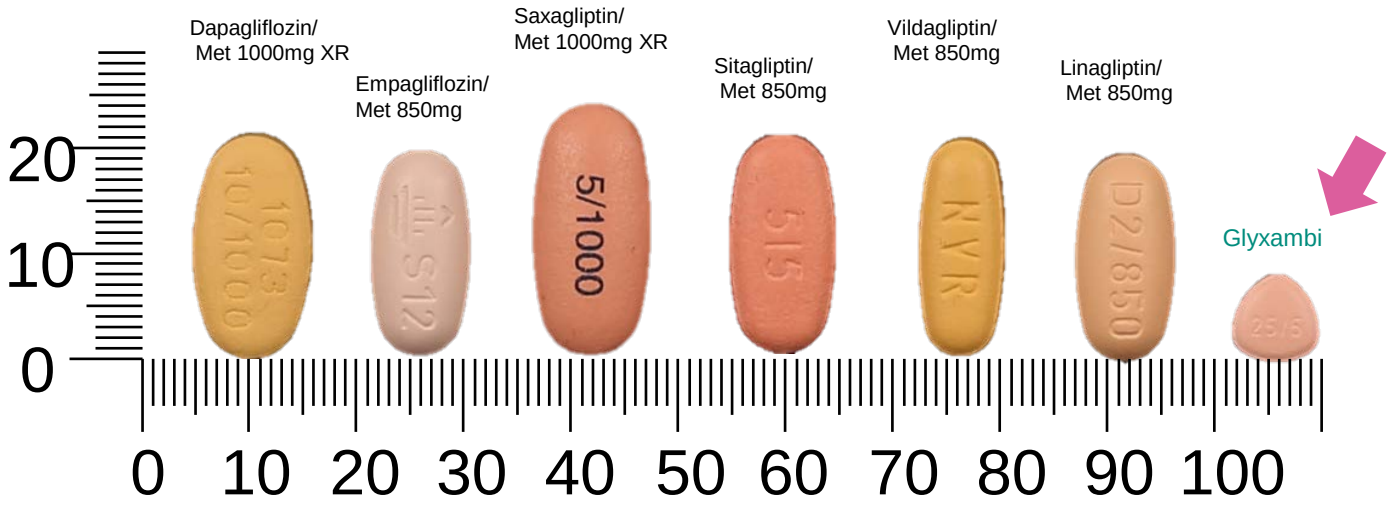
*The combination with empagliflozin 10 mg was only tested up to Week 24 (primary endpoint)
FDC, fixed-dose combination
Kaku K *et al. Diabetes Obes Metab* 2018;doi:10.1111/dom.13496

Combination在病患腎功能 eGFR 30 ml/min/1.73 m² 以上即可使用



…any time of day, with or without food

…by patients with **eGFR ≥30 ml/min/1.73 m²** with **no dose adjustment** required



Glyxambi® is **not recommended** for use in patients with **persistent eGFR <30 ml/min/1.73 m²**

Boehringer Ingelheim and Eli Lilly. Glyxambi® (empagliflozin and linagliptin) Prescribing Information. 2017

Press release

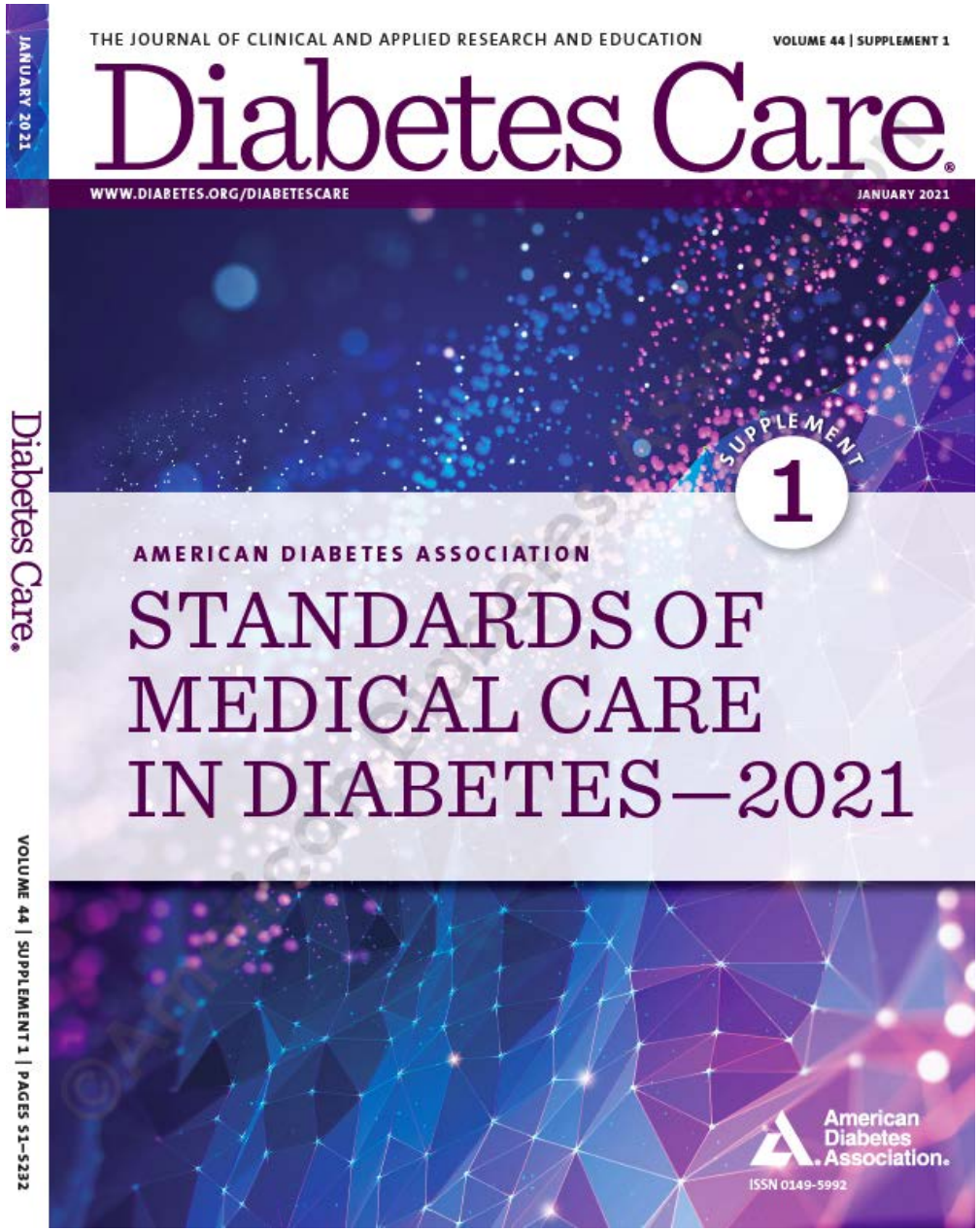
ADA Releases 2021 Standards of Medical Care in Diabetes Centered on Evolving Evidence, Technology, and Individualized Care

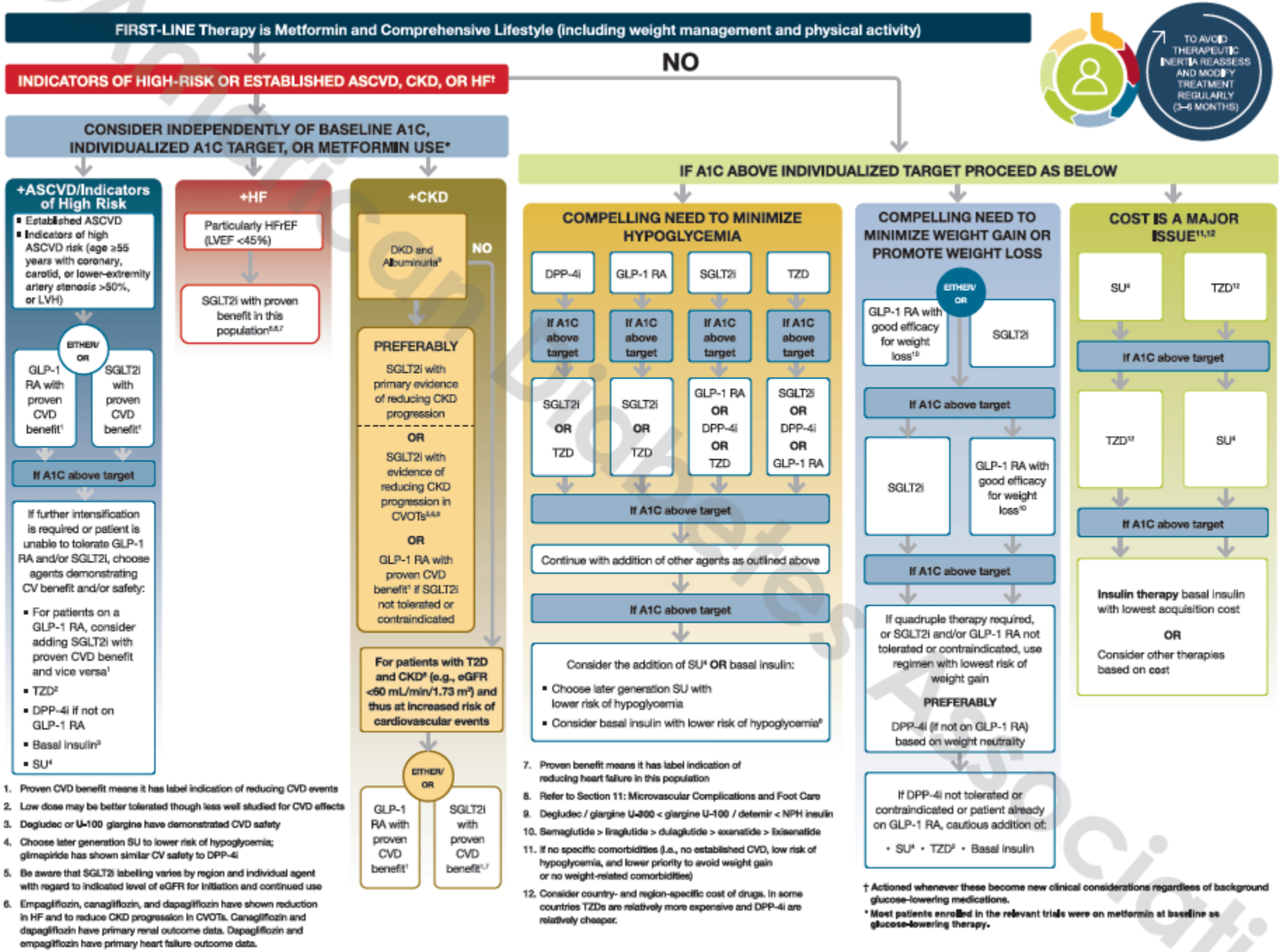
December 09, 2020

Arlington, Virginia

Today, the American Diabetes Association® released the 2021 Standards of Medical Care in Diabetes. The 2021 ***Standards of Care*** is now live online in ***Diabetes Care***. Based upon the latest scientific diabetes research and clinical trials, the *Standards of Care* includes new and updated recommendations and guidelines to care for people with diabetes.

The *Standards of Medical Care in Diabetes—2021* provides the latest in comprehensive, evidence-based recommendations for the diagnosis and treatment of children and adults with type 1, type 2, or gestational diabetes; strategies for the prevention or delay of type 2 diabetes; and therapeutic approaches that can reduce complications, mitigate cardiovascular and renal risk, and improve health outcomes.



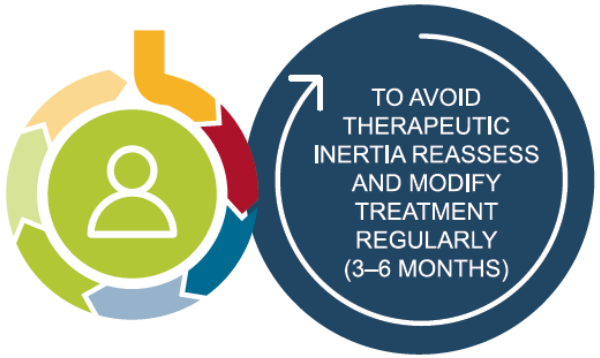


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

First-Line therapy is metformin and comprehensive lifestyle



Indicators of high-risk or established ASCVD, CKD, HF

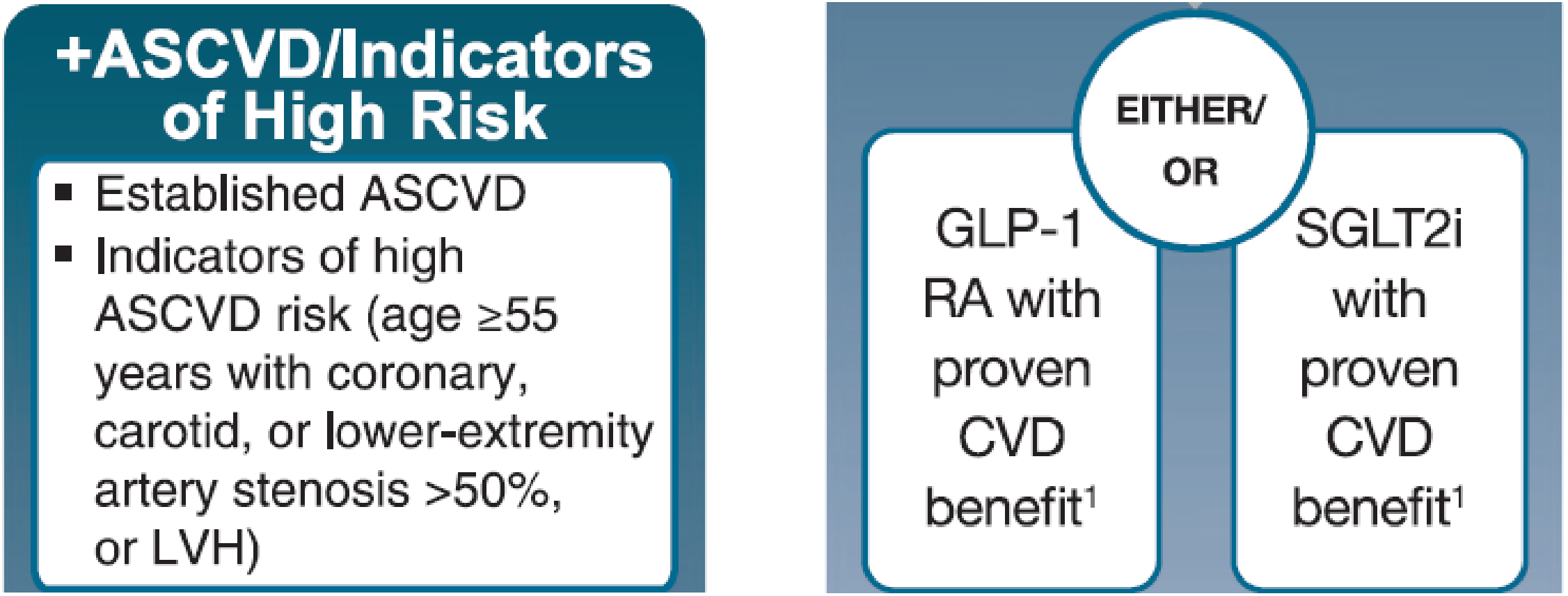
No

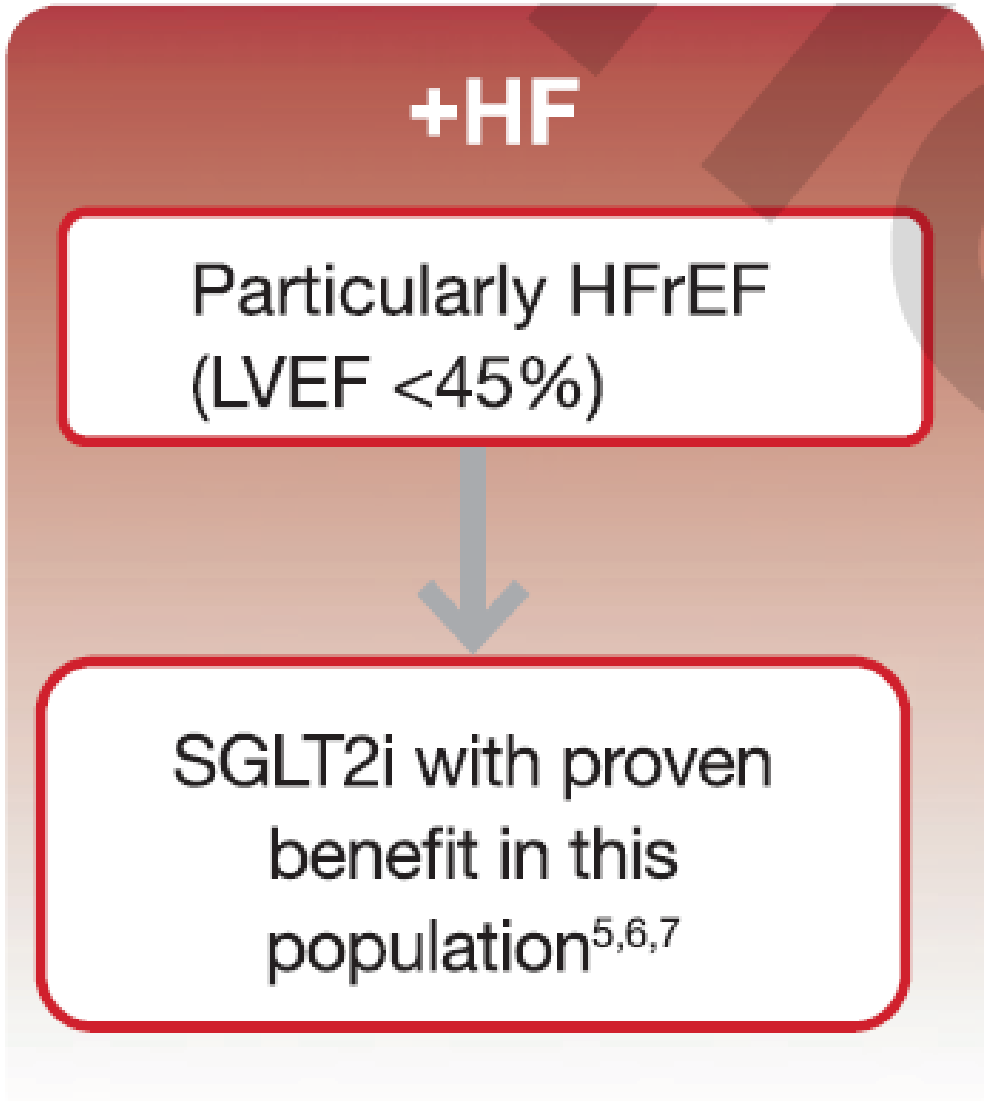
Consider independently of baseline A1C, Individualized A1C target, or metformin use

- **+ASCVD/ Indicators of high risk**
- **+HF**
- **+CKD**

If A1C above individualized target proceed as below

- **Compelling need to minimize hypoglycemia**
- **Compelling need to minimize weight gain or promote weight loss**
- **Cost is a major issue**


+ASCVD/Indicators of High Risk
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]


+HF
Particularly HFrEF (LVEF <45%)
SGLT2i with proven benefit in this population[5,6,7]

eGFR	Albuminuria: <30 mg/g <3 mg/mmol	Albuminuria: 30-299 mg/g 3-29 mg/mmol	Albuminuria: ≥300 mg/g ≥30 mg/mmol
≥90	1 if CKD	Treat 1	Refer* 2
60-89	1 if CKD	Treat 1	Refer* 2
45-59	Treat 1	Treat 2	Refer 3
30-44	Treat 2	Treat 3	Refer 3
15-29	Refer* 3	Refer* 3	Refer 4+
<15	Refer 4+	Refer 4+	Refer 4+

+CKD

DKD and Albuminuria[8]

Yes

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

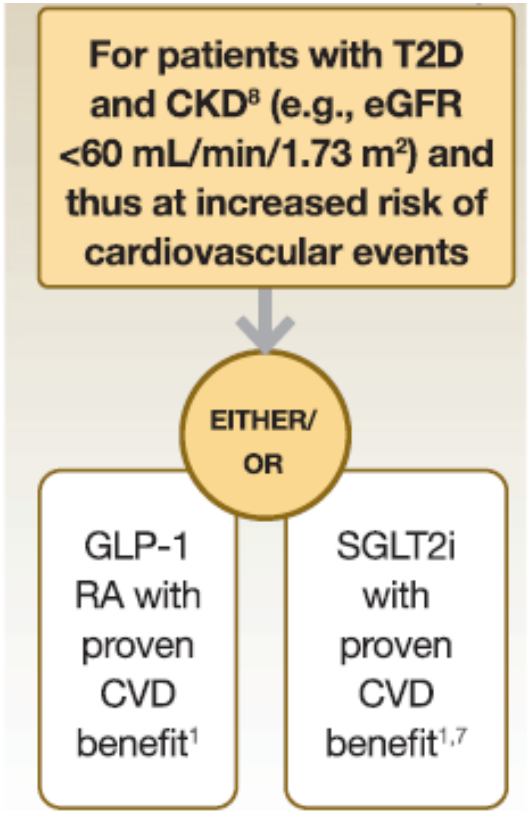
OR

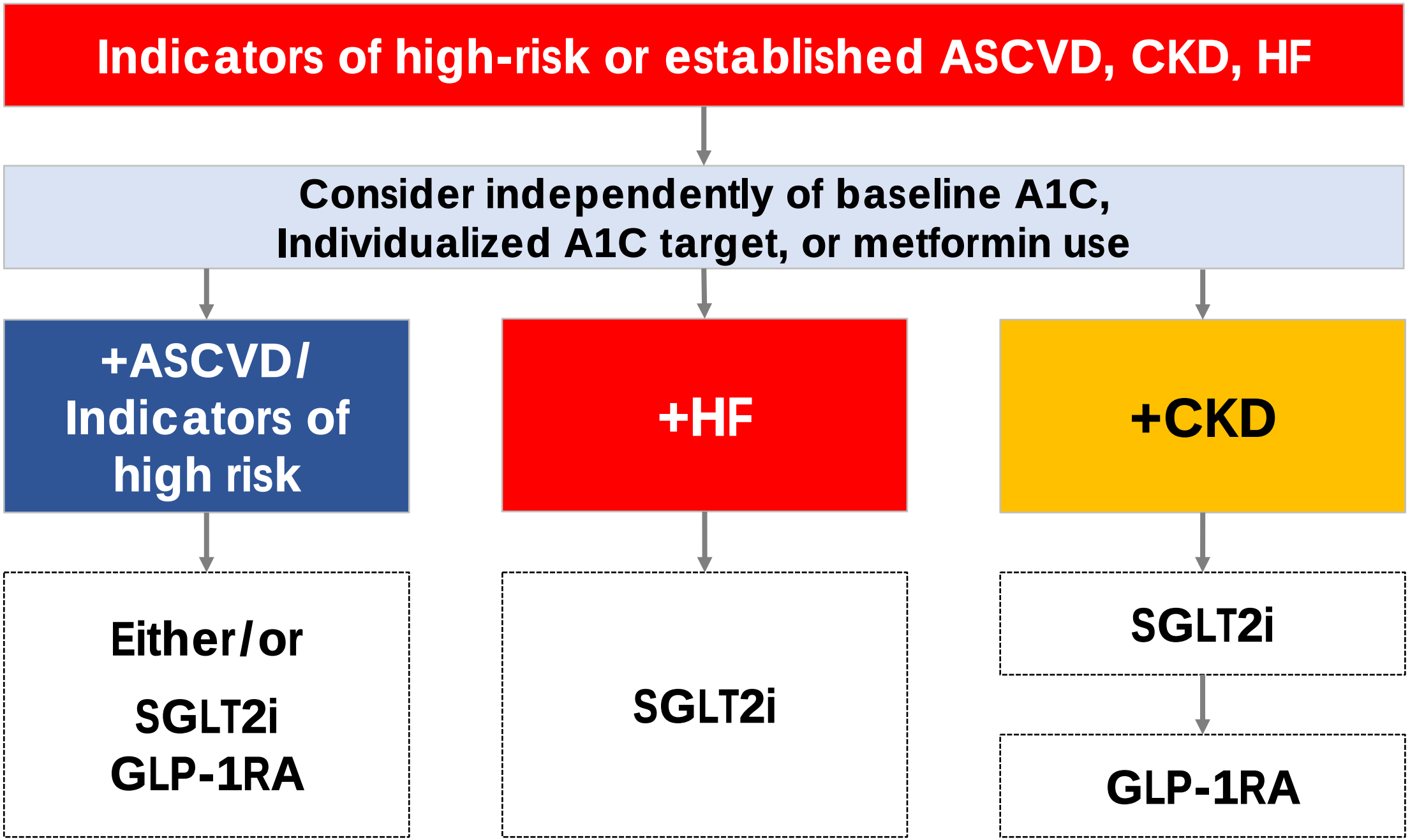
SGLT2i with evidence of reducing CKD progression in CVOTs[5,6,8]

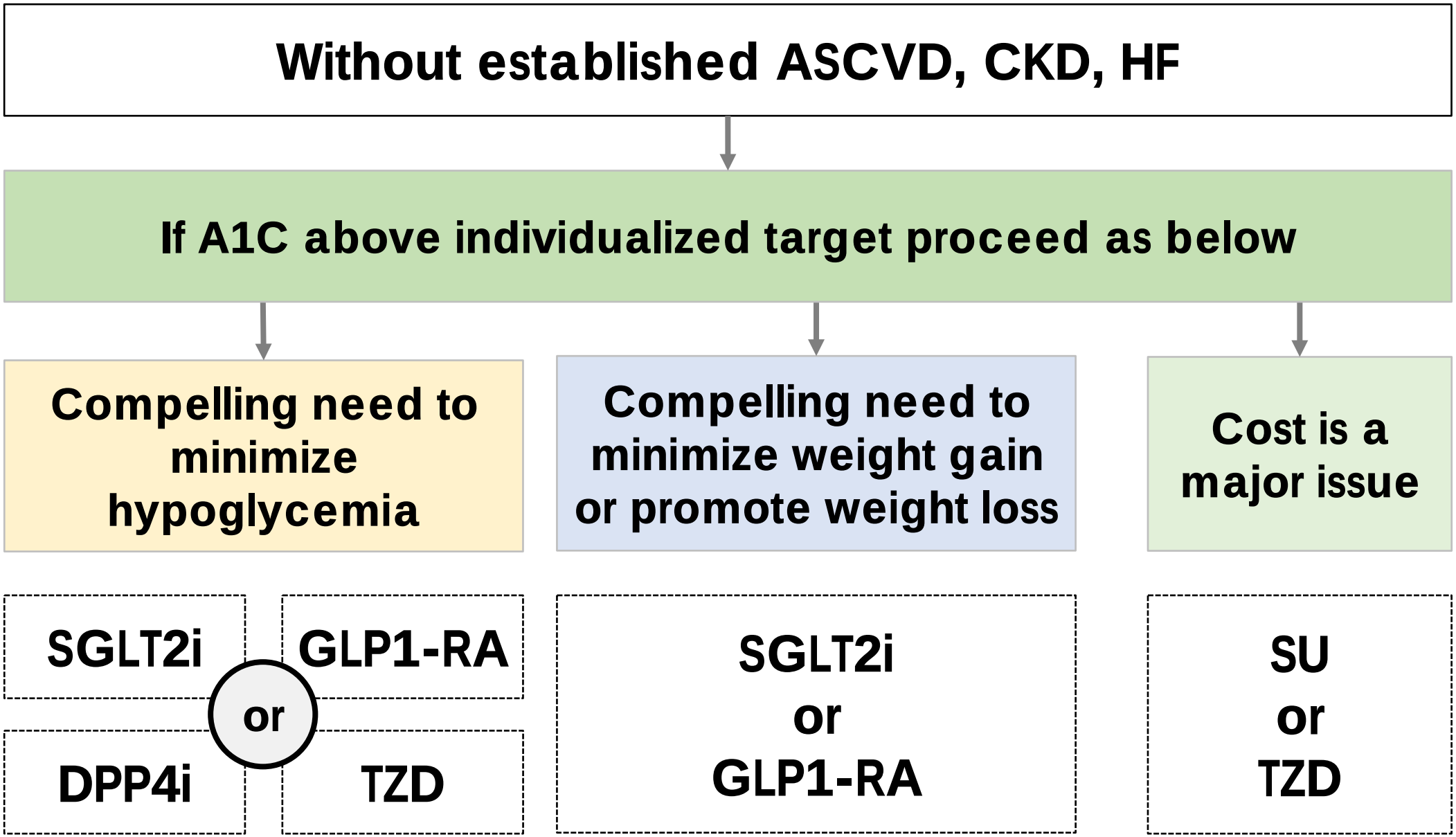
OR

GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated

No




Indicators of high-risk or established ASCVD, CKD, HF
Consider independently of baseline A1C, Individualized A1C target, or metformin use
+ASCVD/ Indicators of high risk
+HF
+CKD
Either/or
SGLT2i
GLP-1RA
SGLT2i
SGLT2i
GLP-1RA


Without established ASCVD, CKD, HF
If A1C above individualized target proceed as below
Compelling need to minimize hypoglycemia
Compelling need to minimize weight gain or promote weight loss
Cost is a major issue
SGLT2i
GLP1-RA
or
DPP4i
TZD
SGLT2i
or
GLP1-RA
SU
or
TZD

Specific and patient factors to consider when selecting SGLT2i

CV effects	
ASCVD	**HF**
Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡

Renal effects	
Progression of DKD	**Dosing/use considerations***
Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)

Additional considerations
▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene

Thanks for your attention