Redefining Diabetic Management: Time for a Paradigm Shift

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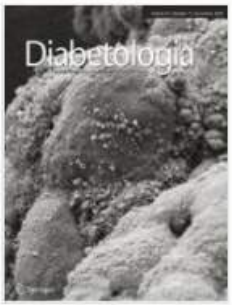

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Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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Consensus Report
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Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

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American Diabetes Association. Diabetes Care

Diabetes Care. 2018 Oct 4. pii: dci180033. doi: 10.2337/dci18-0033.

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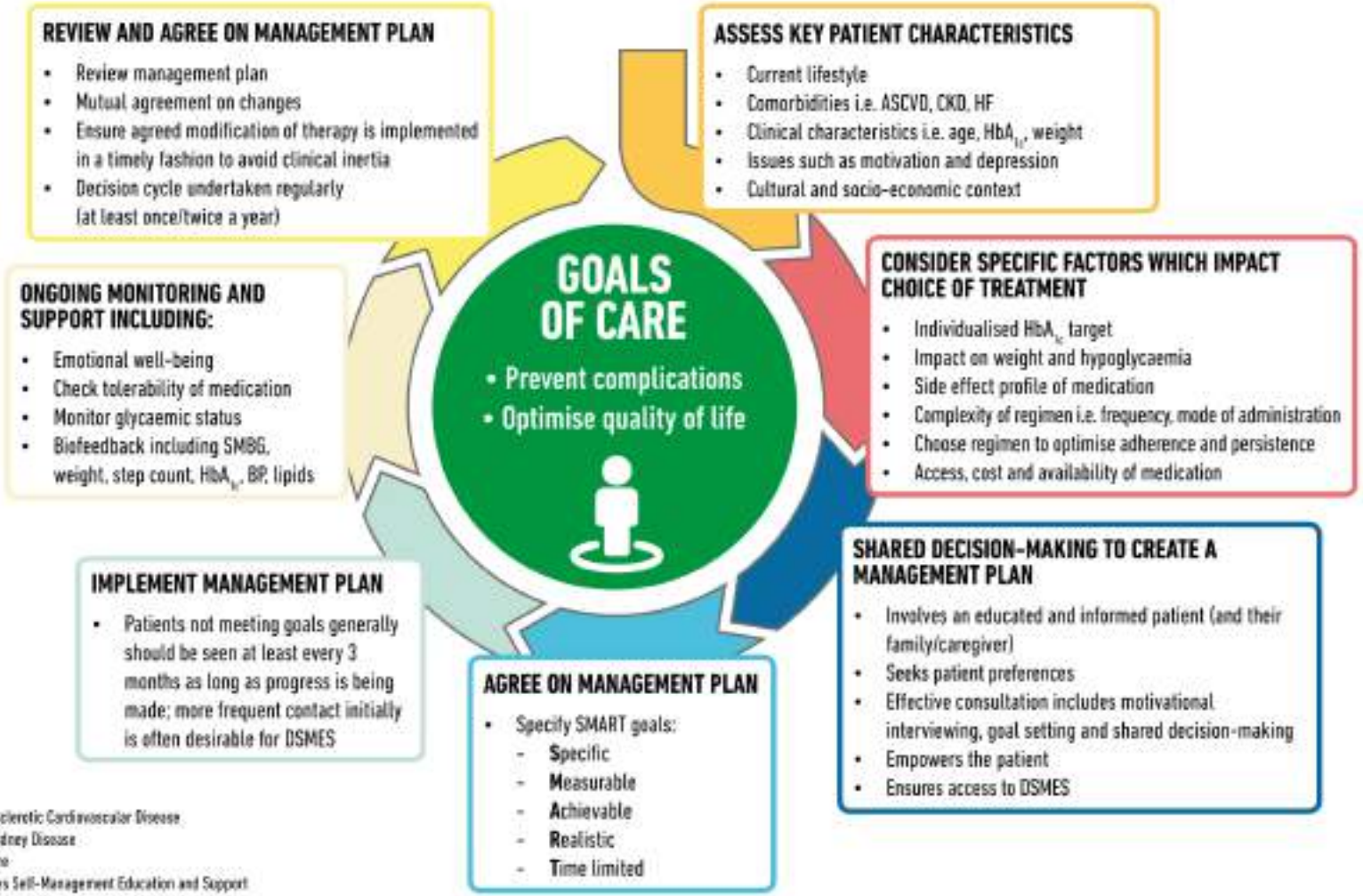
TW-6570_FOR_18/10/2018

Consensus recommendation

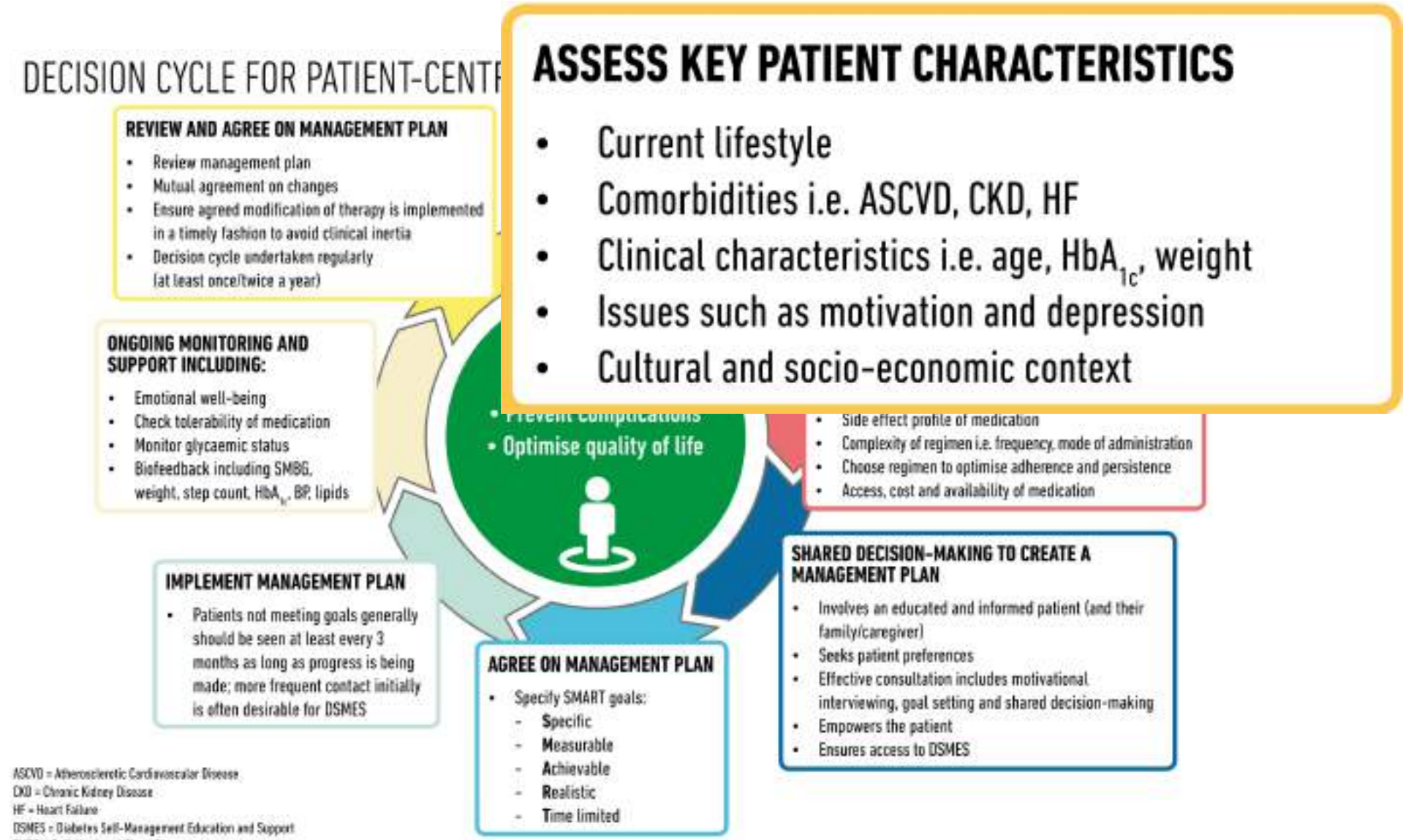
- Providers and healthcare systems should prioritize the delivery of patient-centered care.
- All people with type 2 diabetes should be offered access to ongoing DSMES (Diabetes self-management education and support) programs.
- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medications.

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



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

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes



ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities i.e. ASCVD, CKD, HF
- Clinical characteristics i.e. age, HbA_{1c}, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes

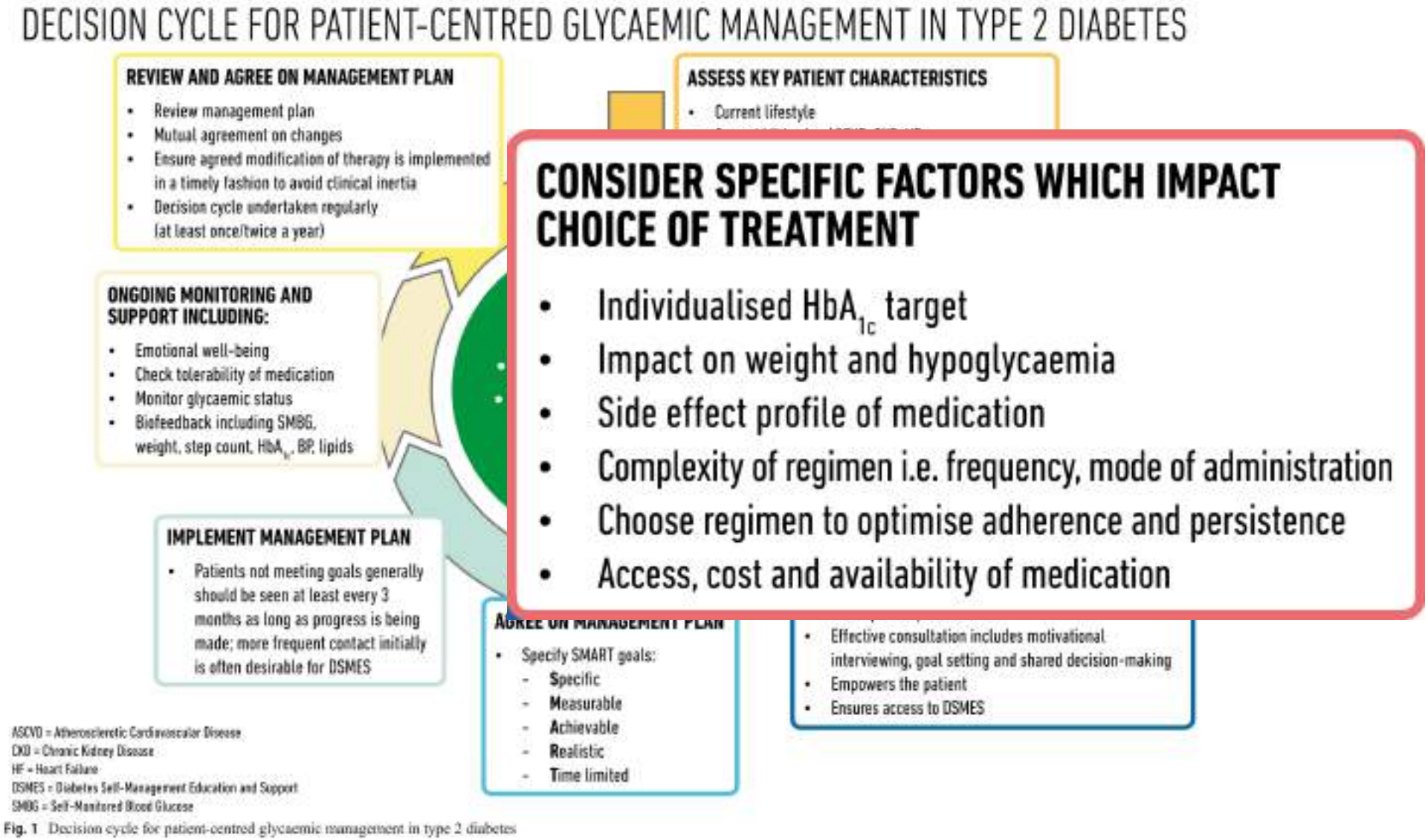
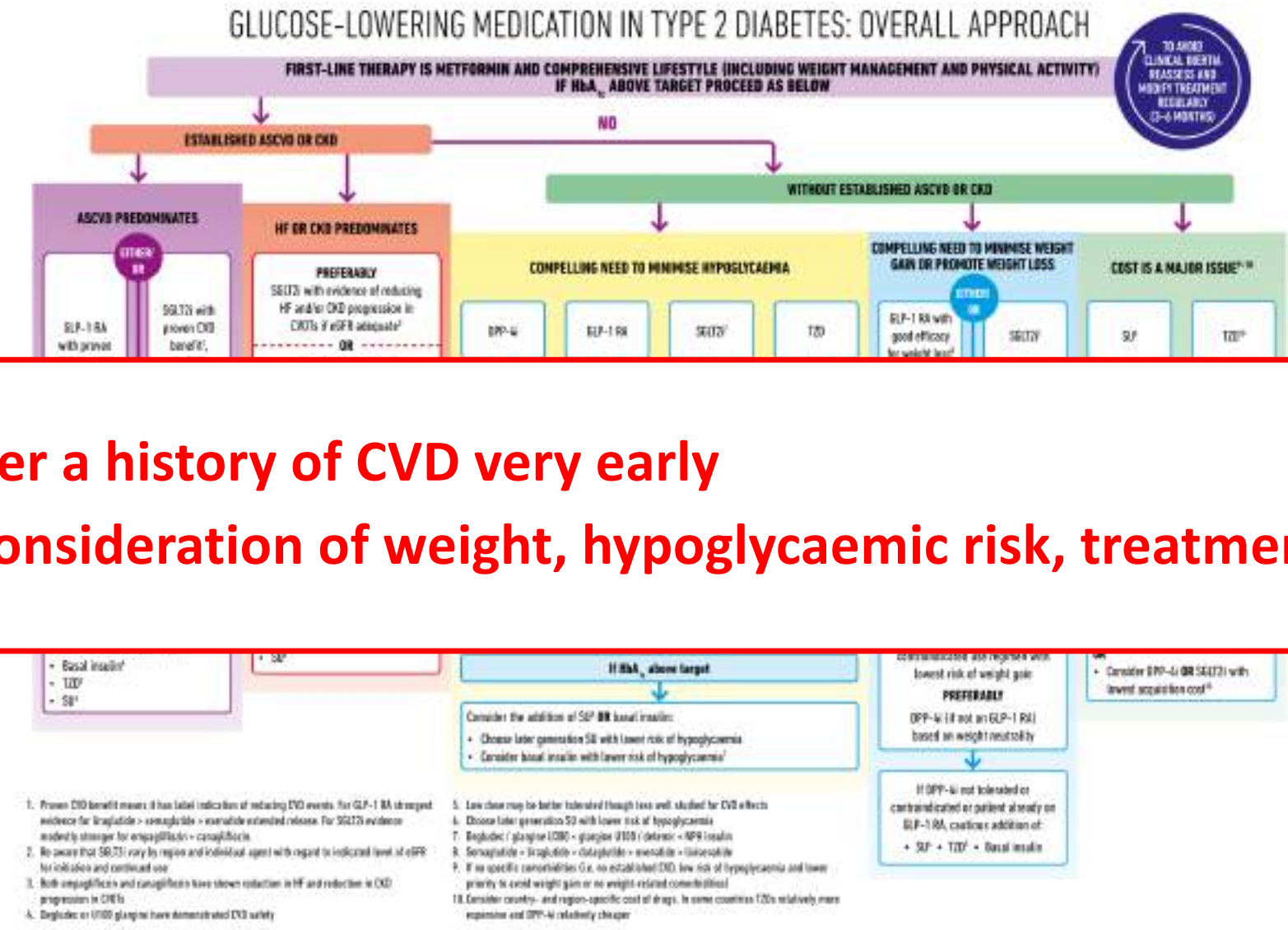


Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes



- **Consider a history of CVD very early**
- **Early consideration of weight, hypoglycaemic risk, treatment cost**

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

CV outcome trials with DPP4 inhibitors, GLP1 receptor agonists, and SGLT2 inhibitors

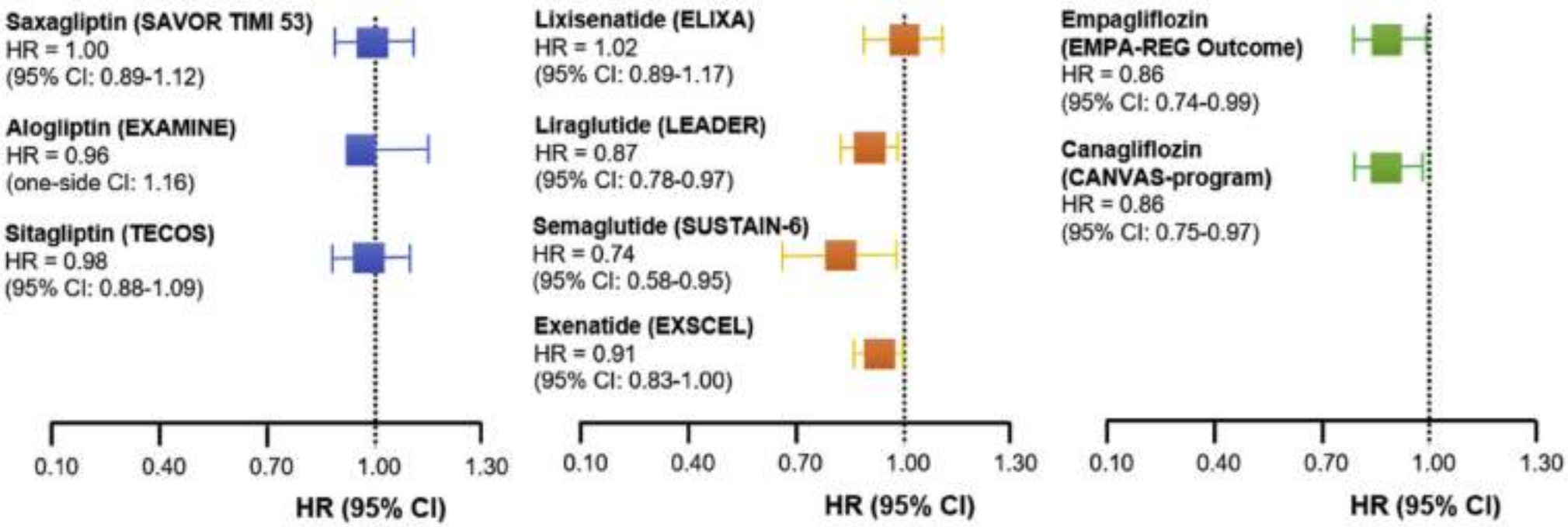
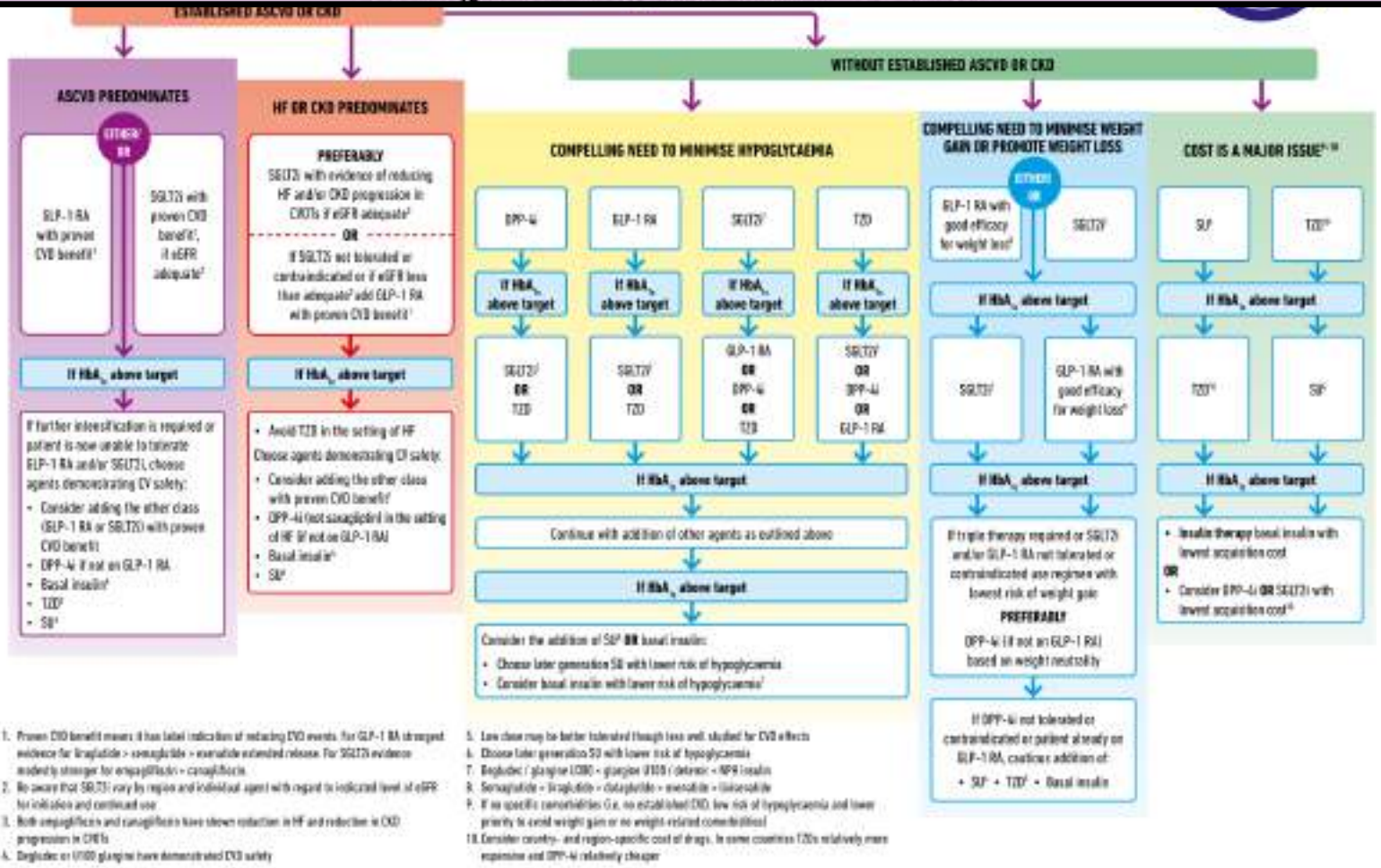


Fig. 1. Cardiovascular outcome trials with DPP4 inhibitors, GLP1 receptor agonists, and SGLT2 inhibitors.
SAVOR TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; SUSTAIN-6, a Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANVAS, Canagliflozin Cardiovascular Assessment Study.

Atherosclerosis 272 (2018) 33e40

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence evident & stronger for empagliflozin > canagliflozin
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CKDTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
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 hypoglycaemia 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

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

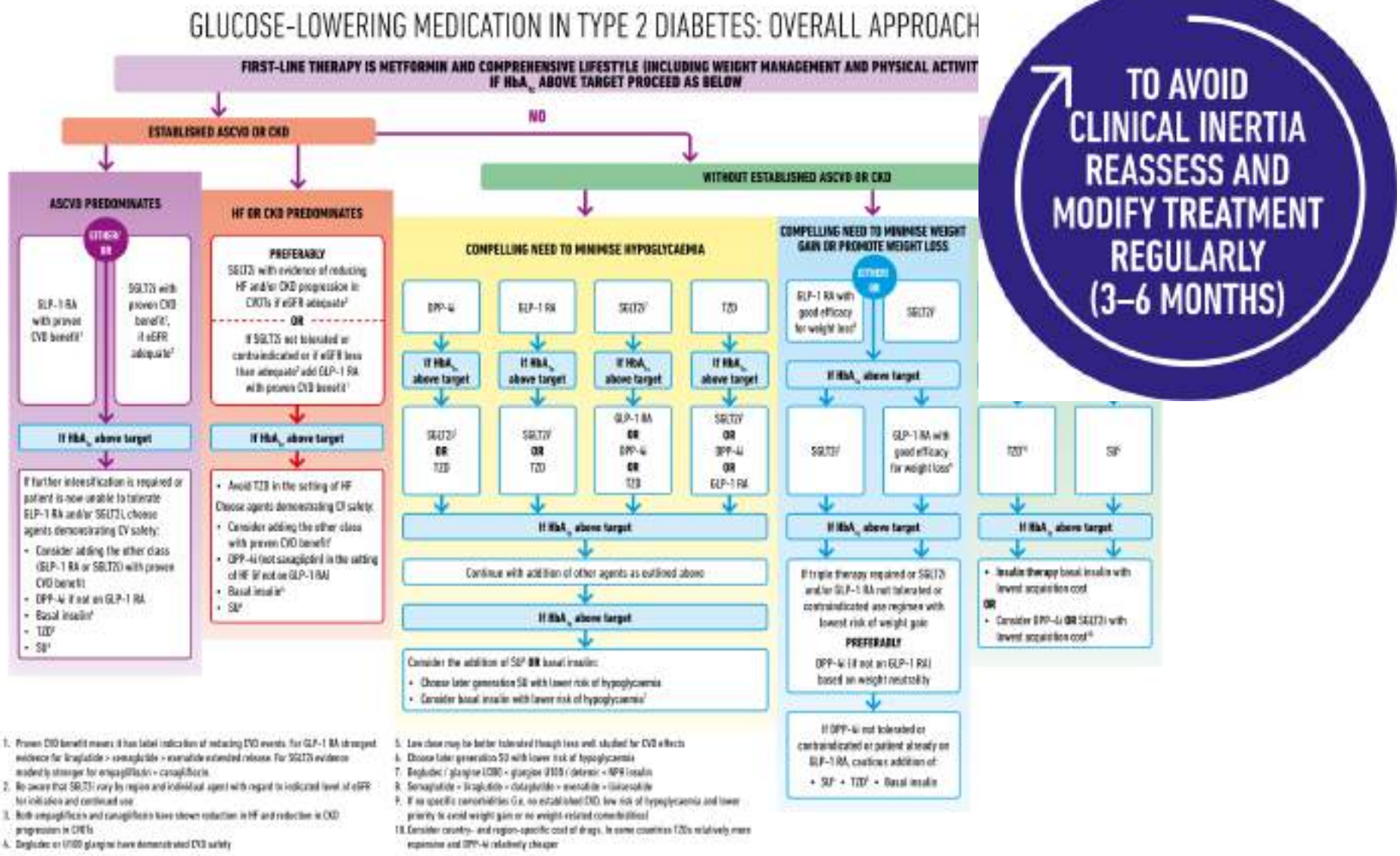


Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

ESTABLISHED ASCVD OR CKD

WITHOUT ESTABLISHED ASCVD OR CKD

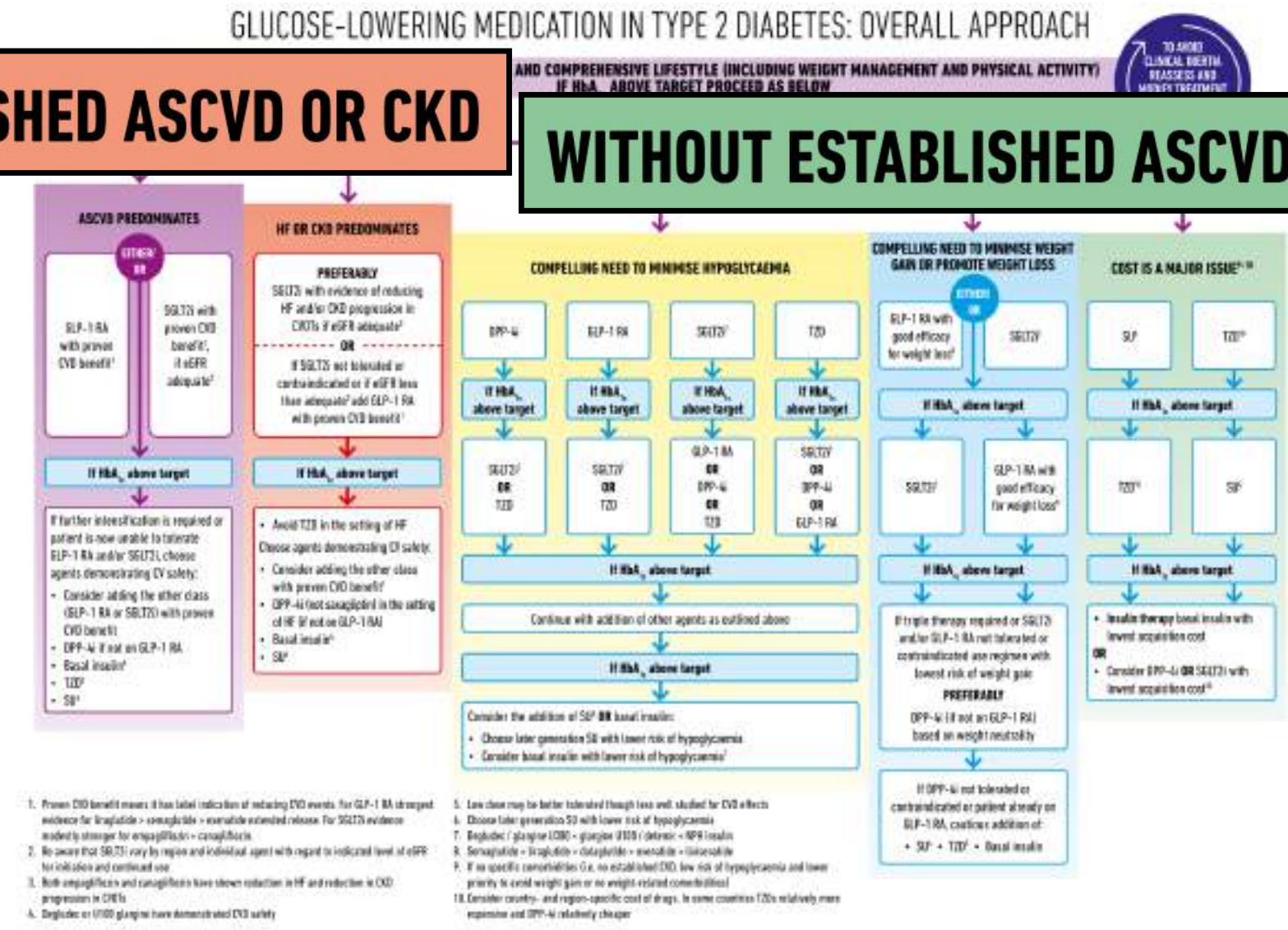
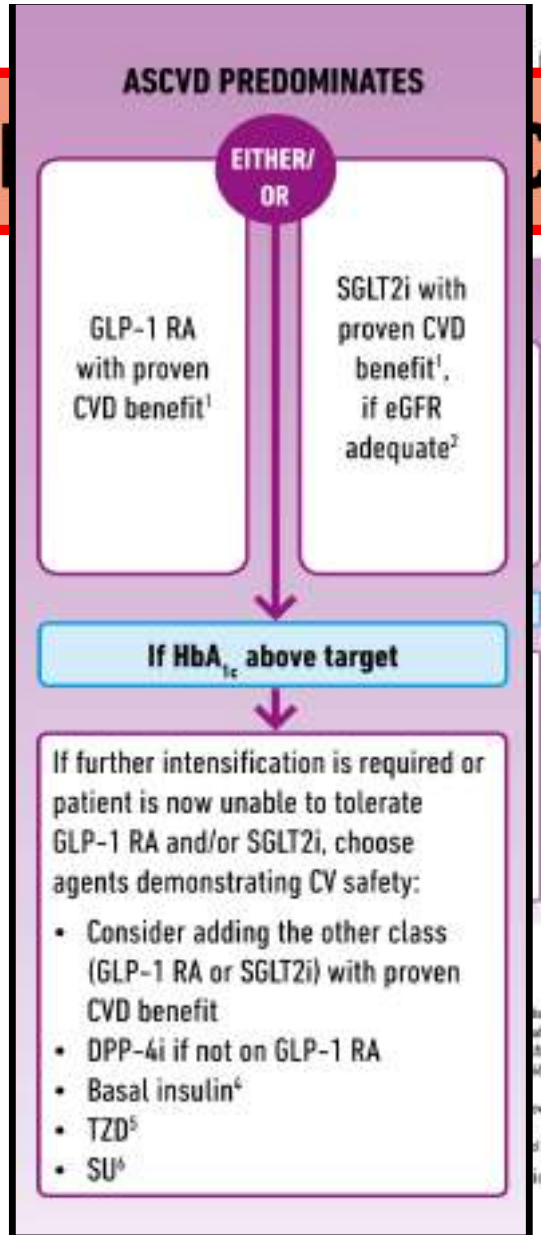
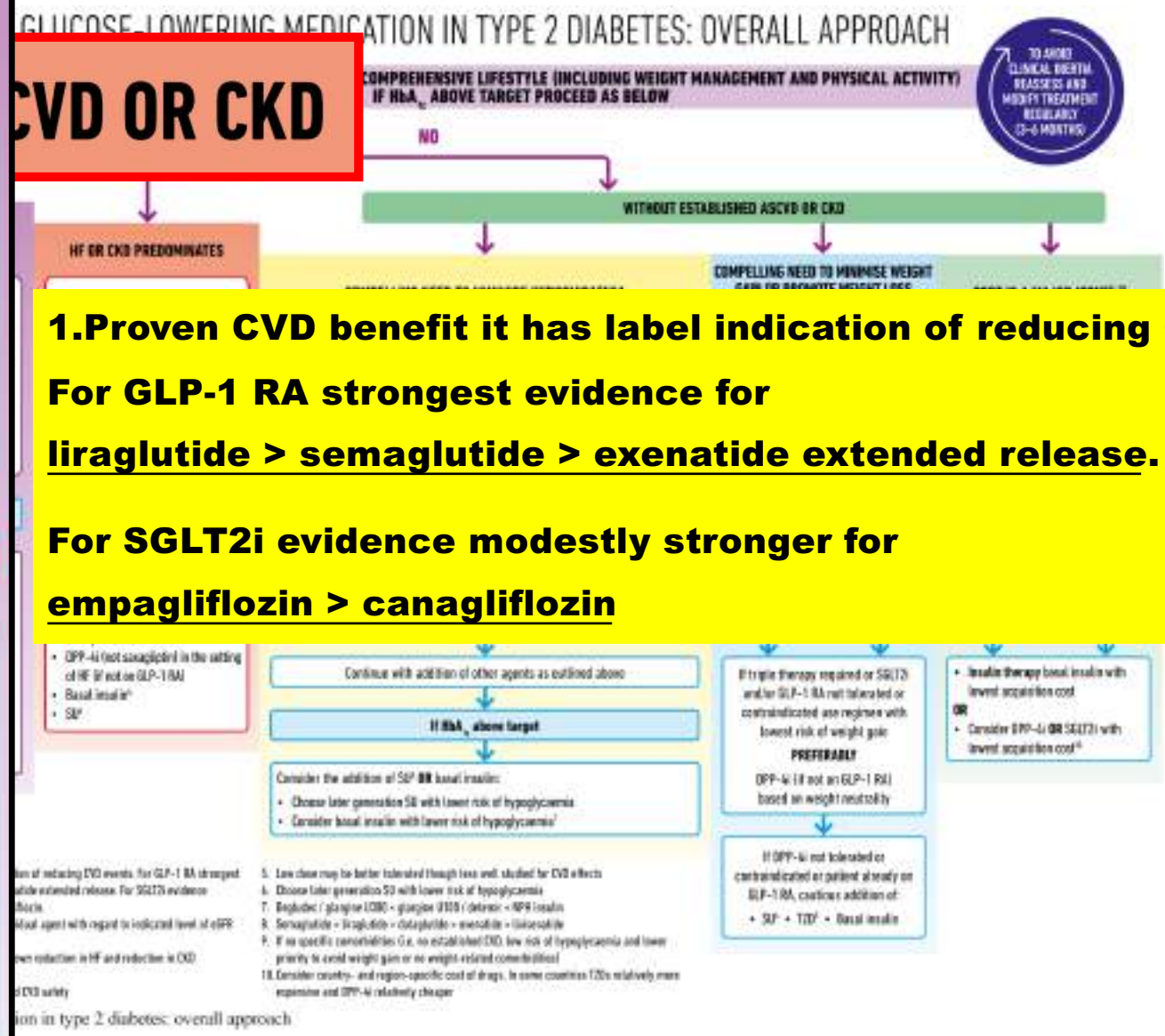


Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach



CVD OR CKD



1.Proven CVD benefit it has label indication of reducing CVD events.

For GLP-1 RA strongest evidence for

liraglutide > semaglutide > exenatide extended release.

For SGLT2i evidence modestly stronger for

empagliflozin > canagliflozin

CVOT of GLP-1RA

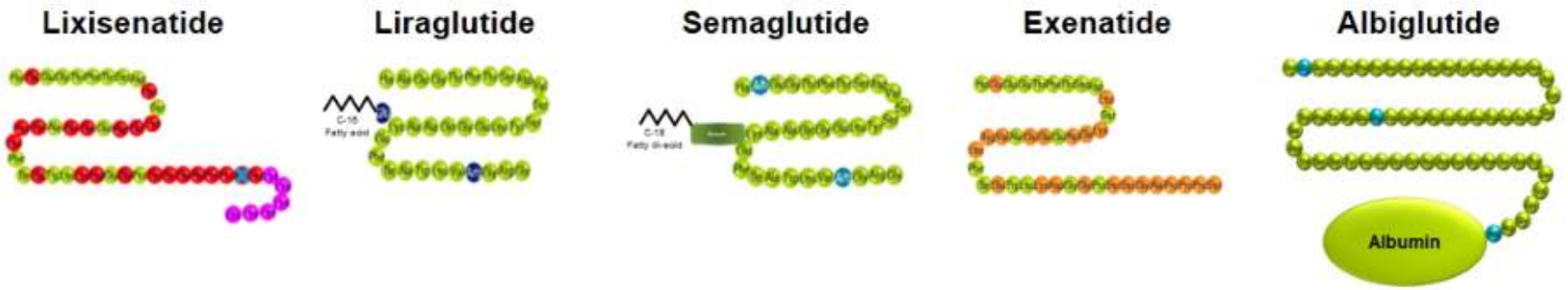
1. Pfeffer MA et al. N Engl J Med. 2015 Dec 3;373(23):2247-57.
2. N Engl J Med. 2017 Sep 28;377(13):1228-1239.
3. Marso SP et al. N Engl J Med. 2016 Jul 28;375(4):311-22.
4. Marso SP et al. N Engl J Med. 2016 Nov 10;375(19):1834-1844
5. Lancet. 2018 Oct 1. pii: S0140-6736(18)32261-X.
6. Diabetes Obes Metab. 2018 Jan;20(1):42-49.

	ELISA[1]	EXSCEL[2]	LEADER[3]	SUSTAIN-6[4]	HARMONY[5]	REWIND[6]
商品名	Lyxumia	Bydureon	Victoza	Ozempic 台灣未上市	Tanzeum 台灣未上市	Trulicity
學名	Lixisenatide	Exenatide ER	Liraglutide	Semaglutide	Albiglutide	Dulaglutide
人數	6,068	14,000	9,340	3,297	9,463	9,901
追蹤時間 (年)	2.1	3.2	3.8	2.1	1.6	6.5
CVD(%)	100%	70%	81%	83%	100%	31%
3P MACE	1.02 (4p MACE)	0.91	0.87*	0.74*	0.78*	尚未發表
CV death	0.98	0.88	0.78*	0.98	0.93	
MI	1.03	0.97	0.88	0.74	0.75*	
Stroke	1.12	0.85	0.89	0.61*	0.86	
HHF	0.96	0.94	0.87	1.11	0.85	
BW change	-0.7	-1.27	-2.3 kg	-2.9~-4.3	-0.83	

Differences Among Agents That May Have Influenced Outcomes

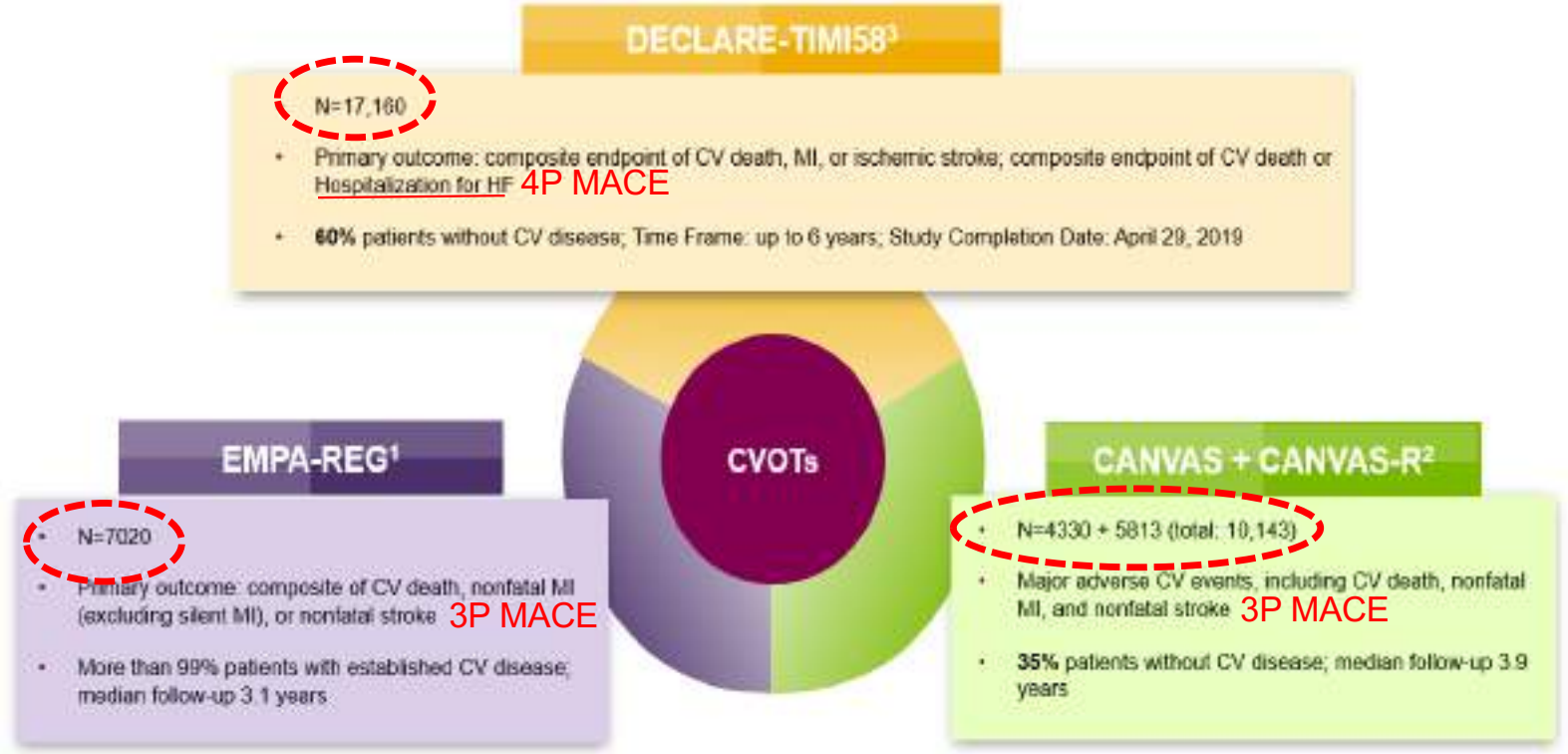
Drug	Lixisenatide od	Liraglutide od	Semaglutide qw	Exenatide XR qw	Albiglutide qw
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%)
In vivo EC_{50} nmol/kg)*	0.02	0.5	NA	0.01	1.4
t½	2–4 h	11.6–13 h	7 days	2 weeks	~ 5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg

Albiglutide has high human GLP-1 homology, long t½ and lowest glycaemic potency



**Dose producing 50% maximal glucose AUC following OGTT in db/db mice (data on file). Exenatide EC50 values from exenatide not exenatide XR. Other data from Clin Pharmacokin 2018 (in press)*
Green circles within molecular depictions represent amino acids homologous to human GLP-1
AUC, area under curve; t1/2, terminal half-life; OGTT, oral glucose tolerance test

3 CVOTs With SGLT2 Inhibitors

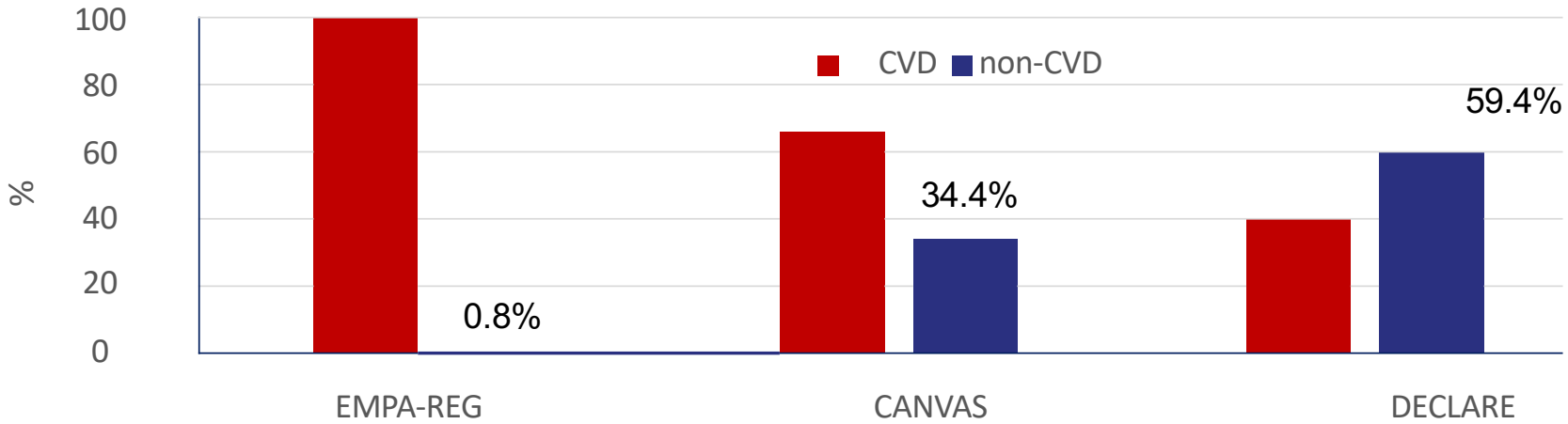


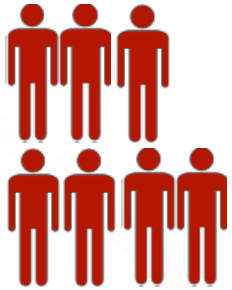
*It is randomized 17,160 patients with T2DM and either known cardiovascular disease (secondary prevention cohort) or at least two risk factors for CV disease (primary prevention cohort)

CV, cardiovascular; CVOT, cardiovascular outcomes trial; MI, myocardial infarction; SGLT2. sodium–glucose co-transporter 2

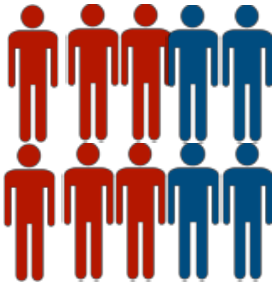
1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Bruce Neal et al. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925.; 3. https://clinicaltrials.gov/ct2/show/NCT01730534

CVD and Non-CVD proportion in 3 CVOTs of SGLT2i

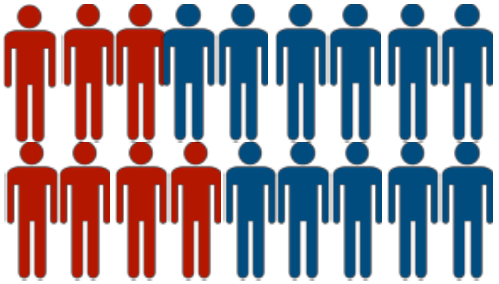




CVD 7,020 pt's



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



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

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

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

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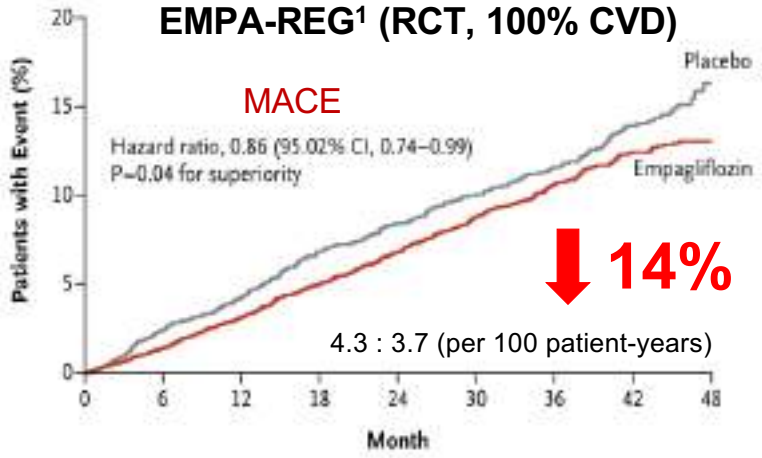
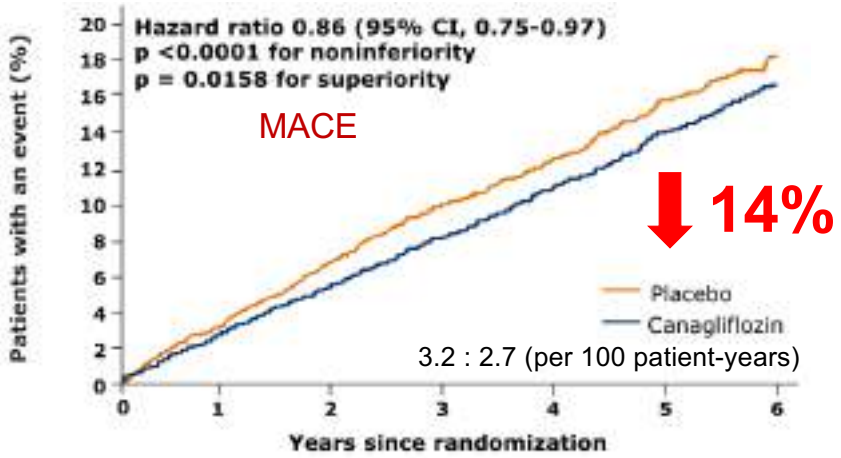
Lower MACE incidence of SGLT2i in RCT

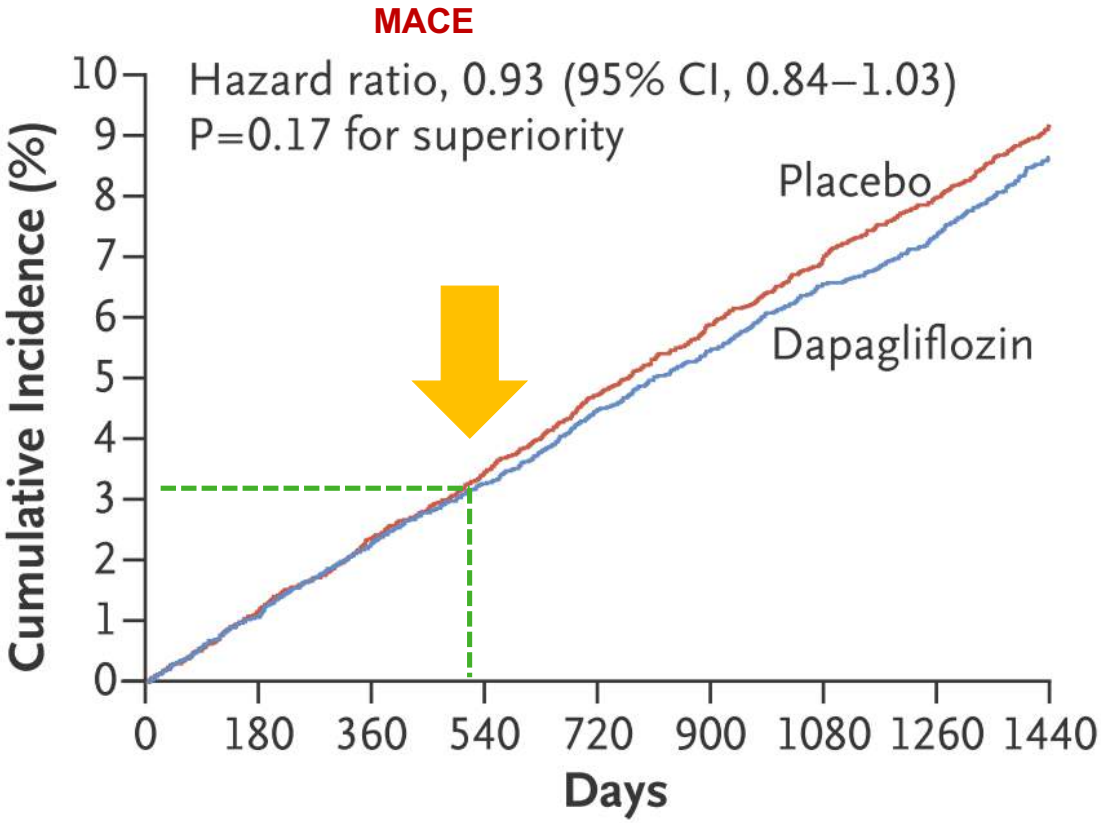
EMPA-REG[1] (RCT, 100% CVD)



CANVAS[2] (RCT, 66% CVD)



DECLARE –TIMI (RCT, 30.6% 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.

Meta-analysis of MACE result by ASCVD vs MRF

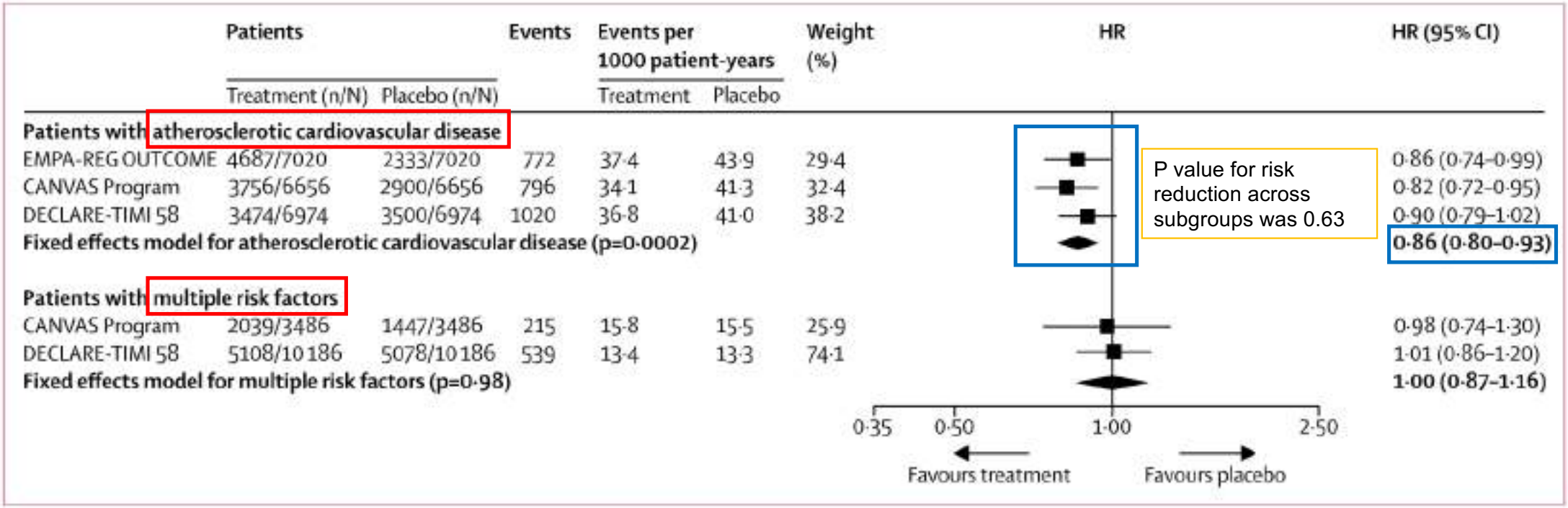


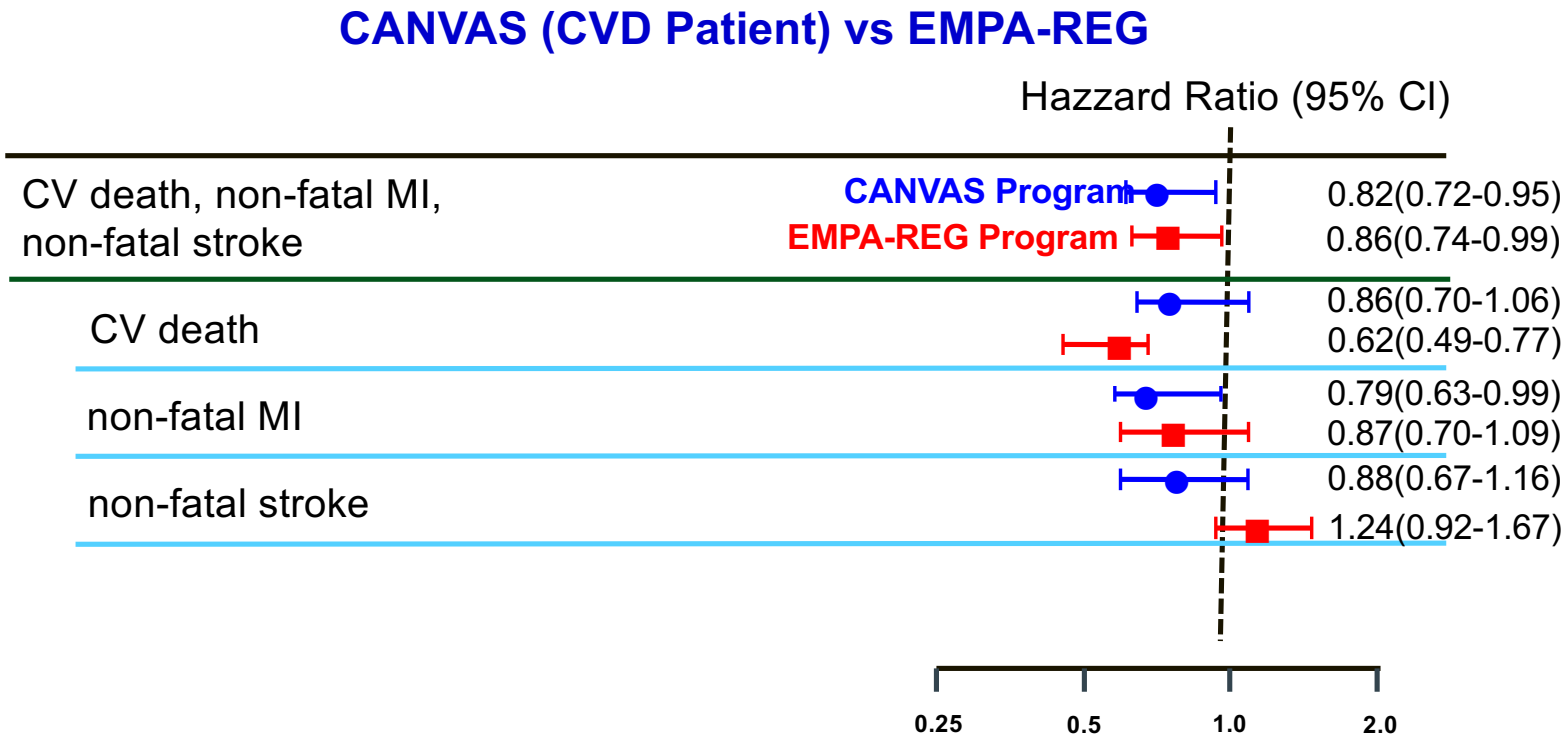
Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

THE LANCET

Zelniker TA et al. Lancet. 2018 Nov 9. pii: S0140-6736(18)32590-X.
doi: 10.1016/S0140-6736(18)32590-X.

AstraZeneca does not recommend the use of dapagliflozin for indication other than T2DM.

Comparison of the effects of canagliflozin (CANVAS focus on CVD Patient) and empagliflozin (EMPA-REG OUTCOME) on the key outcomes



Circulation 2018 Jan 23;137(4):323-334 (Ref.14)
N Engl J Med 2015; 373:2117-28 (Ref. 12)

Comparison of the effects of canagliflozin (CANVAS focus on CVD Patient) and empagliflozin (EMPA-REG OUTCOME) on the key outcomes

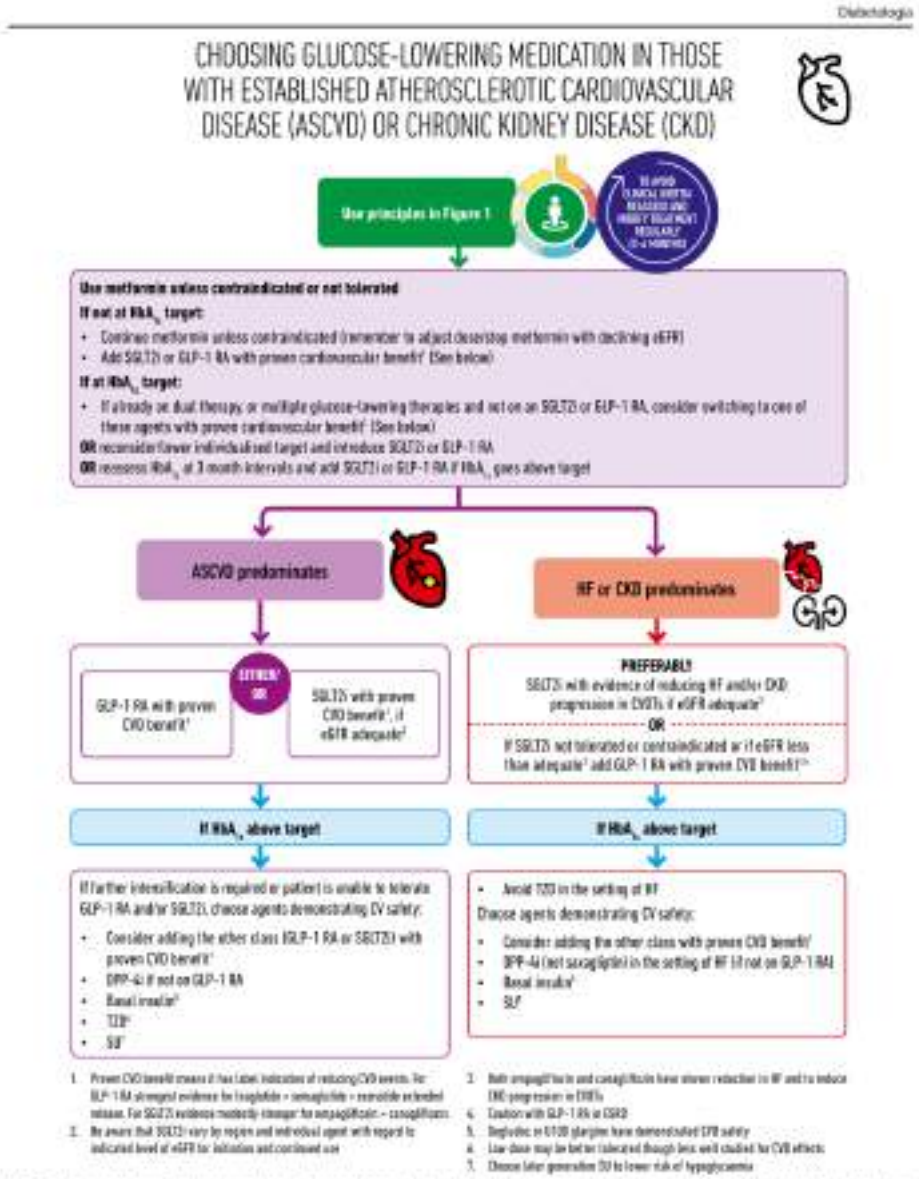
CANVAS (CVD Patient) vs EMPA-REG

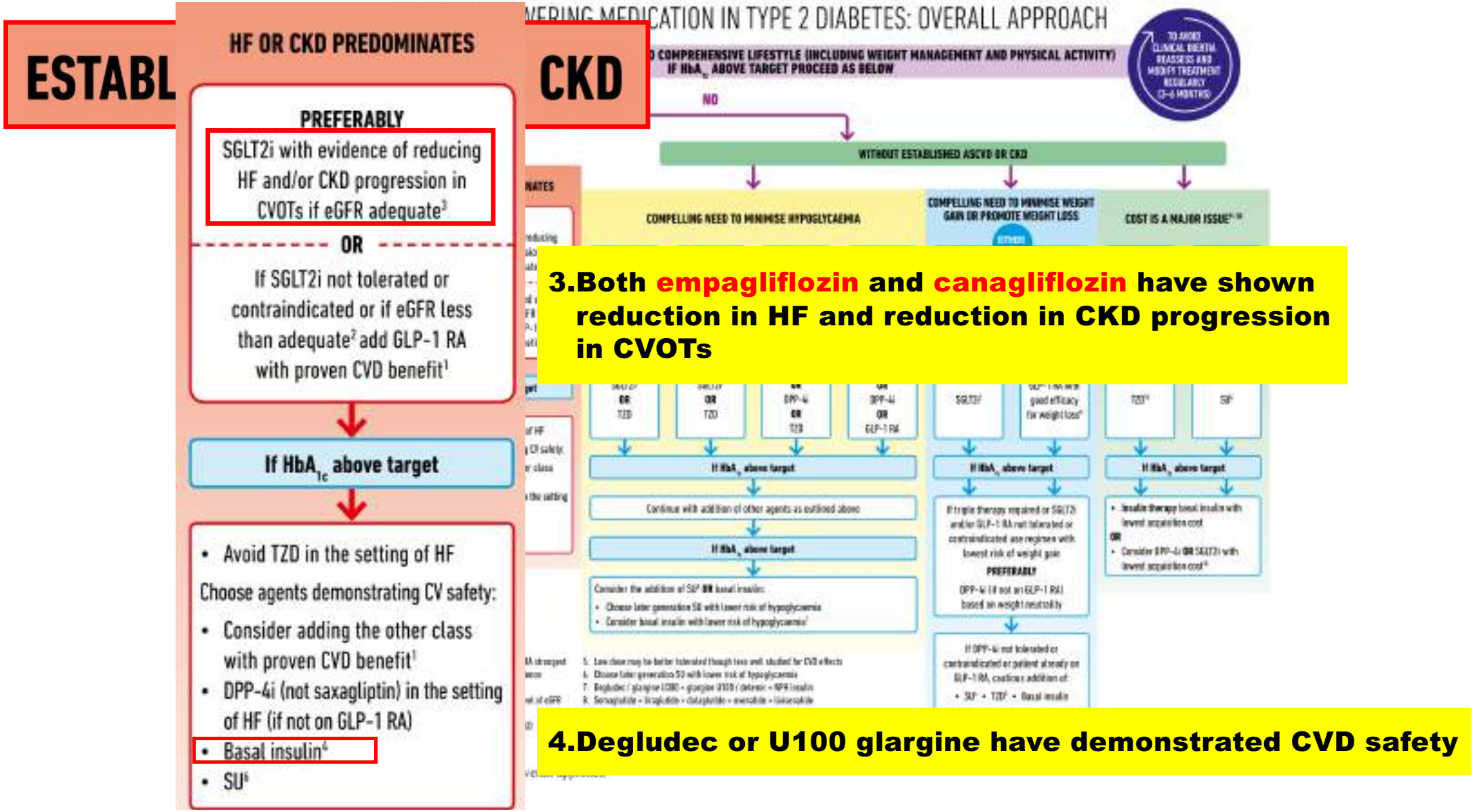
	MACE		MI		CVD		Stroke	
	CANVAS	EMPA-REG	CANVAS	EMPA-REG	CANVAS	EMPA-REG	CANVAS	EMPA-REG
Active (pt/ 1,000pt-yr)	34.1	37.4	12.5	16	14.8	12.3	8.8	11.2
Placebo (pt/ 1,00pt-yr)	41.3	43.9	16	18.5	16.8	20.2	10.4	9.1
Hazard Ratio	0.82	0.86	0.79	0.87	0.86	0.62	0.88	1.24

DOI: 10.1161/CIRCULATIONAHA.117.032038
N Engl J Med 2015; 373:2117-28 (Ref. 12)

Consensus recommendation

- Among patients with type 2 diabetes who have established ASCVD (atherosclerotic cardiovascular disease), SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management.





3.Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs

4.Degludec or U100 glargine have demonstrated CVD safety

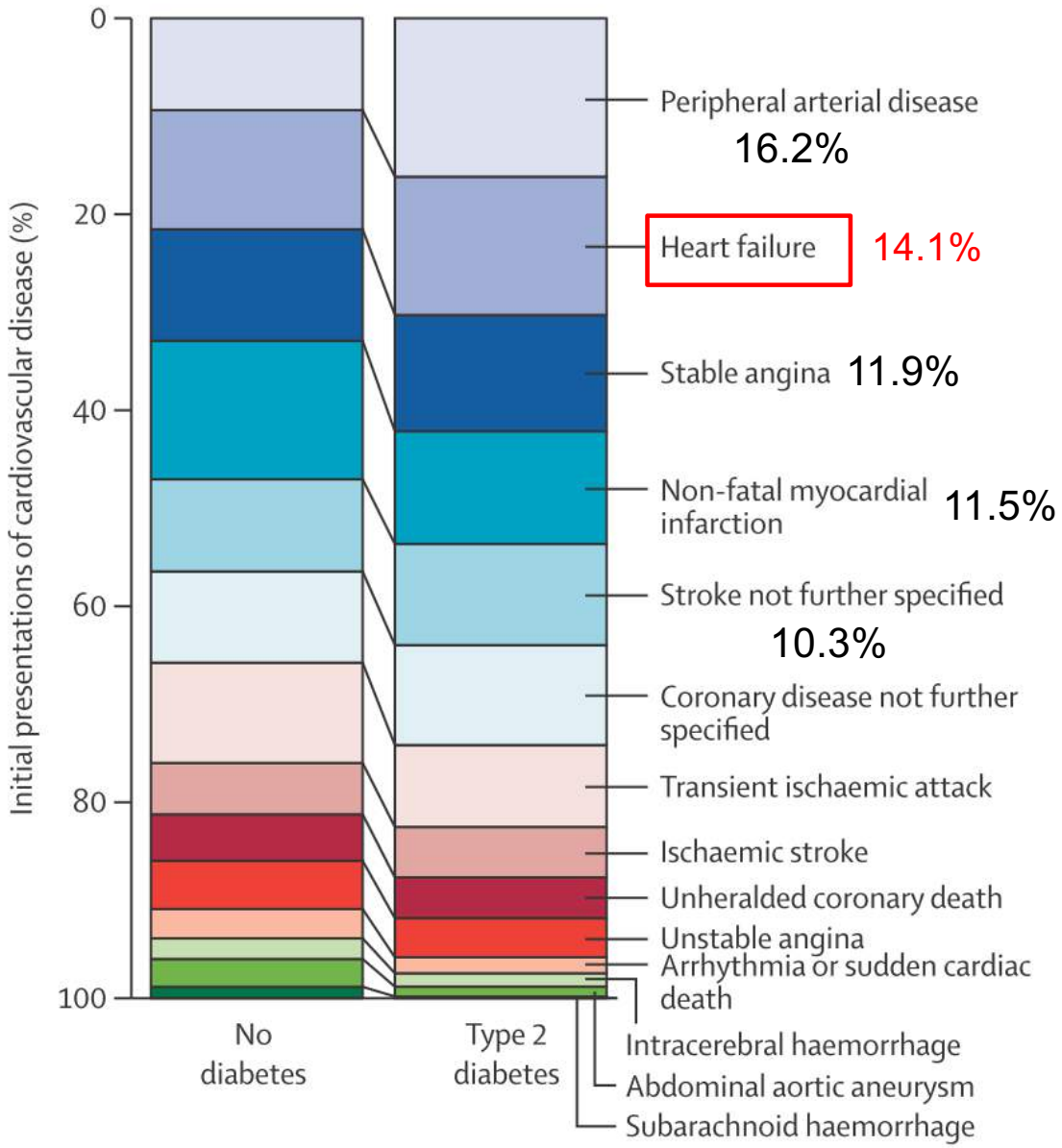
2018 DAROC Clinical Practice Guidelines for Diabetes Care

種類	治療的建議與考量
鈉 - 葡萄糖共同輸送器 -2 抑制劑 Canagliflozin Dapagliflozin Empagliflozin	1. 較少發生低血糖，使用後通常可降低體重與血壓。 2. 會增加泌尿道與生殖器感染的風險。 3. 可減少糖尿病腎臟病惡化與因心臟衰竭住院的風險。

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

AstraZeneca does not recommend the use of dapagliflozin for indication other than T2DM.

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

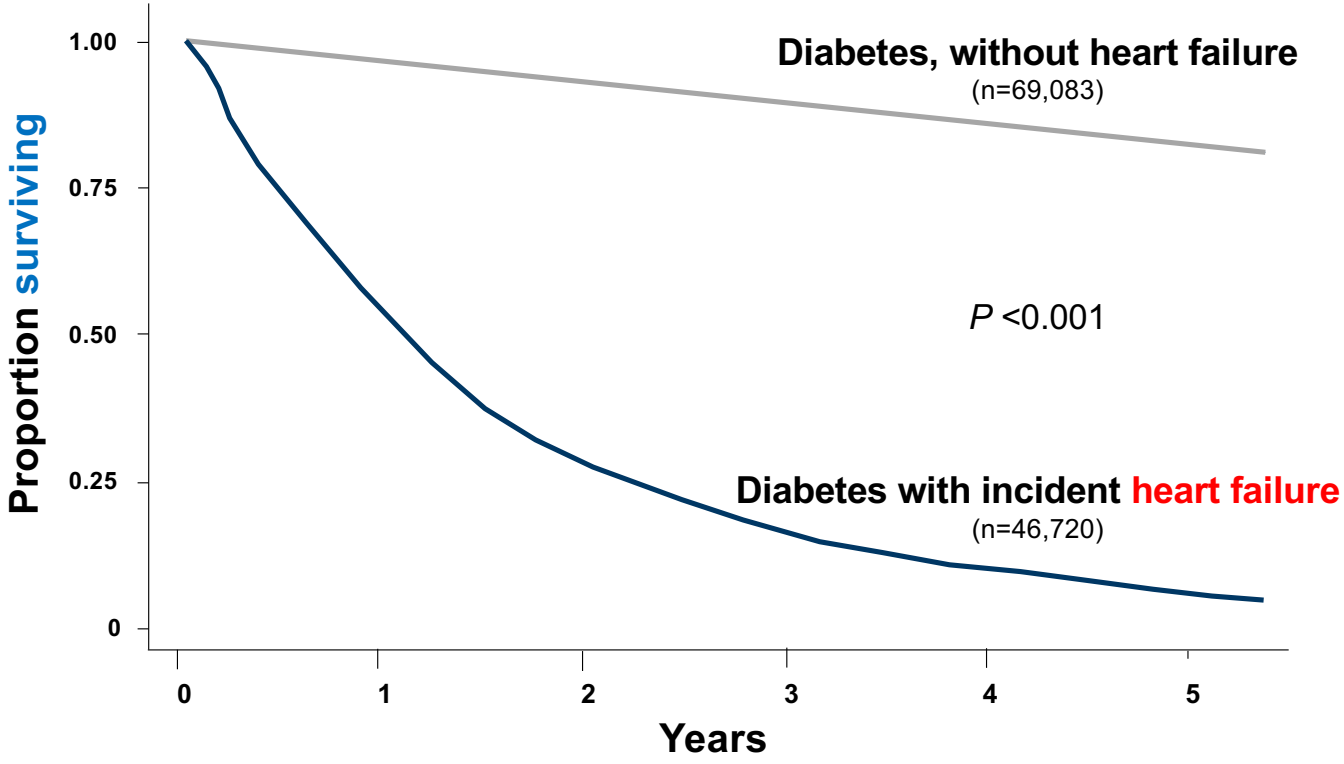


Heart failure and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes.

Heart failure was defined by coded diagnoses in primary care, secondary care and death certificates.

Shah AD, et al. Lancet Diabetes Endocrinol 2015;3:105–113

The presence of HF in patients with diabetes is associated with an increased risk of death

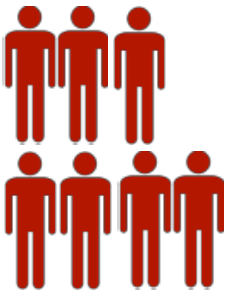


- 115,803 adults 65 years and older in fee-for-service Medicare without a prior HF claim were followed for 5 years
- Incident HF was determined using DRG codes
- Survival was significantly lower in those who developed HF compared with those without HF

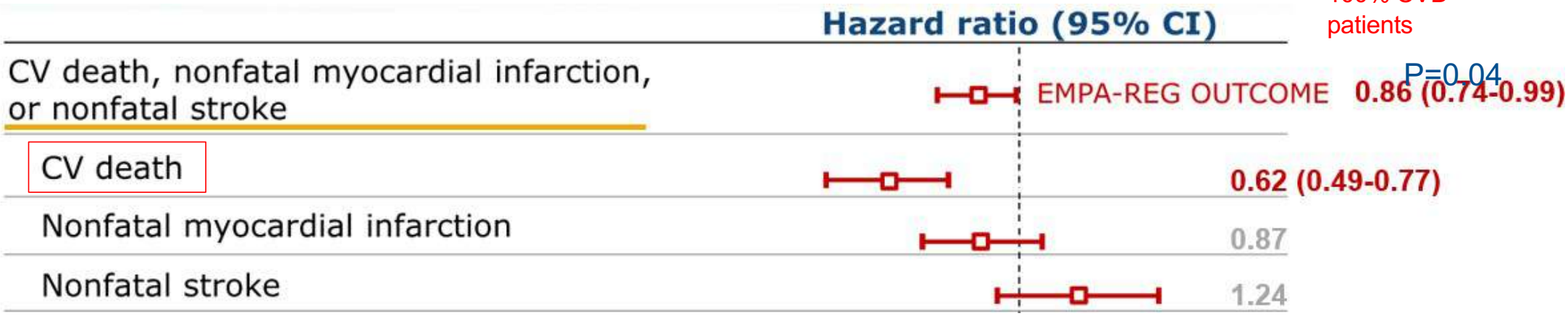
HF, heart failure; DRG, diagnosis related group

Bertoni AG, et al. *Diabetes Care.* 2004;27:699–703.

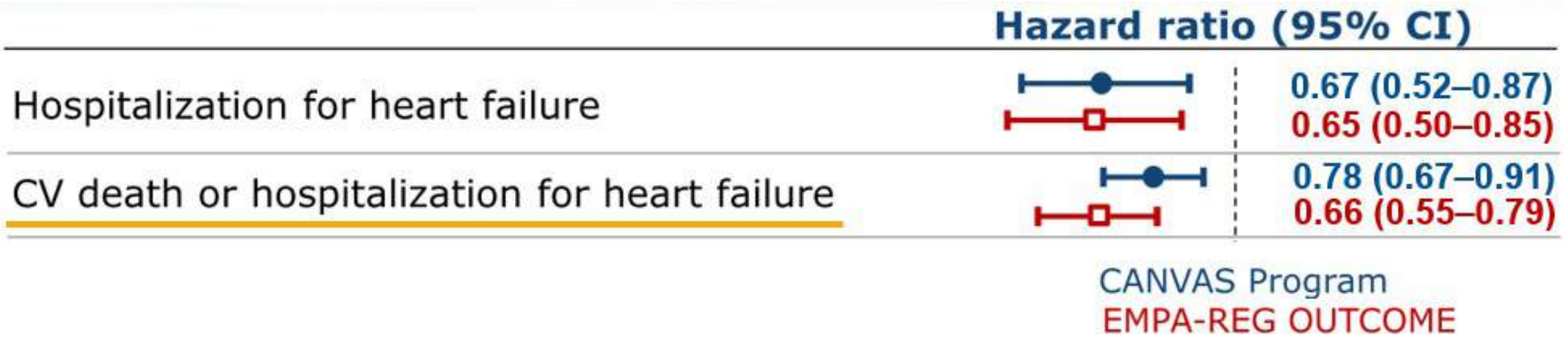
MACE of EMPA-REG



100% CVD patients



HHF & CV death


Hazard ratio (95% CI)
Hospitalization for heart failure
0.67 (0.52–0.87)
0.65 (0.50–0.85)
CV death or hospitalization for heart failure
0.78 (0.67–0.91)
0.66 (0.55–0.79)
CANVAS Program
EMPA-REG OUTCOME

CV death of EMPA-REG

	Placebo (N = 2333)	Pooled empagliflozin (N = 4687)
	no. (%)	
Patients with cardiovascular death	137 (5.9)	172 (3.7)
Sudden death	38 (1.6)	53 (1.1)
Worsening of heart failure	19 (0.8)	11 (0.2)
Acute myocardial infarction	11 (0.5)	15 (0.3)
Stroke	11 (0.5)	16 (0.3)
Cardiogenic shock	3 (0.1)	3 (0.1)
Other cardiovascular death*	55 (2.4)	74 (1.6)

Sudden cardiac death may occur in 40% of patients who suffer from heart failure[1].

-0.5%

-0.6%

-0.2%

-0.2%

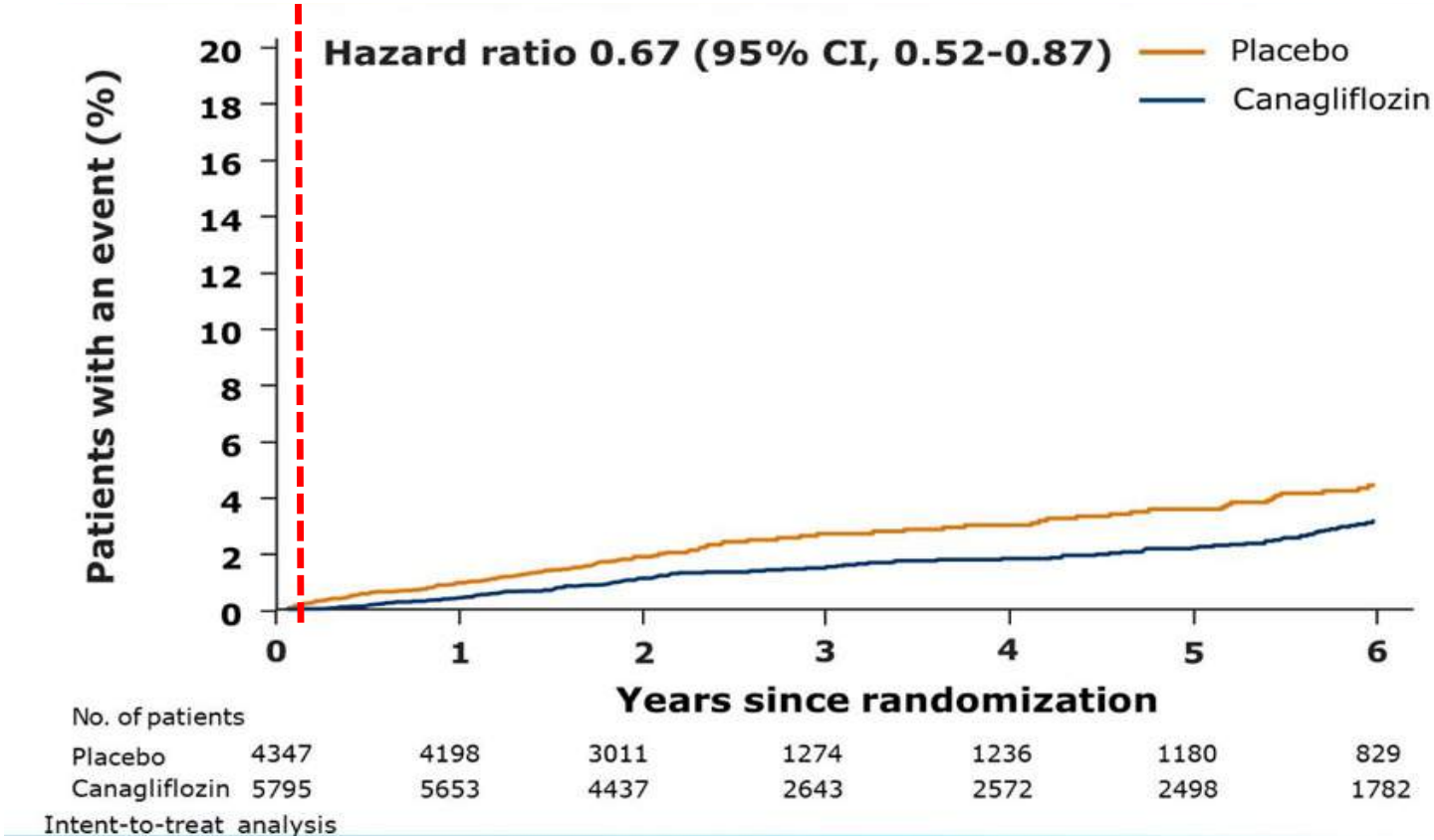
1. Journal of the American College of Cardiology, Volume 30, Issue 7, December 1997 DOI: 10.1016/S0735-1097(97)00361-6

Demographics and Disease History

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

For the purpose of scientific medical exchange

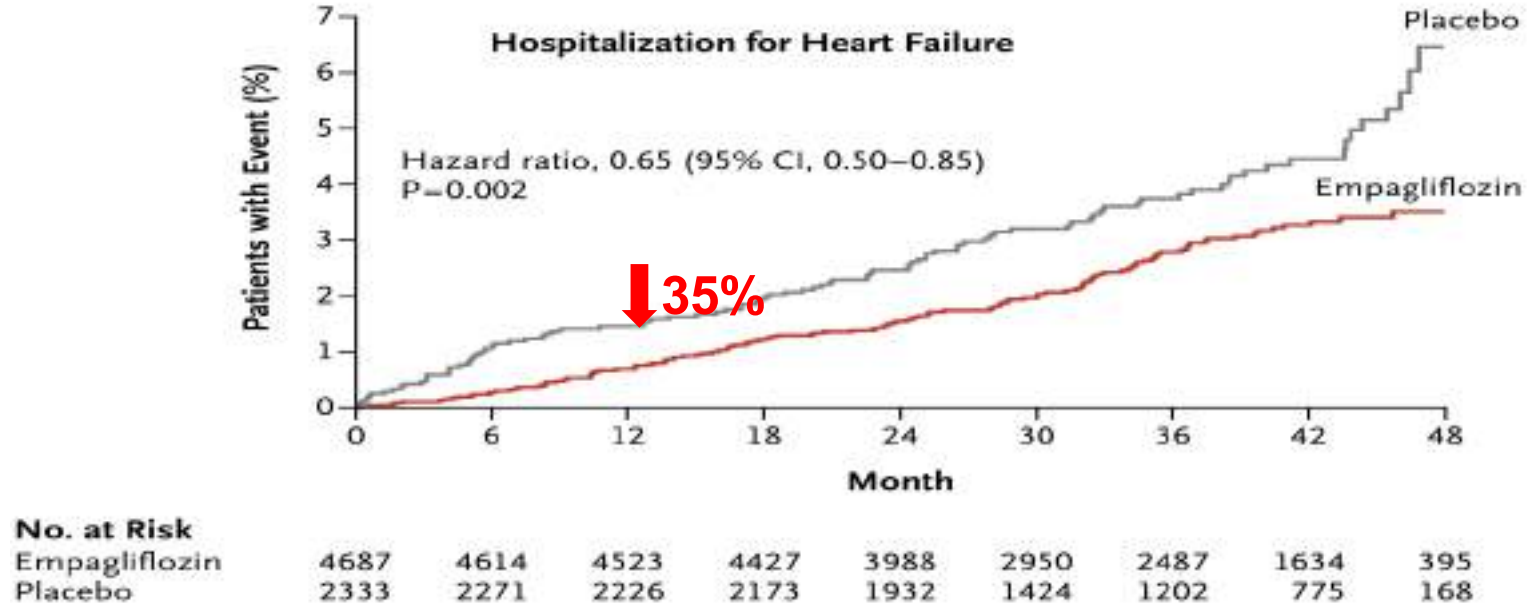
CANVAS: Hospitalization for Heart Failure



N Engl J Med 2017; 377:644-657 (Ref. 9)

Lower HF hospitalization incidence of SGLT2i in RCT

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

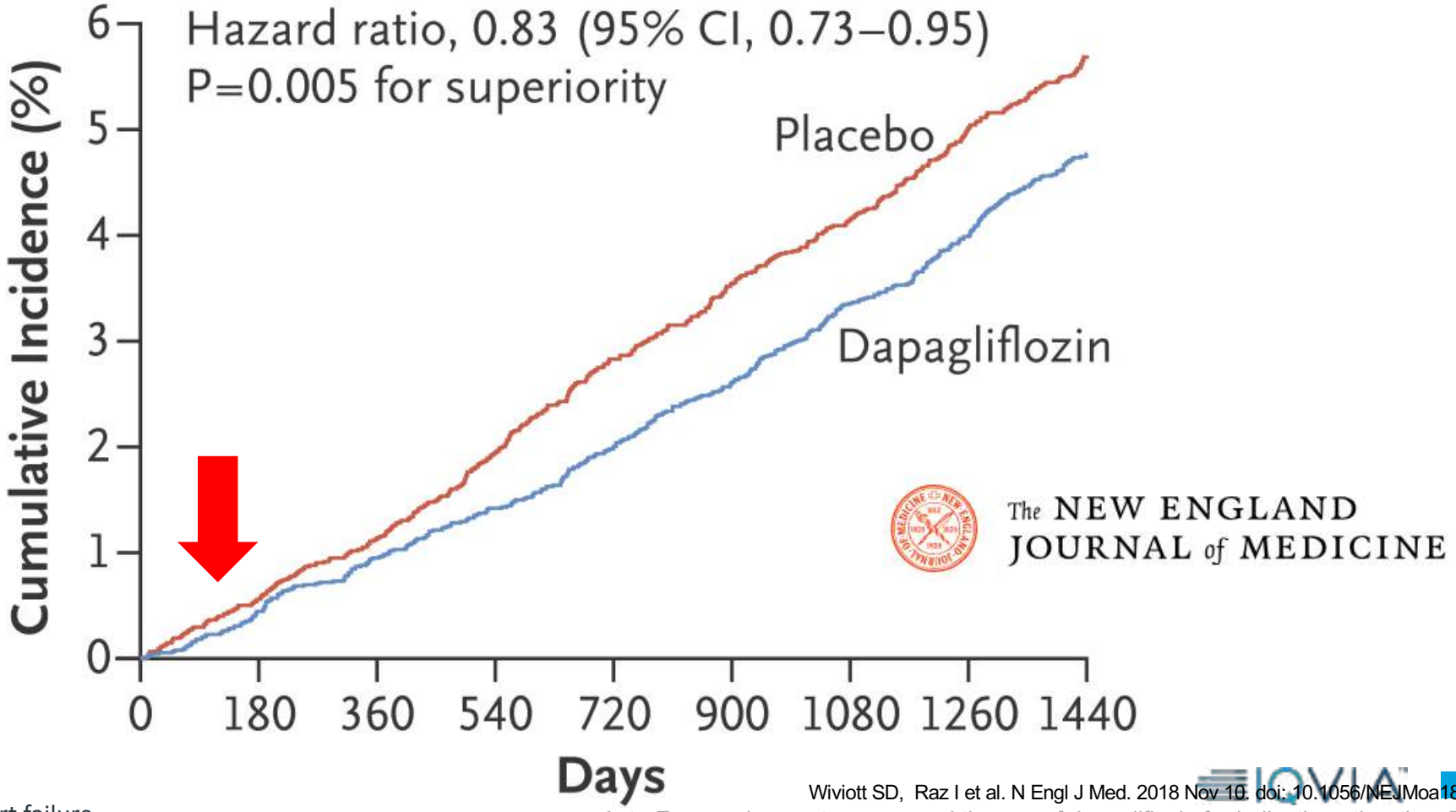


1.5 vs 0.9 events per 100 patient-years

RWE: real-world evidence

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

DECLARE TIMI:
Primary Endpoint – CV death or HHF



HHF: hospitalization for heart failure

Wiviott SD, Raz I et al. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389.

AstraZeneca does not recommend the use of dapagliflozin for indication other than T2DM.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

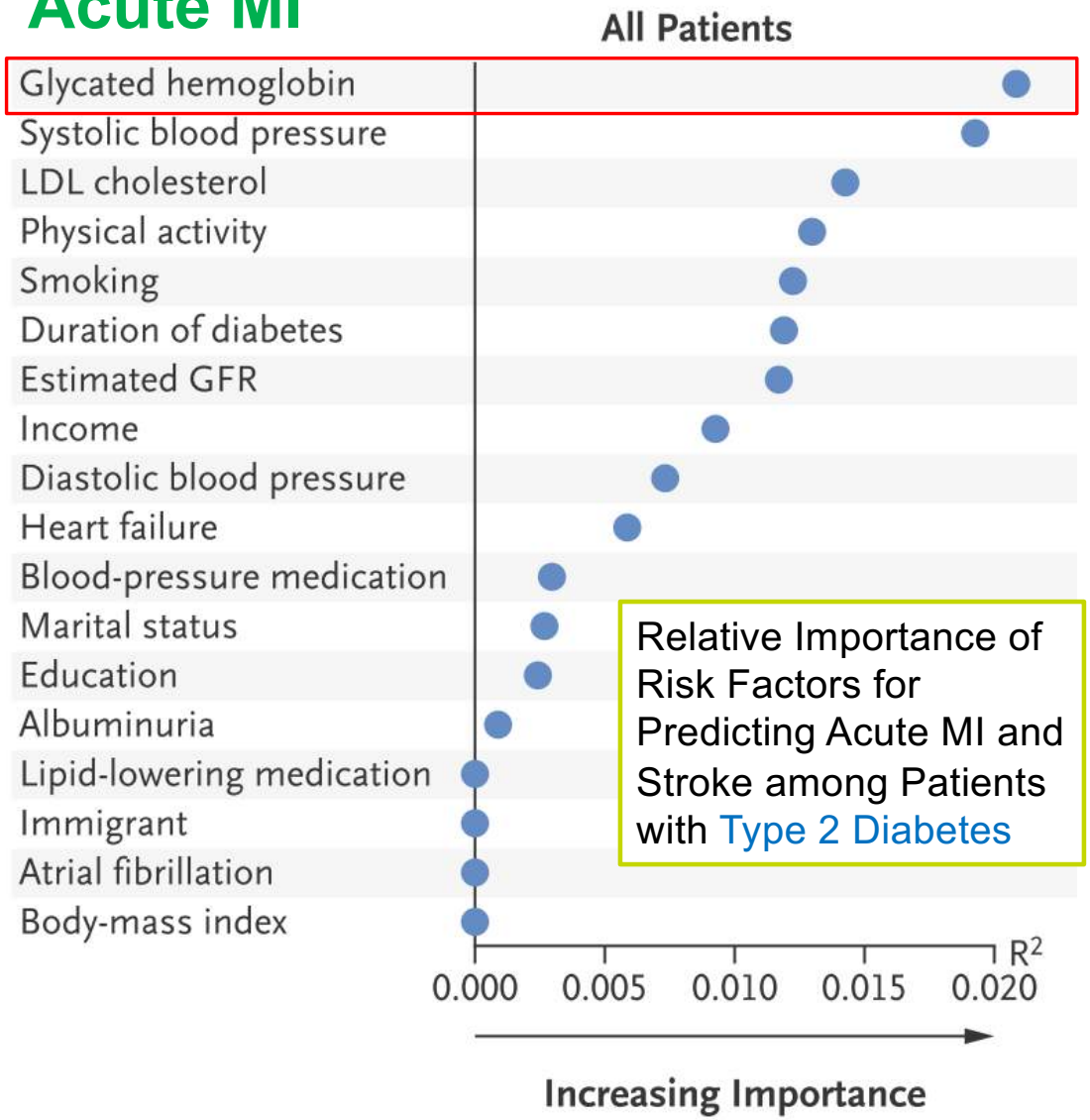
Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

- A national cohort study included 271,174 patients with T2DM
- Median follow-up 5.7 years
- Swedish National Diabetes Register

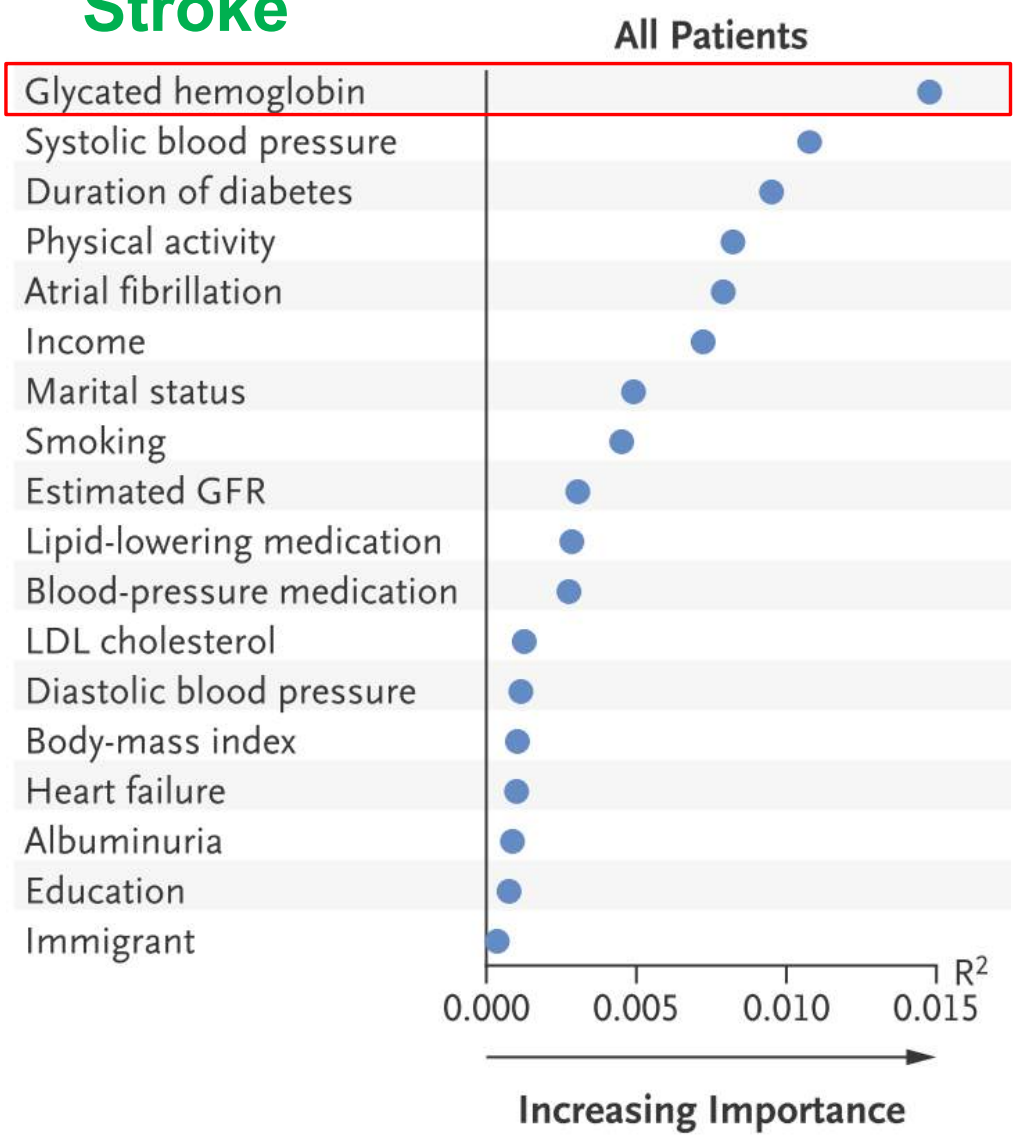
The NEW ENGLAND JOURNAL of MEDICINE

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.

Acute MI

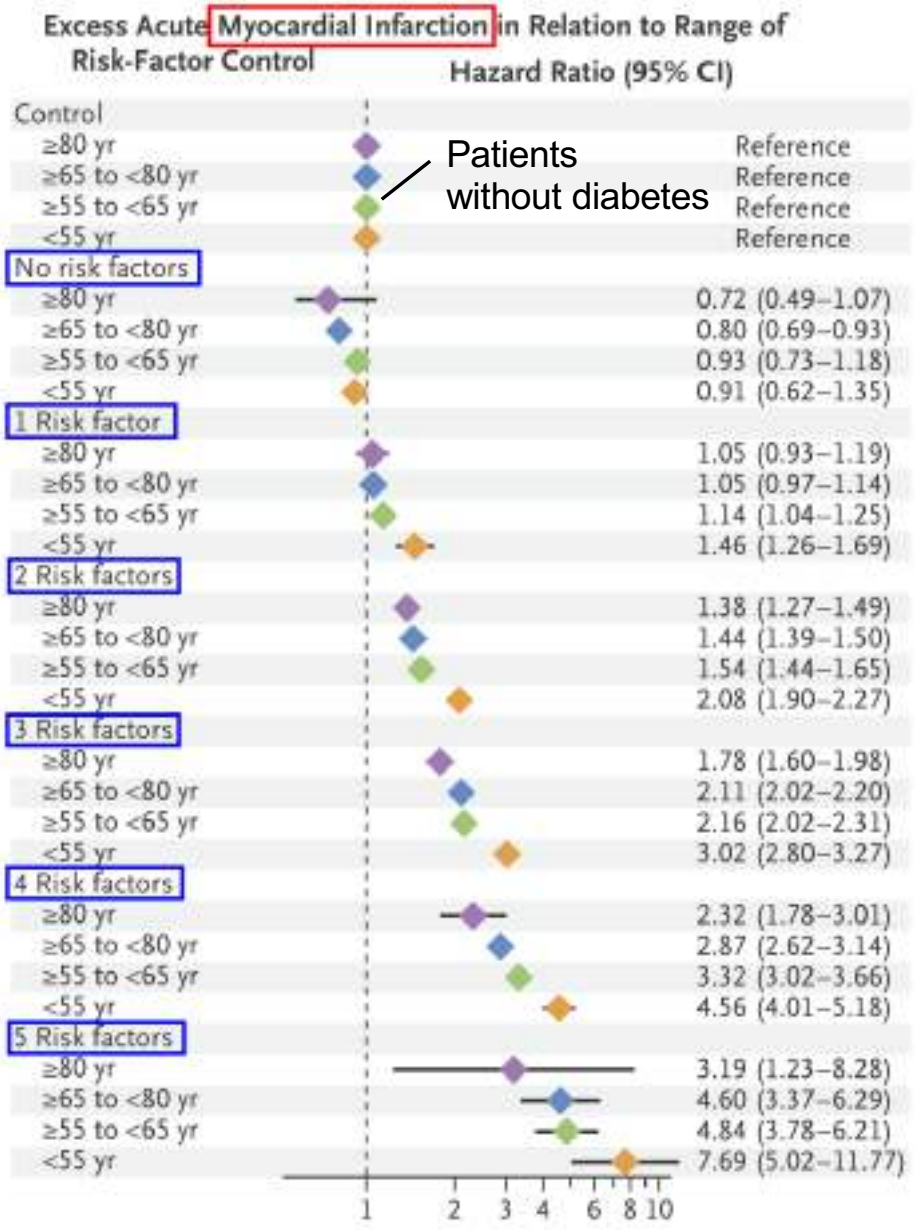


Stroke



Relative Importance of Risk Factors for Predicting Acute MI and Stroke among Patients with Type 2 Diabetes

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.

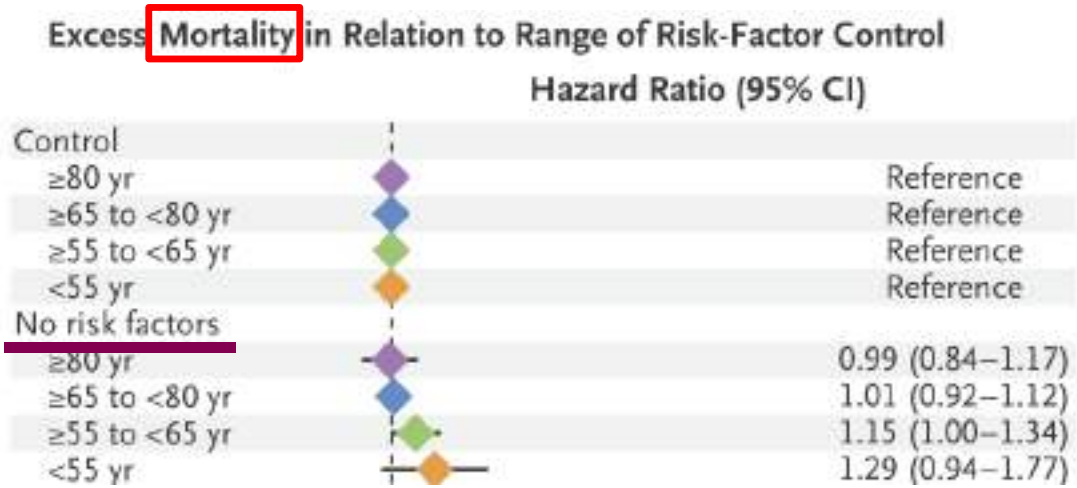


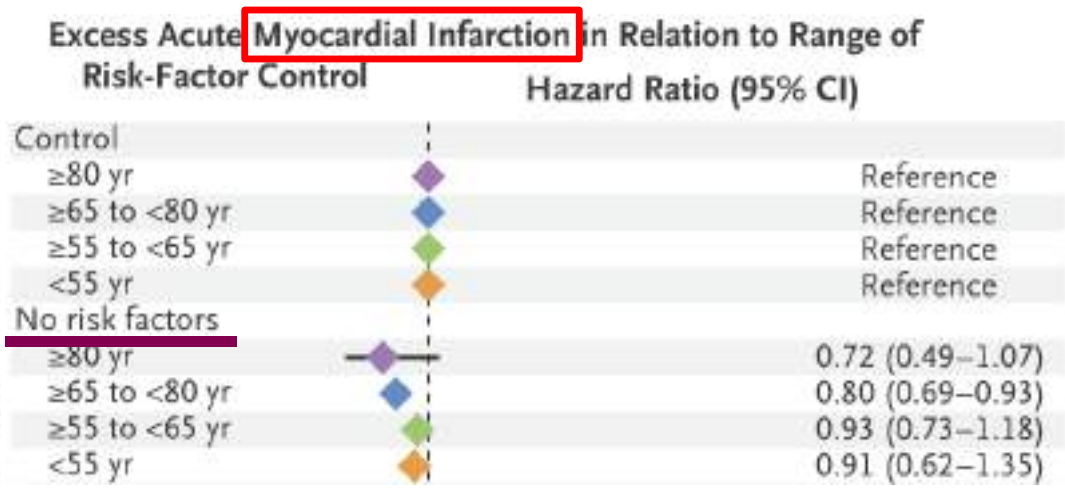
Patients with more risk factors within target ranges are associated with lower risk of mortality

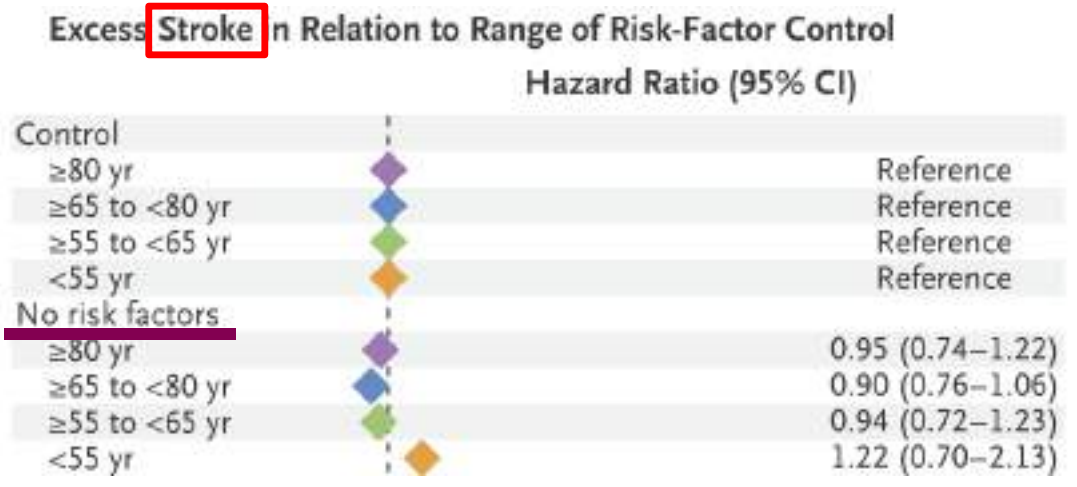
Five risk factors:

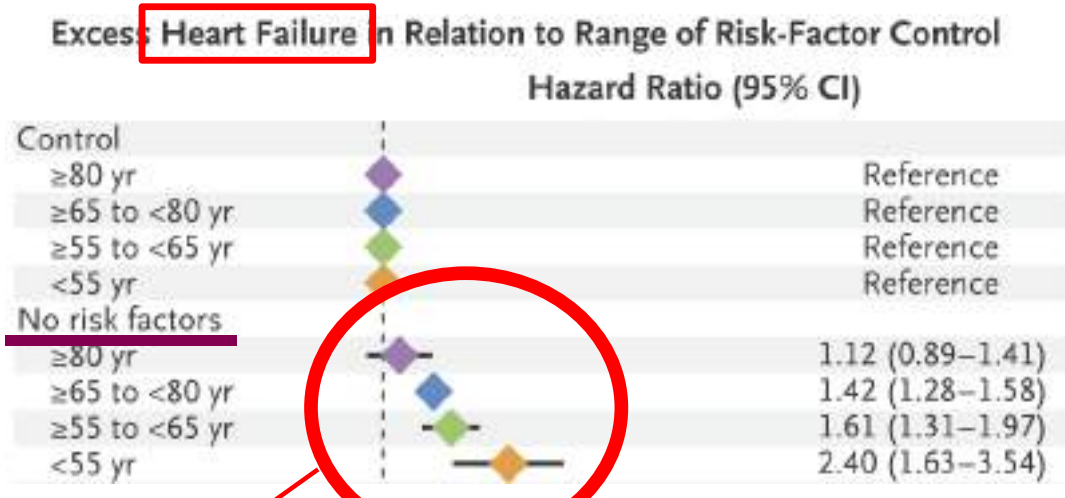
1. Elevated A1c (≥7.0%)
2. Elevated LDL (≥2.5 mmol; 97 mg/dl)
3. Elevated BP (≥140/80 mm Hg)
4. Albuminuria (presence of microalbuminuria or macroalbuminuria)
5. Smoking (current smoker)

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.









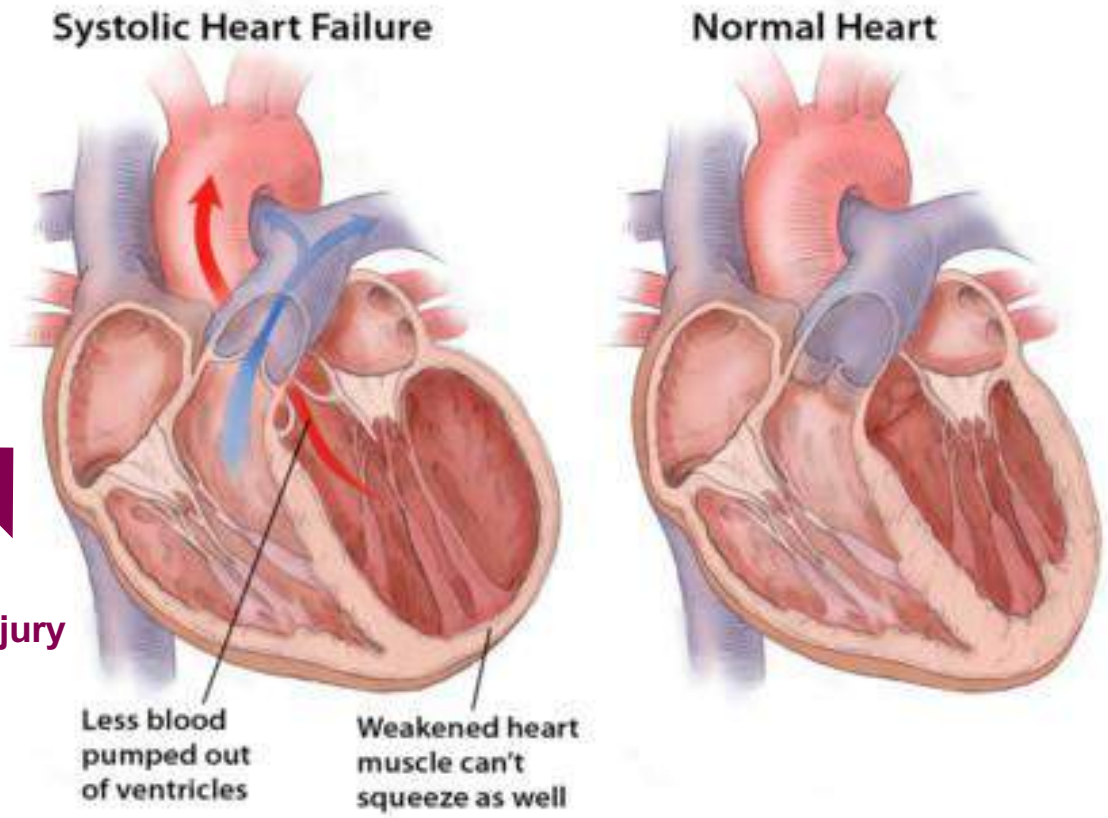
Heart Failure is still increased in patients with 5 risk factors within target ranges

Rawshani A et al. N Engl J Med. 2018 Aug 16;379(7):633-644.

Heart Failure

HFrEF
(Heart failure with reduced ejection fraction)

LVEF<40%



Myocardial injury (ex. post-MI)

HFpEF (preserved)

LVEF ≥50%

Endothelial inflammation

↓

Cardiac dysfunction

(ex.Diabetes, hypertension, obesity, metabolic syndrome, smoking)

~50% of all patients with heart failure have a normal EF

http://trends.medicalexpo.com/project-43696.html
European Heart Journal (2016) 37, 2129–2200

臨床標準藥物常見的有：

	照字母排序常見成分名	使用目的
血管張力素轉化抑制劑 (Angiotensin converting enzyme inhibitor, ACEI)	Enalapril, Lisinopril, Perindopril, Ramipril	可擴張血管，降低血壓，減少心臟的負荷
血管張力素受器阻斷 (Angiotensin receptor blocker, ARB)	Candesartan, Valsartan	可擴張血管，降低血壓，減少心臟的負荷
乙型交感神經阻斷劑 (Beta-blocker)	Bisoprolol, Carvedilol, Metoprolol succinate	可減緩心跳，降低血壓，減少心臟的負荷
腎上腺皮質酮拮抗劑 (Mineralocortocoid receptor antagonist, MRA)	Spirono-lactone , Eplernone,	輕度利尿劑、對抗賀爾蒙對心血管之危害、減少心臟纖維化、保留血鉀

Current HFrEF therapeutic classes

血管收縮素受體中性溶酶抑制劑 (Angiotensin receptor neprilysin inhibitor, ARNI)	Sacubitril/ valsartan	利鈉尿，擴張血管，降低血壓，減少心臟的負荷
If離子電流選擇性抑制劑 (I f inhibitor)	Ivabradine	可減緩心跳，增加心肌血流的作用
利尿劑 (Diuretic)	Thiazide, thiazide-like agent	可排出體內多餘水份，減少水腫及呼吸困難
毛地黃(Digoxin)	Digoxin	增加心臟收縮的強度，使心臟流出的血量增加

中華民國心臟學會-心衰竭委員會: 心臟衰竭自我照護手冊 2016

In contrast, current HF classes with proven outcomes in HFrEF fail to improve outcomes in patients with HFpEF

Trial	Drug (Class)	Primary Endpoint	Results
PEP-CHF[1]	**Perindopril** (ACE-I)	Composite of all-cause mortality or unplanned heart failure related hospitalization	HR 0.92; (p=0.545)
CHARM-Preserved[2]	**Candesartan** (ARB)	Composite of CV death or unplanned admission to hospital for the management of worsening HF	HR 0.89 (p=0.12)
I-PRESERVED[3]	**Irbesartan** (ARB)	Composite outcome of death from any cause or hospitalization for a CV cause (HF, MI, unstable angina, arrhythmia, or stroke).	HR 0.95; (p=0.35)
TOPCAT[4]	**Spironolactone** (Aldosterone antagonist)	Composite of death from CV causes, aborted cardiac arrest, or hospitalization for the management of heart failure.	HR 0.89 (p=0.14)
DIG-preserved[5]	**Digoxin**	Composite of heart failure hospitalization or heart failure mortality	HR 0.82 (p=0.136)

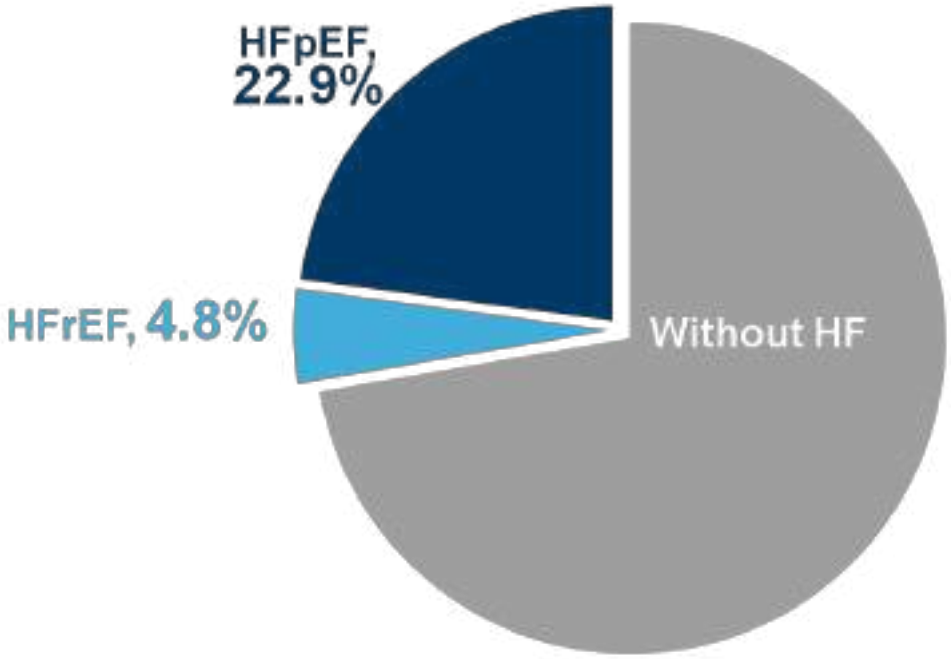
CV, cardiovascular; ACE, angiotensin converting enzyme; ACE-I, ACE inhibitor; ARB angiotensin receptor blocker; HR Hazard ratio

1. Cleland JG, et al**.** *European Heart Journal* (2006) 27, 2338–2345; **2.** Yusuf s et al. *Lancet* 2003; 362: 777–81. **3**. Massie BM et al. *N Engl J Med* 2008;359:2456-67.**4.** Pitt B, et al *N Engl J Med* 2014;370:1383-92.. 5. Ahmed A et al. Circulation. 2006 Aug 1;114(5):397-403.

HF remains under-diagnosed in patients with T2D, suggesting a high index of suspicion is warranted

27.7% of a T2D population had undiagnosed HF

Diabetologia
Journal of the European Association for the Study of Diabetes (EASD)



- 581 patients aged 60 years or over with T2DM without cardiologist-confirmed diagnosis of HF
- An expert panel used the criteria of the ESC (European Society of Cardiology) to diagnose HF
- **27.7%** were found to have previously **unknown** HF
- **The majority of newly detected HF had HFpEF**
- **The prevalence of undiagnosed HF was higher:**
  - increasing age, hypertension, females, BMI ≥30 kg/m^2, patients with dyspnea, patients complaining of fatigue
- Screening of patients with T2D should be considered given the high prevalence of previously unknown HF

BMI, body mass index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.
Boonman-de Winter LJ, et al. *Diabetologia.* 2012;55:2154–2162.

All 4 CVOT of DPP4i demonstrated cardiovascular safety

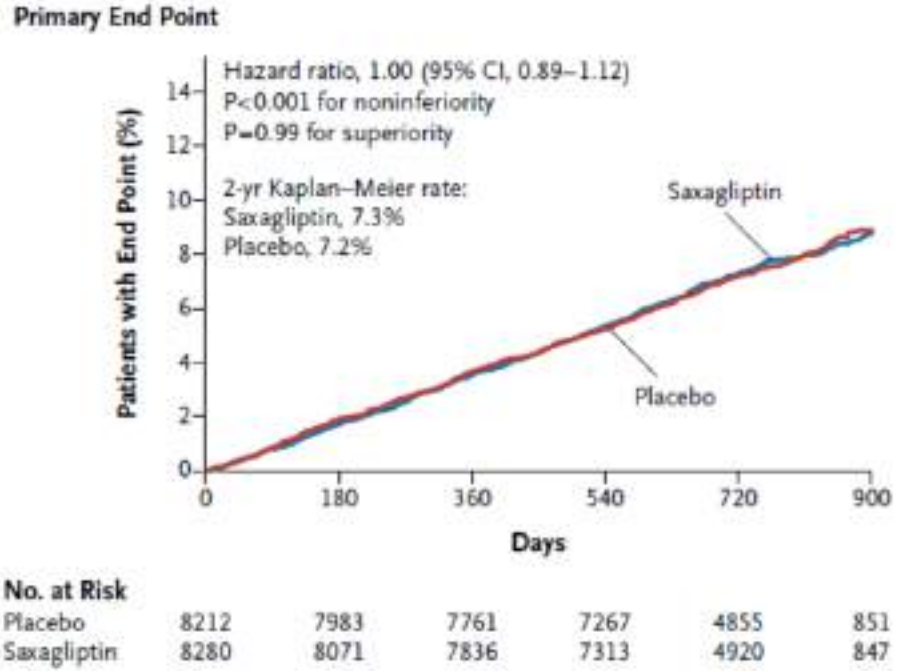
	SAVOR TIMI 53[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	-
商品名	Onglyza	Nesina	Januvia	Tradjenta	Galvus
學名	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Vildagliptin
人數	16,496	5,380	14,671	6,979	因肝指數異常，未獲FDA核准，在美國沒有上市，不用做CVOT
Follow-up (year)	2.1	1.5	3.0	2.2	
MACE	1.00 (0.89-1.12)	0.96	0.98 (0.88-1.09)	1.02 (0.89-1.17)	

Neutral

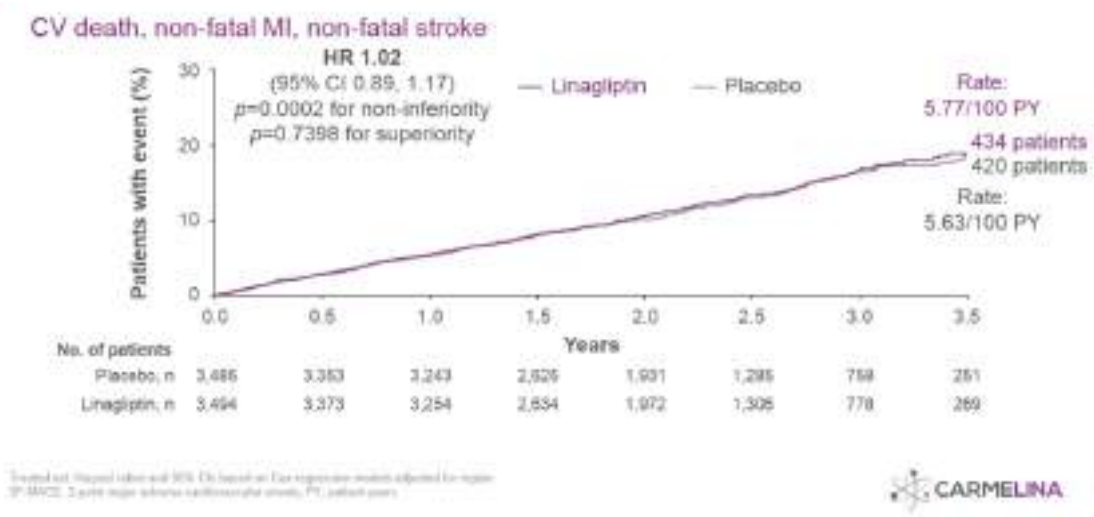
1. N Engl J Med. 2013 Oct 3;369(14):1317-26.
2. N Engl J Med. 2013 Oct 3;369(14):1327-35.
3. N Engl J Med. 2015 Jul 16;373(3):232-42.
4. 54th Annual Meeting of European Association for the Study of Diabetes (EASD) 2018: Oral Presentation # S35. https://www.easd.org/virtualmeeting/home.html#!contentsessions/2873

3P MACE of CVOTs

2013 SAVOR[1]



2018 CARMELINA[2]



1. N Engl J Med. 2013 Oct 3;369(14):1317-26. 2. 4. 54th Annual Meeting of European Association for the Study of Diabetes (EASD) 2018: Oral Presentation # S35. https://www.easd.org/virtualmeeting/home.html#!contentsessions/2873

Subgroup analysis

Time to first occurrence of 3P-MACE by select baseline characteristics

	Linagliptin n with event / N analysed	Placebo n with event / N analysed	p-value for interaction
All patients	434/3,494	420/3,485	
Age, years			0.3477
<65	154/1,467	140/1,501	
≥65	280/2,027	280/1,984	
Region			0.3349
North America	91/593	72/587	
Latin America	132/1,156	119/1,154	
Europe (incl. S. Africa)	182/1,473	196/1,461	
Asia	29/272	33/283	
HbA1c, %			0.0407
<8	229/1,915	243/1,855	
≥8	205/1,579	177/1,630	
Heart failure			0.9588
Yes	159/952	151/921	
No	275/2,542	269/2,564	
eGFR, ml/min/1.73 m^2			0.6197
<60	331/2,200	310/2,148	
≥60	103/1,294	110/1,337	
UACR, mg/g			0.6994
<30	67/696	60/696	
30-300	158/1,463	160/1,431	
>300	208/1,333	199/1,357	

3P-MACE, 3-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; UACR, urinary albumin-to-creatinine ratio

CARMELINA

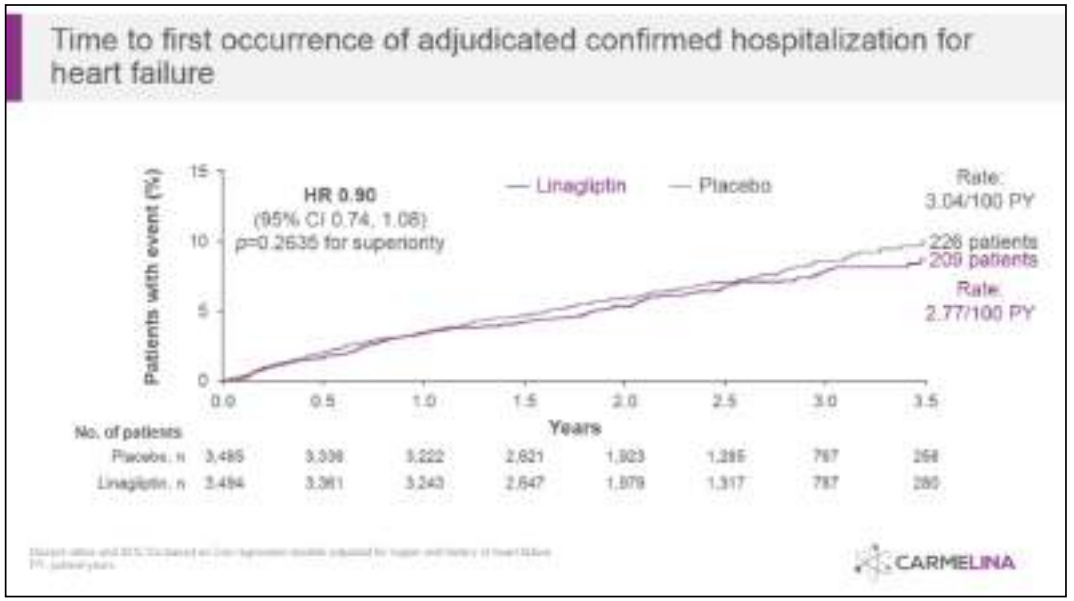
54th Annual Meeting of European Association for the Study of Diabetes (EASD) 2018: Oral Presentation # S35. https://www.easd.org/virtualmeeting/home.html#!contentsessions/2873

SAVOR

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	176 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

CARMELINA

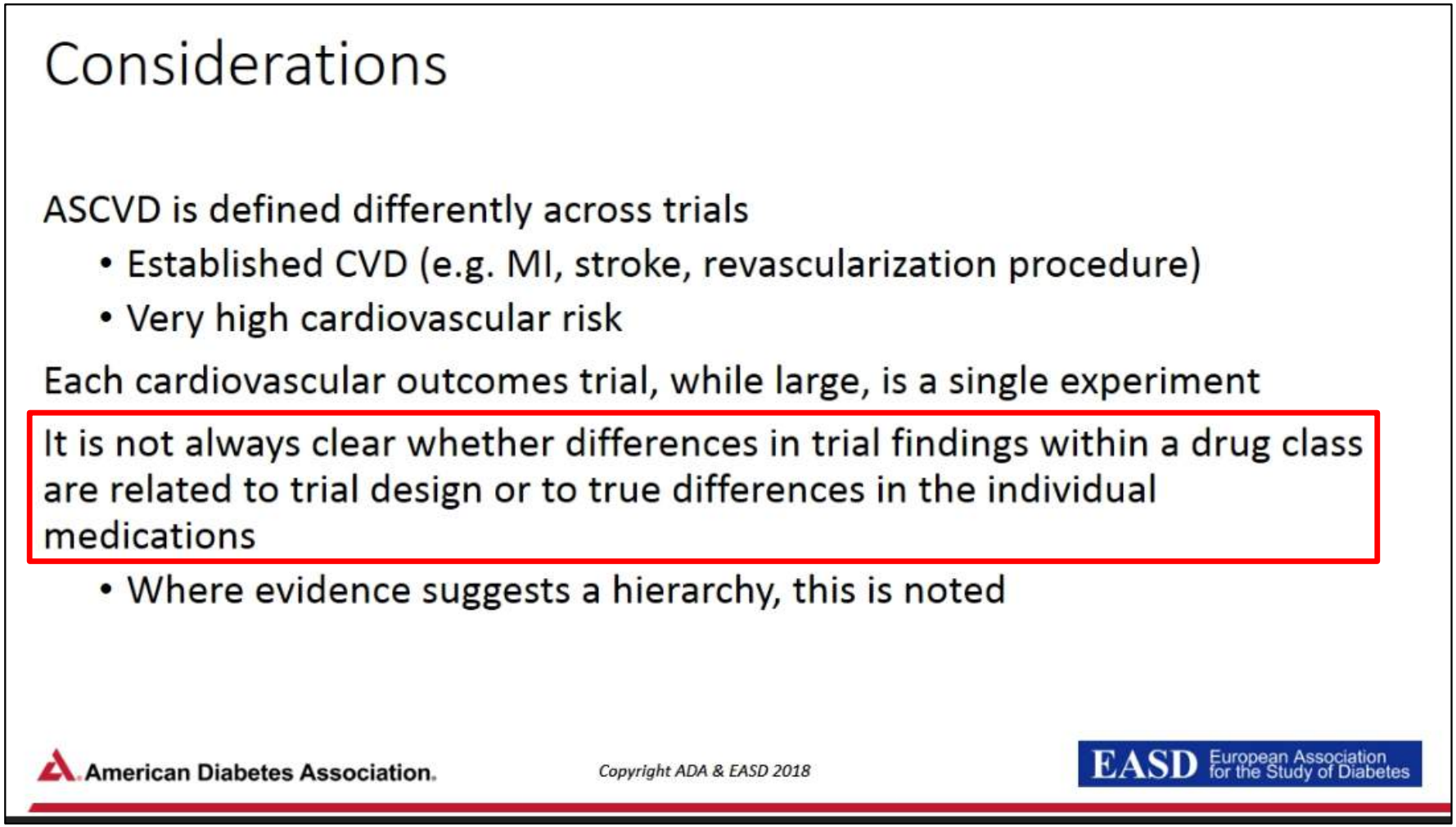


	SAVOR[1]	EXAMINE	TECOS[3]	CARMELINA[4]
Drug	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
HHF	1.27* (1.07-1.51)	1.07 (0.79-1.46) 無HF病史病患 1.76* (1.07-2.90)[2]	1.00 (0.83-1.20)	0.90 (0.74-1.08)

VIVIDD Trial
Vildagliptin
左心室容積增加[5]

1. N Engl J Med. 2013 Oct 3;369(14):1317-26
2. Lancet. 2015 May 23;385(9982):2067-76.
3. N Engl J Med. 2015 Jul 16;373(3):232-42.
4. 54th Annual Meeting of European Association for the Study of Diabetes (EASD) 2018: Oral https://www.easd.org/virtualmeeting/home.html#!contentsessions/2873
5. JACC Heart Fail. 2018 Jan;6(1):8-17.

2018 ADA-EASD consensus:



 54th Annual Meeting of European Association for the Study of Diabetes (EASD) 2018: Oral Presentation # S41.
https://www.easd.org/virtualmeeting/home.html#!contentsessions/2879

HF warning by FDA

TRADJENTA® (linagliptin) tablets, for oral use
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Warnings and Precautions	
Heart Failure (5.2)	8/2017
Bullous Pemphigoid (5.6)	12/2016

----------WARNINGS AND PRECAUTIONS----------

- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue TRADJENTA. (5.1)
- Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of TRADJENTA in patients who have known risk factors for heart failure. Monitor for signs and symptoms. (5.2)

FDA Turns Down Sitagliptin Heart Data for Drug Label

— TECOS results apparently not good enough to warrant new claim

by Kristen Monaco, Contributing Writer, MedPage Today
April 02, 2001

MEDPAGE TODAY

JANUVIA® (sitagliptin) Tablets
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES ----------

Dosage and Administration	
Recommendations for Use in Renal Impairment (2.2)	02/2018
Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin (2.3)	Removal 02/2018
Warnings and Precautions	
Heart Failure (5.2)	08/2017
Assessment of Renal Function (5.3)	02/2018
Macrovascular Outcomes (5.8)	02/2018

- Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of JANUVIA in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)

5.2 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of TRADJENTA prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of TRADJENTA.

HF warning by EMA

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Galvus

- if you have type 1 diabetes (i.e. your body does not produce insulin) or if you have a condition called diabetic ketoacidosis.
- if you are taking an anti-diabetic medicine known as a sulphonylurea (your doctor may want to reduce your dose of the sulphonylurea when you take it together with Galvus in order to avoid low blood glucose [hypoglycaemia]).
- if you have moderate or severe kidney disease (you will need to take a lower dose of Galvus).
- if you are on dialysis.
- if you have liver disease.
- if you suffer from heart failure.
- if you have or have had a disease of the pancreas.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

RESEARCH

OPEN ACCESS

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

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Correspondence to: E Patorno epatorno@bwh.harvard.edu

Additional material is published online only. To view please visit the journal online.

ABSTRACT

OBJECTIVE

To evaluate the cardiovascular safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus, in direct comparisons with DPP-4 inhibitors (DPP-4i), GLP-1 receptor agonists (GLP-1RA), or sulfonylureas, as used in routine practice.

DESIGN

Population based retrospective cohort study.

SETTING

Nationwide sample of patients with type 2 diabetes from a large de-identified US commercial healthcare database (Optum Clinformatics Datamart).

PARTICIPANTS

Three pairwise 1:1 propensity score matched cohorts of patients with type 2 diabetes 18 years and older who initiated canagliflozin or a comparator non-gliflozin antidiabetic agent (ie, a DPP-4i, a GLP-1RA, or a sulfonylurea) between April 2013 and September 2015.

RESULTS

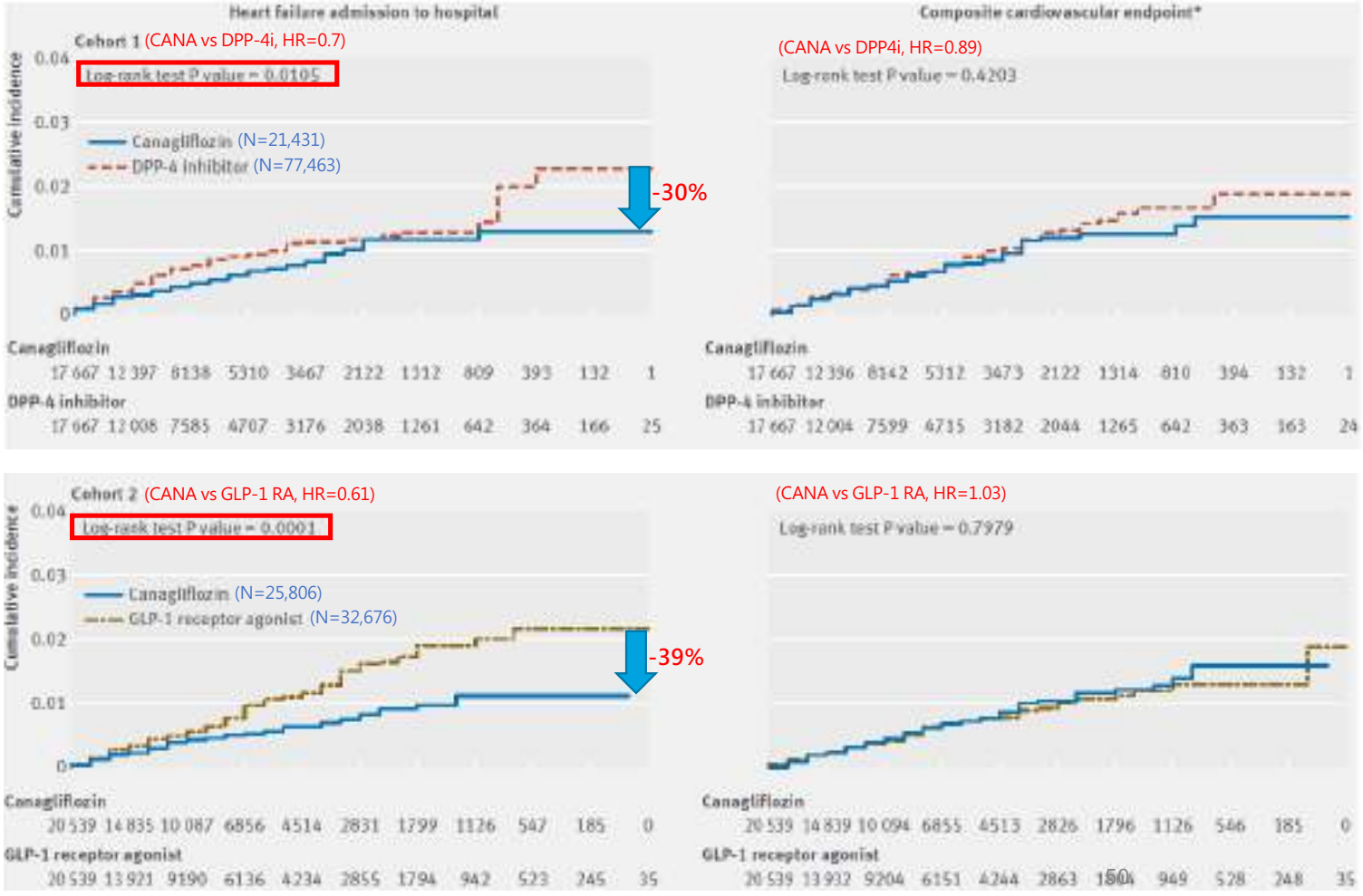
During a 30 month period, the hazard ratio for heart failure admission to hospital associated with canagliflozin was 0.70 (95% confidence interval 0.54 to 0.92) versus a DPP-4i (n=17 667 pairs), 0.61 (0.47 to 0.78) versus a GLP-1RA (20 539), and 0.51 (0.38 to 0.67) versus a sulfonylurea (17 354). The hazard ratio for the composite cardiovascular endpoint associated with canagliflozin was 0.89 (0.68 to 1.17) versus a DPP-4i, 1.03 (0.79 to 1.35) versus a GLP-1RA, and 0.86 (0.65 to 1.13) versus a sulfonylurea. Results were similar in sensitivity analyses further adjusting for baseline hemoglobin A1c levels and in subgroups of patients with and without prior cardiovascular disease or heart failure.

CONCLUSIONS

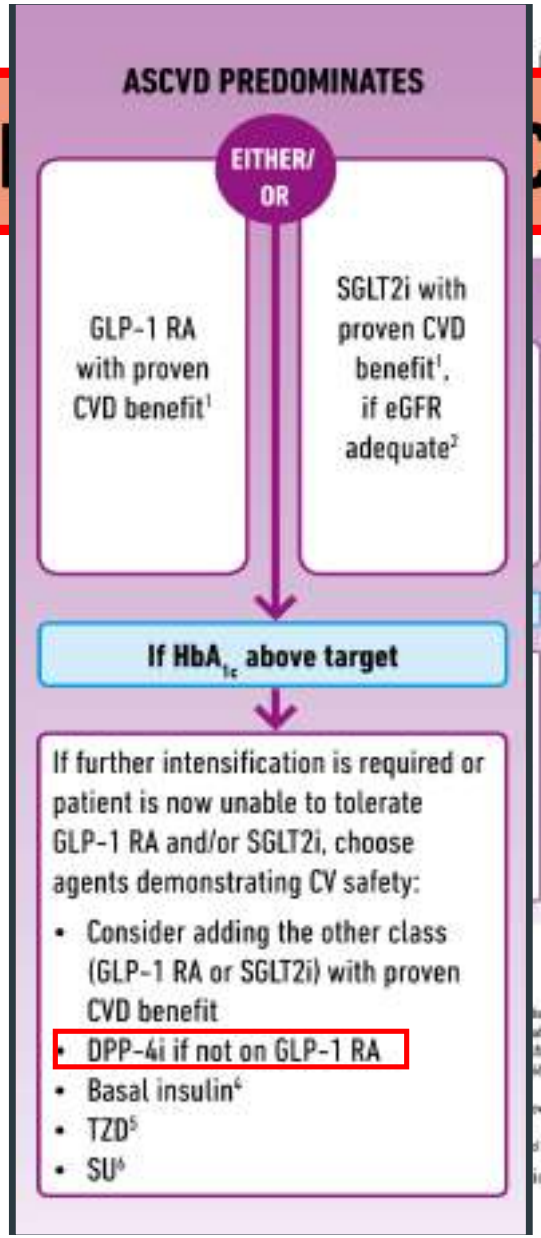
myocardial infarction, ischemic stroke, or hemorrhagic stroke). Hazard ratios and 95% confidence intervals were estimated in each propensity score matched cohort controlling for more than 100 baseline characteristics.

BMJ 2018;360:k119

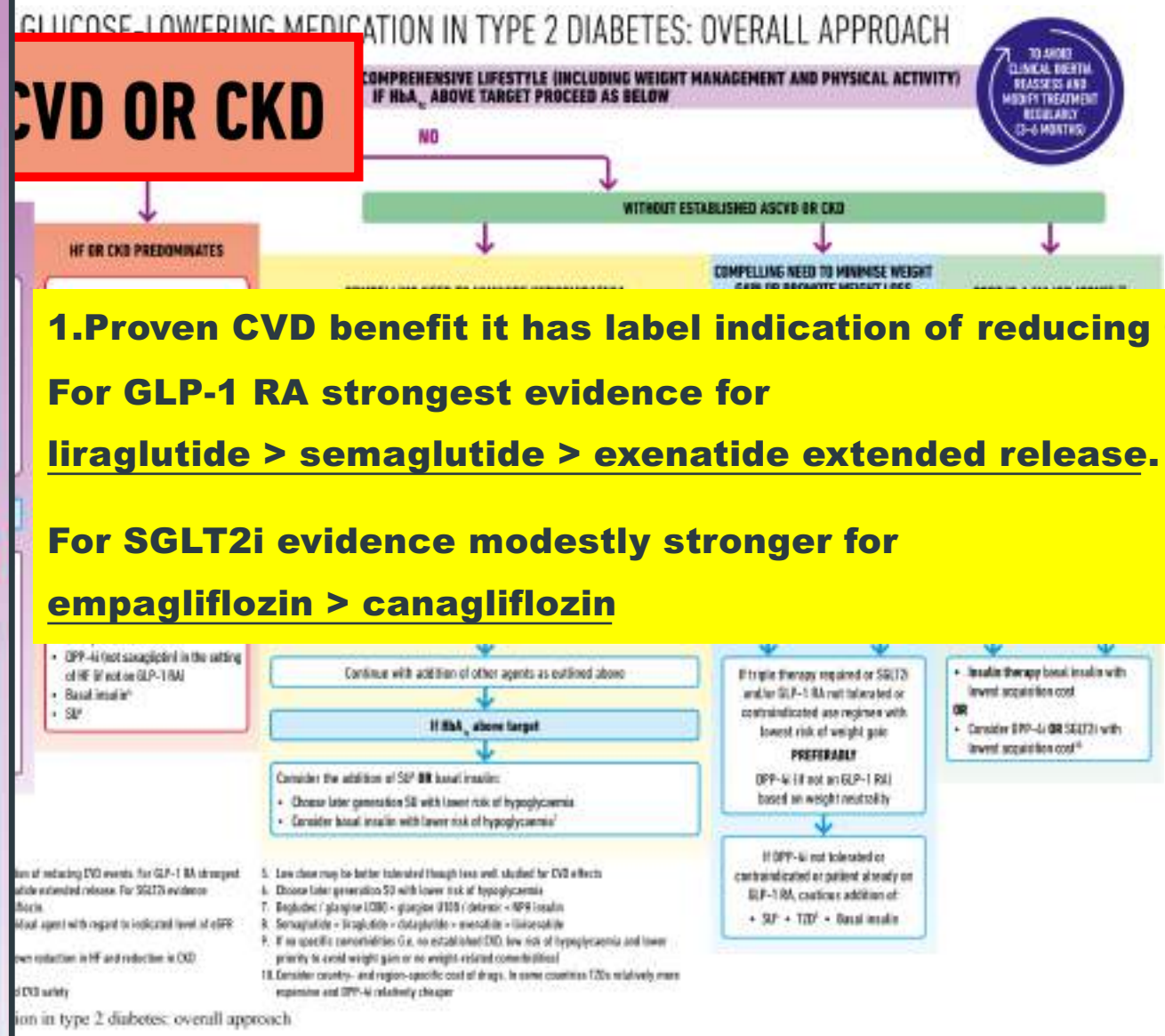
Cardiovascular outcomes associated with canagliflozin versus DPP-4i and GLP-1 RA



BMJ 2018:360:k119



CVD OR CKD



1.Proven CVD benefit it has label indication of reducing CVD events.

For GLP-1 RA strongest evidence for

liraglutide > semaglutide > exenatide extended release.

For SGLT2i evidence modestly stronger for

empagliflozin > canagliflozin

2018 DAROC Clinical Practice Guidelines for Diabetes Care

若單一治療未達控制目標時，加上以下不同機轉的抗糖尿病藥

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

未達控制目標

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

未達控制目標

建議照會專科或強化注射型藥物治療

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

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2018 DAROC Clinical Practice Guidelines for Diabetes Care

了 linagliptin 外，均需根據腎功能減少劑量。使用 vildagliptin 需注意肝功能的變化。二肽基酶 -4 抑制劑可和雙胍類、磺醯脲類和 thiazolidinedione 等藥物合併使用。對於心血管疾病的影響，目前證據顯示並不會增加發生率 [252-254]，但個別藥物對心臟衰竭風險的影響，例如 saxagliptin，仍待後續研究釐清 [252, 255, 256]。

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

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

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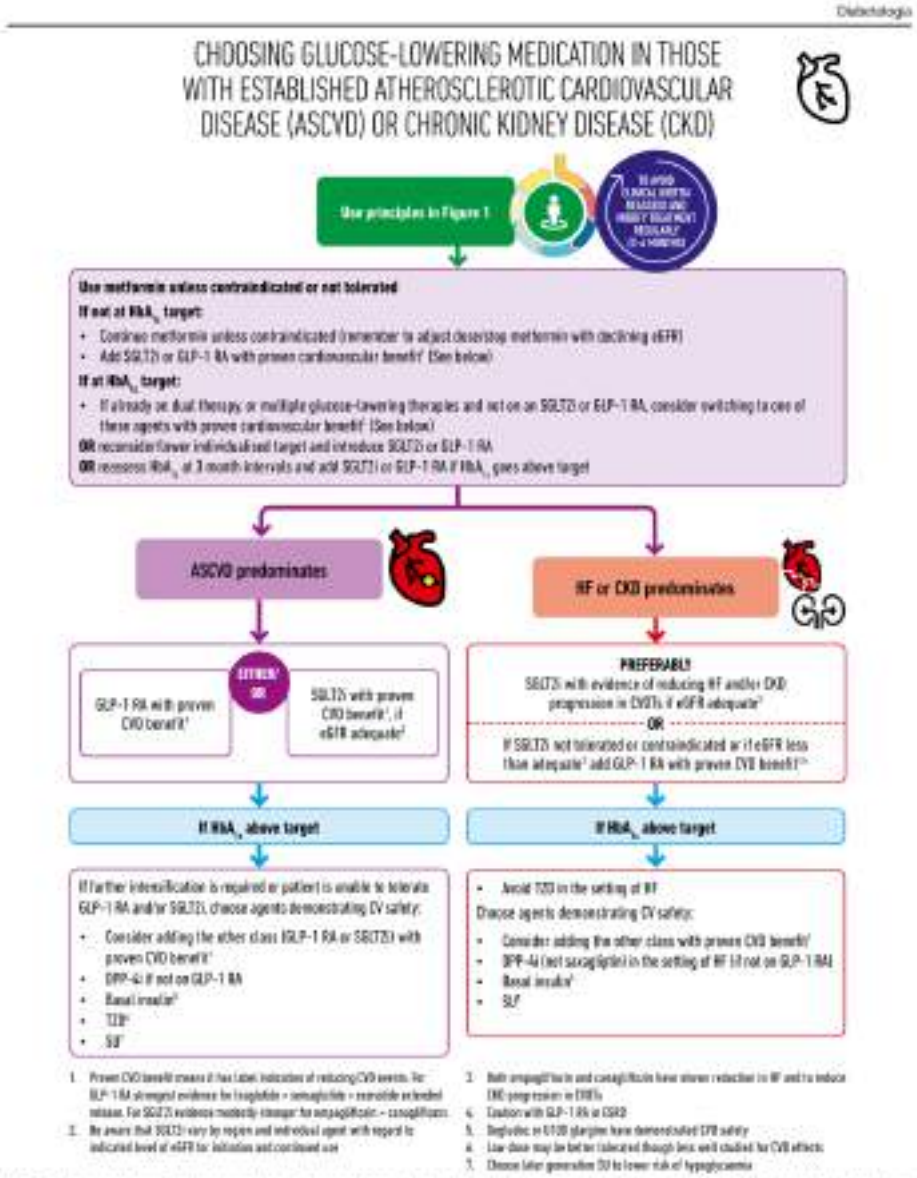
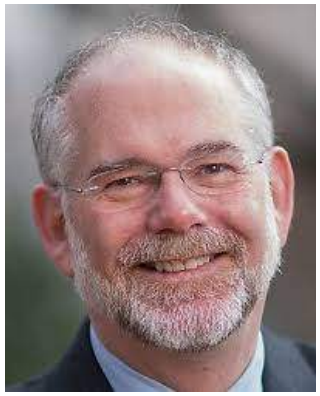


Fig. 3 Choosing glucose-lowering medication in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)

Consensus recommendation

- Among patients with ASCVD in whom HF coexists or is of special concern, SGLT2 inhibitors are recommended

Real-World Meta-Analysis of 4 Observational Database (Observe-4D)



John Buse, former ADA President

Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D)

Patrick B. Ryan PhD[1] | John B. Buse MD[2] | Martijn J. Schuemie PhD[1] | Frank DeFalco BA[3] | Zhong Yuan MD, PhD[1] | Paul E. Stang PhD[1] | Jesse A. Berlin ScD[4] | Norman Rosenthal MD[3]

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[3]Janssen Research & Development, LLC, Raritan, New Jersey

[4]Johnson & Johnson, Titusville, New Jersey

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Funding information
This study was supported by Janssen Research & Development, LLC.

Aims: Sodium glucose co-transporter 2 inhibitors (SGLT2i) are indicated for treatment of type 2 diabetes mellitus (T2DM); some SGLT2i have reported cardiovascular benefit, and some have reported risk of below-knee lower extremity (BKLE) amputation. This study examined the real-world comparative effectiveness within the SGLT2i class and compared with non-SGLT2i anti-hyperglycaemic agents.

Materials and methods: Data from 4 large US administrative claims databases were used to characterize risk and provide population-level estimates of canagliflozin's effects on hospitalization for heart failure (HHF) and BKLE amputation vs other SGLT2i and non-SGLT2i in T2DM patients. Comparative analyses using a propensity score–adjusted new-user cohort design examined relative hazards of outcomes across all new users and a subpopulation with established cardiovascular disease.

Results: Across the 4 databases (142 800 new users of canagliflozin, 110 897 new users of other SGLT2i, 460 885 new users of non-SGLT2i), the meta-analytic hazard ratio estimate for

Diabetes Obes Metab. 2018;1–13 (published on 2018/06/25)

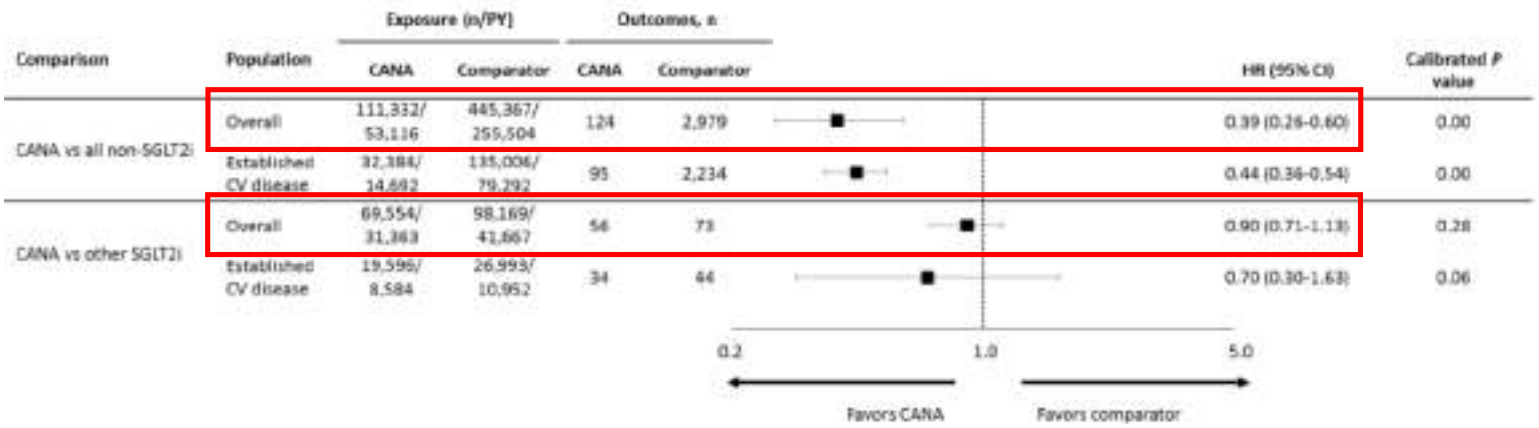
內部訓練用資料請勿外流

Real-World Meta-Analysis of >700,000 US T2DM Patients in 4 Observational Databases (OBSERVE-4D)

- HHF(Hospitalization of Heart Failure)

  CANA vs Non-SGLT2i ; HR = 0.39 (P<0.01)

  CANA vs Other-SGLT2i ; HR = 0.90 (P=0.28)



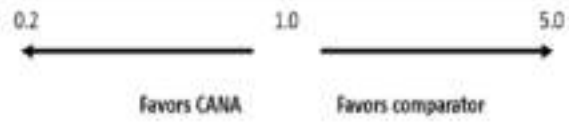
Real-World Meta-Analysis of >700,000 US T2DM Patients in 4 Observational Databases (OBSERVE-4D)

- **BKLE Amputation :**

  CANA vs Non-SGLT2i : HR = 0.75 (P=0.3)

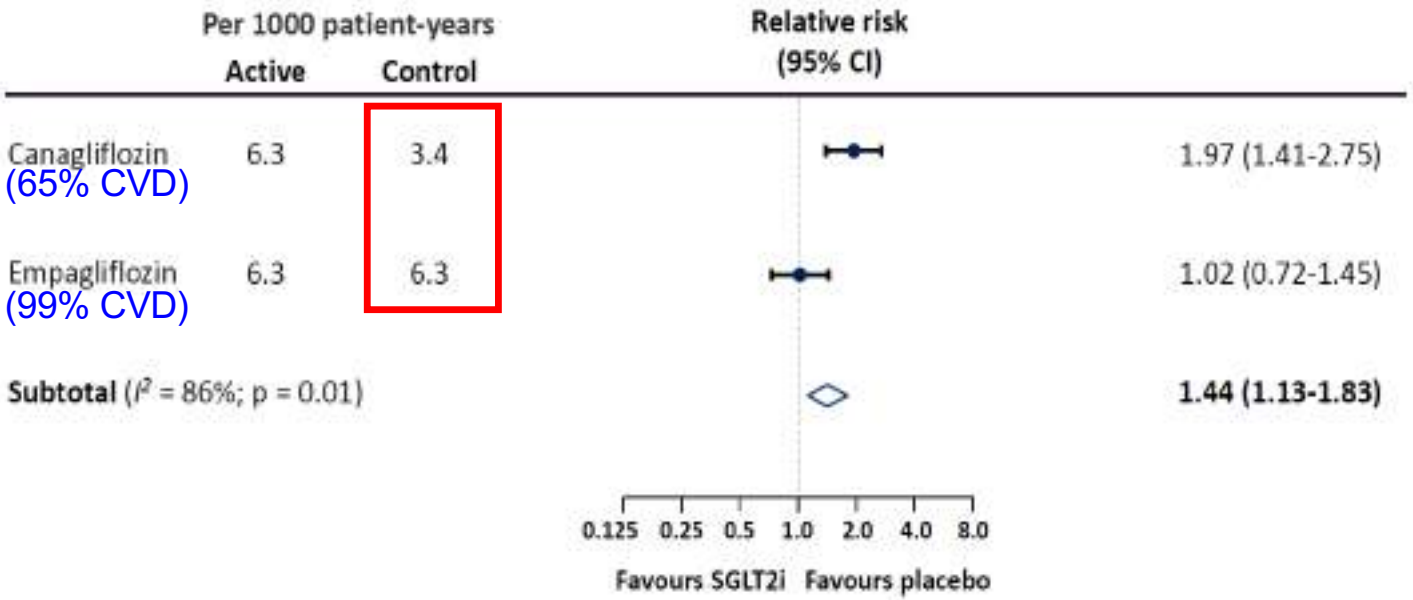
  CANA vs Other-SGLT2i : HR = 1.14 (P=0.53)

Comparison	Population	Exposure (n/PY)		Outcomes, n		HR (95% CI)	Calibrated *P* value
		CANA	Comparator	CANA	Comparator		
CANA vs all non-SGLT2i	Overall	111,332/ 53,125	445,367/ 256,646	60	481	0.75 (0.40-1.41)	0.30
	Established CV disease	32,384/ 14,702	135,006/ 80,176	33	271	0.72 (0.34-1.51)	0.29
CANA vs other SGLT2i	Overall	69,554/ 31,369	98,169/ 41,666	40	53	1.14 (0.67-1.93)	0.53
	Established CV disease	19,596/ 8,584	26,993/ 10,951	23	35	1.08 (0.63-1.82)	0.85



Meta-analytic estimate in the on-treatment population.

Amputation : CANVAS vs EMPA-REG



(20% CVD)

Country	Year of Registration	Number of Patients	Annual Incidence (%/yr)	
			Foot Ulcer	Amputation
America[1)]	1993–95	8,905	1.9	0.3(3/1000p-yr)

N Engl J Med 2017; 377:644-657 (Ref. 9) N Engl J Med 2015; 373:2117-28 (Ref. 12)

內部訓練用資料請勿外流

Truven Marketscan Database for Amputation Risk with AHAs

Received: 17 July 2017 | Revised: 29 August 2017 | Accepted: 1 September 2017
DOI: 10.1111/dom.13115

WILEY

ORIGINAL ARTICLE

Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study

Zhong Yuan MD, PhD[1] | Frank J. DeFalco BA[2] | Patrick B. Ryan PhD[1] | Martijn J. Schuemie PhD[1] | Paul E. Stang PhD[1] | Jesse A. Berlin ScD[3] | Mehul Desai MD[2] | Norm Rosenthal MD[2]

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Correspondence
Zhong Yuan, MD, PhD, Janssen Research &

Aims: To examine the incidence of amputation in patients with type 2 diabetes mellitus (T2DM) treated with sodium glucose co-transporter 2 (SGLT2) inhibitors overall, and canagliflozin specifically, compared with non-SGLT2 inhibitor antihyperglycaemic agents (AHAs).
Materials and Methods: Patients with T2DM newly exposed to SGLT2 inhibitors or non-SGLT2 inhibitor AHAs were identified using the Truven MarketScan database. The incidence of below-knee lower extremity (BKLE) amputation was calculated for patients treated with SGLT2

Diabetes Obes Metab. 2017;1–8

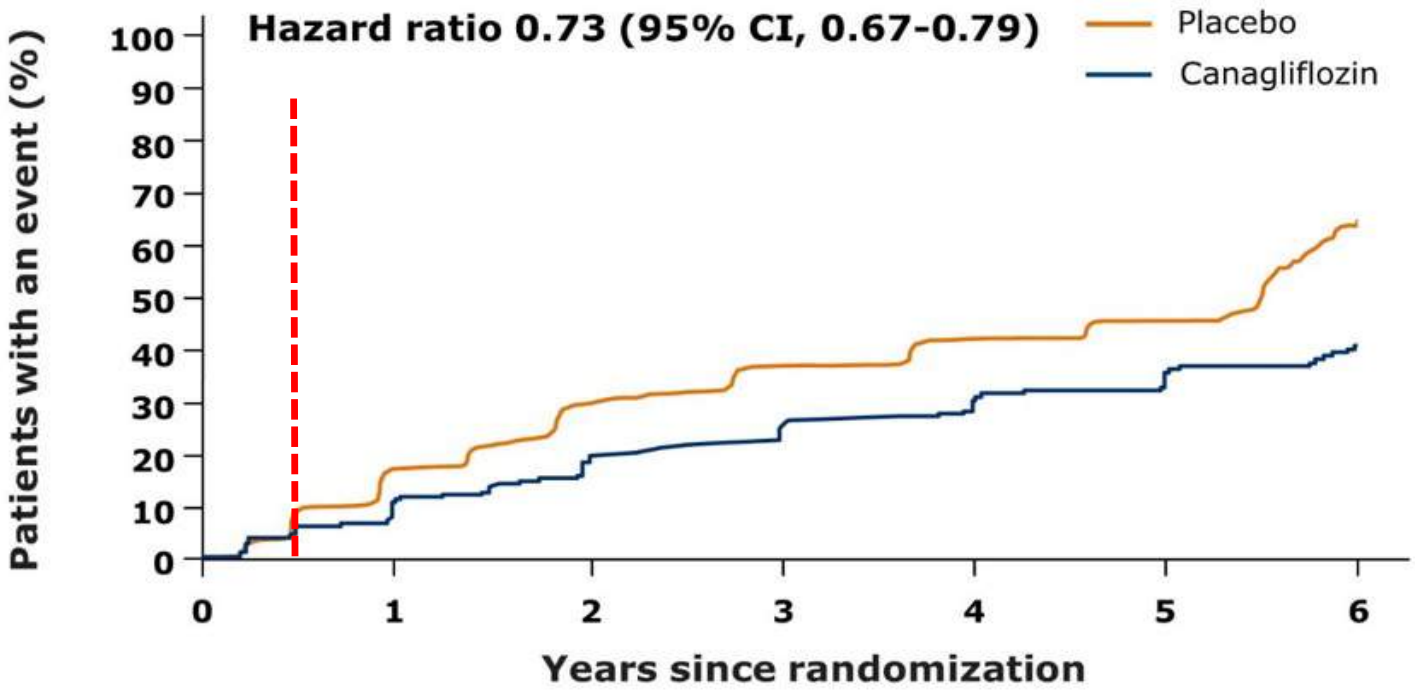
Risk of lower extremity amputations in people with T2DM treated with SGLT2i in the USA

TABLE 1 Crude incidence rate of BKLE amputation from the Truven MarketScan CCAE database

New users cohort	Number of exposed persons	Persons with amputation before exposure	Person-years at risk	Persons with BKLE amputation post-exposure	Incidence rate, per 1000 person-years
Overall					
SGLT2 inhibitors	119 567	225	140 145	171	1.22
Canagliflozin	73 024	139	95 422	120	1.26
Dapagliflozin	39 117	76	38 541	37	0.96
Empagliflozin	24 433	55	17 930	25	1.39
Non-SGLT2 inhibitor AHA	226 623	722	283 406	530	1.87
High CV risk					
SGLT2 inhibitors	25 781	120	30 050	61	2.03
Canagliflozin	15 850	75	20 594	41	1.99
Dapagliflozin	8045	46	7829	10	1.28
Empagliflozin	5568	22	4098	14	3.42
Non-SGLT2 inhibitor AHA	48 483	357	58 903	194	3.29
Non-high CV risk					
SGLT2 inhibitors	93 786	105	110 095	110	1.00
Canagliflozin	57 174	64	74 827	79	1.06
Dapagliflozin	31 072	30	30 712	27	0.88
Empagliflozin	18 865	33	13 831	11	0.80
Non-SGLT2 inhibitor AHA	178 140	365	224 503	336	1.50

Diabetes Obes Metab. 2017;1–8

Progression of Albuminuria

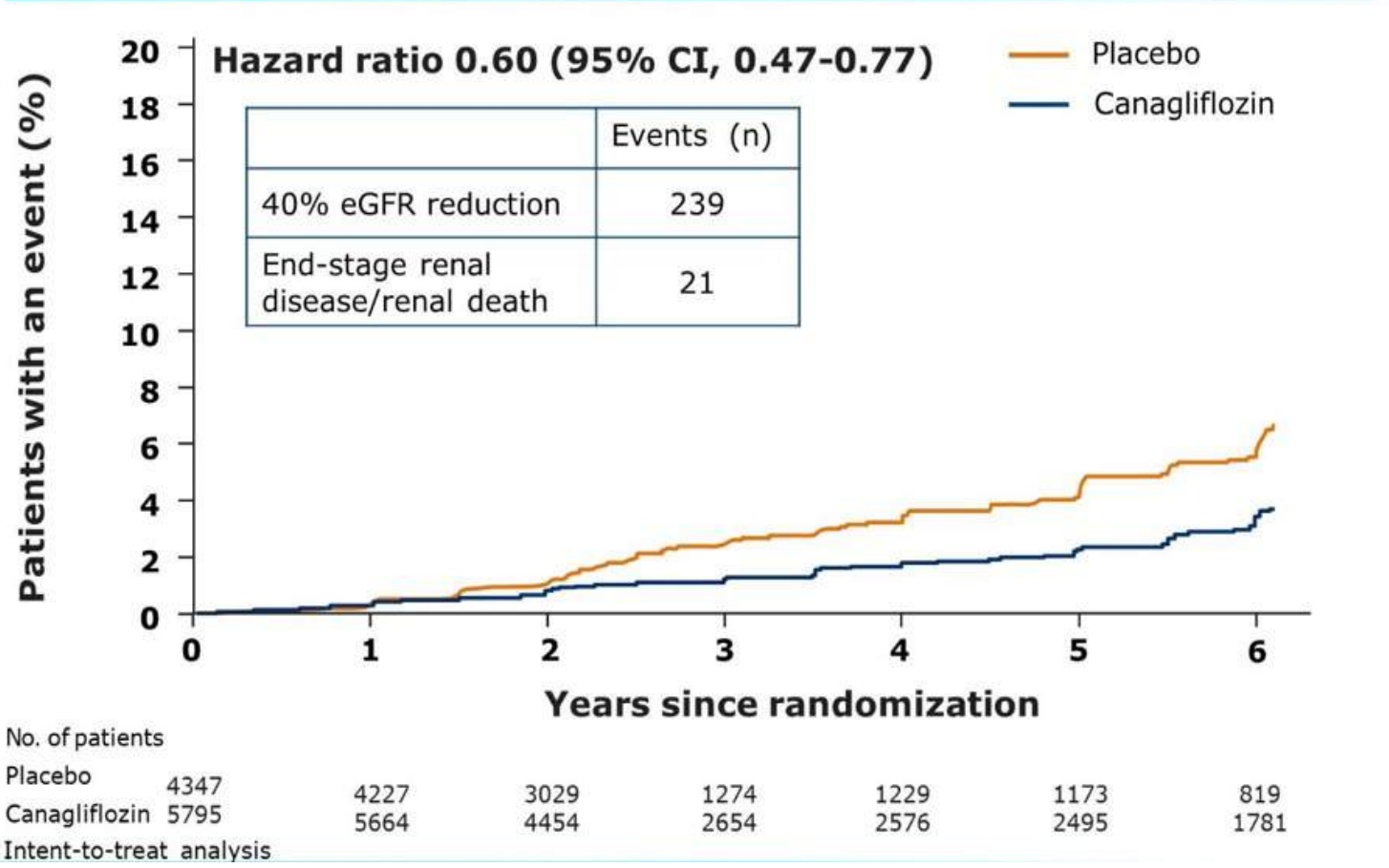


No. of patients							
Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

Intent-to-treat analysis

N Engl J Med 2017; 377:644-657 (Ref. 9)

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

N Engl J Med 2017; 377:644-657 (Ref. 9)

Primary & Secondary Prevention : Result of CANVAS

ORIGINAL RESEARCH ARTICLE

Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

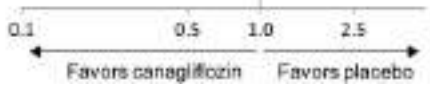
ORIGINAL RESEARCH ARTICLE

CONCLUSIONS: Patients with type 2 diabetes mellitus and prior cardiovascular events had higher rates of cardiovascular outcomes compared with the primary prevention patients. Canagliflozin reduced cardiovascular and renal outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups. Additional studies will provide further insights into the effects of canagliflozin in these patient populations.

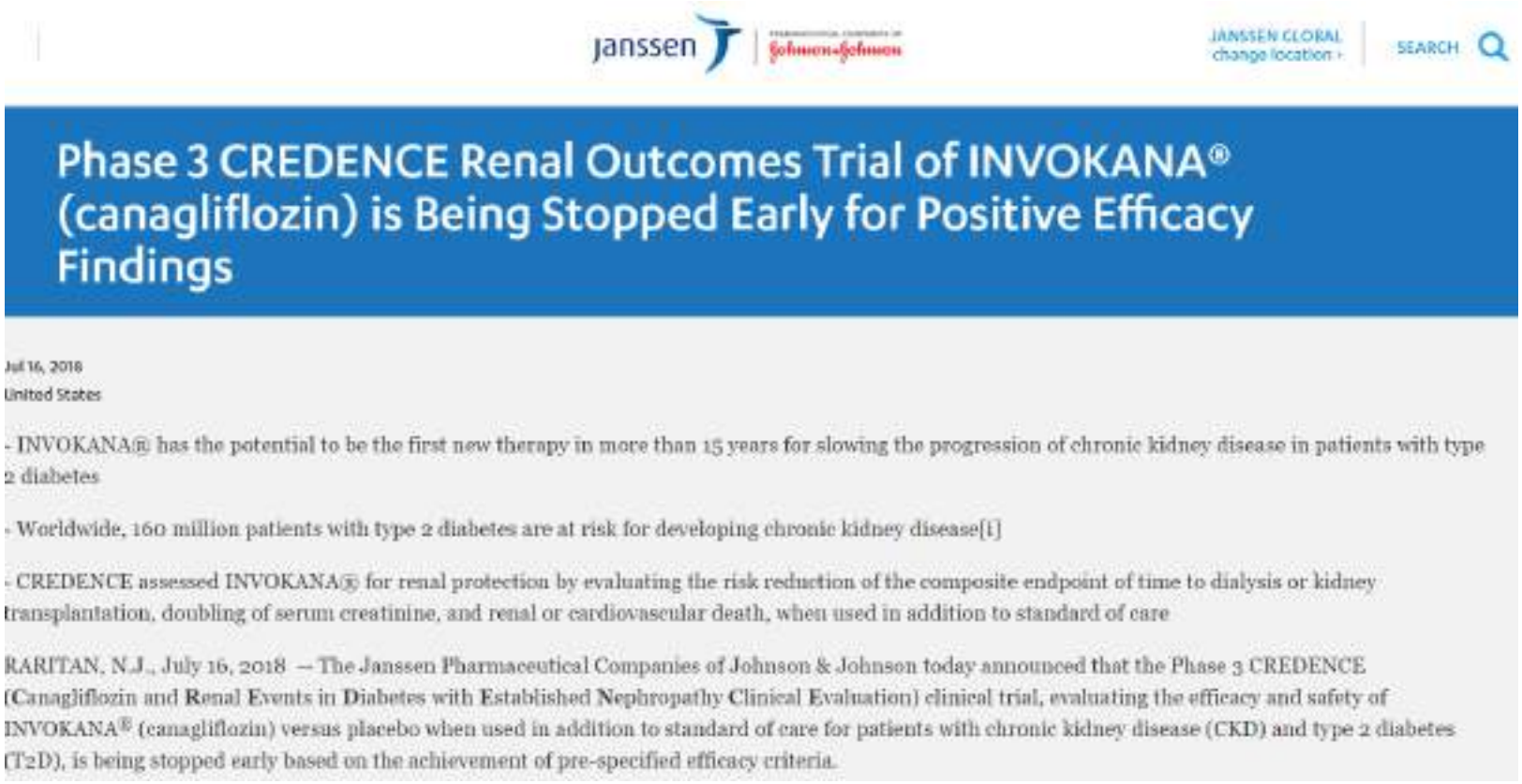
Circulation 2017;1-12 (Ref. 14)

CV Outcome by baseline eGFR Result of CANVAS

Outcome	eGFR	Canagliflozin	Placebo	Hazard ratio (95% CI)	Interaction p value
		No. events per 1000 patients/yr			
MACE	All	26.9	31.5	0.86 (0.75-0.97)	0.33
	<45	44.7	63.3	0.65 (0.41-1.03)	
	45-<60	33.2	44.4	0.71 (0.53-0.95)	
	60-<90	26.8	29.0	0.95 (0.80-1.13)	
	≥90	20.8	23.6	0.84 (0.62-1.13)	
CV death	All	11.6	12.8	0.87 (0.72-1.06)	0.53
	<45	29.5	30.2	1.01 (0.57-1.81)	
	45-<60	19.4	18.6	0.94 (0.62-1.42)	
	60-<90	10.7	11.3	0.93 (0.72-1.22)	
	≥90	6.4	9.6	0.60 (0.37-0.97)	
Fatal/non-fatal MI	All	11.2	12.6	0.89 (0.73-1.09)	0.09
	<45	13.6	23.3	0.49 (0.22-1.07)	
	45-<60	12.8	19.0	0.65 (0.41-1.04)	
	60-<90	12.1	11.0	1.14 (0.87-1.49)	
	≥90	8.0	10.8	0.72 (0.46-1.13)	
Fatal/non-fatal stroke	All	7.9	9.6	0.87 (0.69-1.09)	0.01
	<45	5.2	16.8	0.32 (0.11-0.96)	
	45-<60	7.1	13.5	0.56 (0.31-1.00)	
	60-<90	7.7	9.3	0.89 (0.65-1.21)	
	≥90	9.5	6.6	1.42 (0.86-2.36)	
Hospitalization for heart failure	All	5.5	8.7	0.67 (0.52-0.87)	0.62
	<45	16.9	34.3	0.45 (0.23-0.88)	
	45-<60	9.6	16.5	0.62 (0.37-1.03)	
	60-<90	4.6	6.1	0.76 (0.52-1.12)	
	≥90	3.7	5.1	0.76 (0.40-1.47)	



CREDENCE Study Early Termination for Positive Findings



janssen | Johnson & Johnson

JANSSEN GLOBAL change location › SEARCH

Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

Jul 16, 2018
United States

- INVOKANA® has the potential to be the first new therapy in more than 15 years for slowing the progression of chronic kidney disease in patients with type 2 diabetes

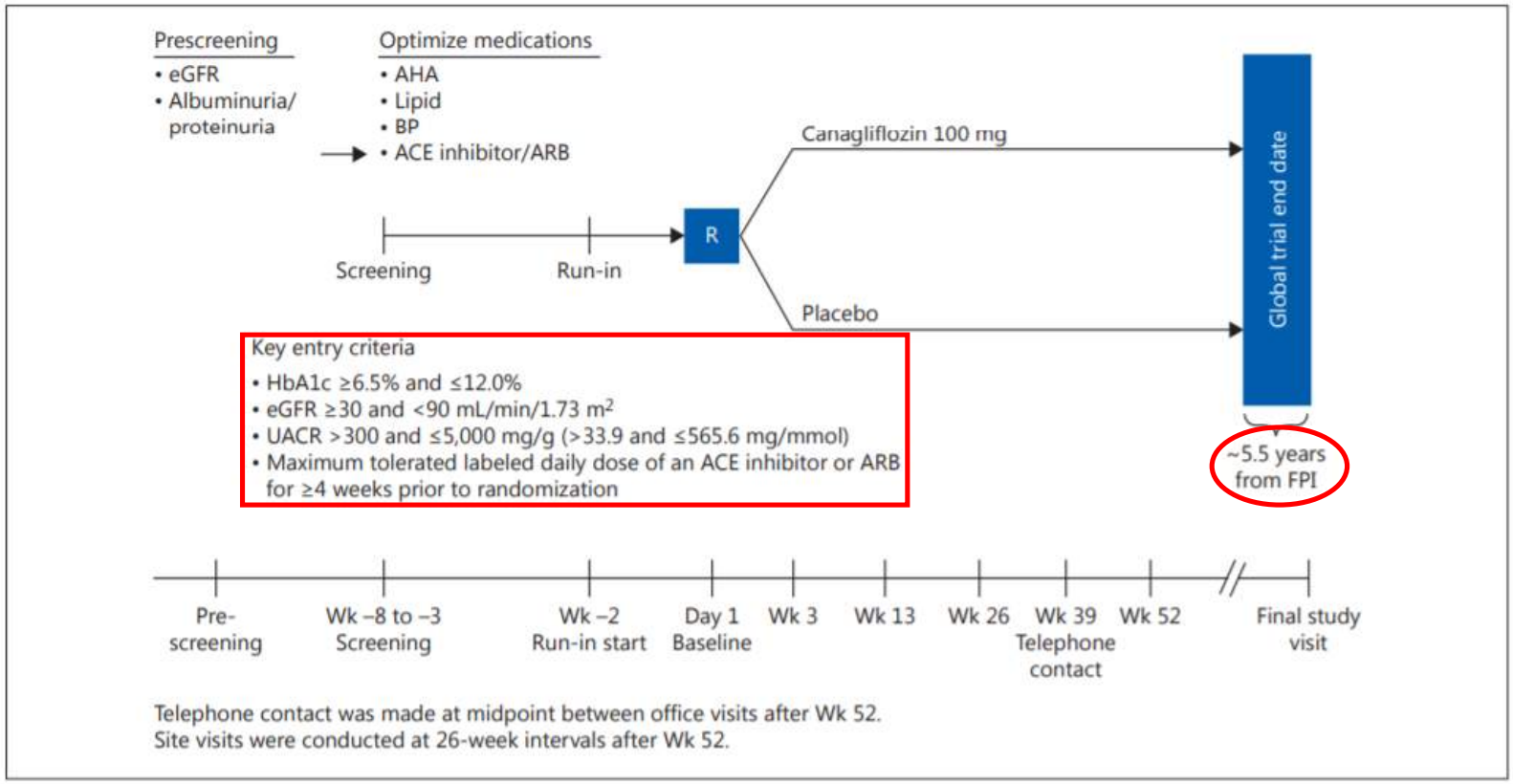
- Worldwide, 160 million patients with type 2 diabetes are at risk for developing chronic kidney disease[1]

- CREDENCE assessed INVOKANA® for renal protection by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine, and renal or cardiovascular death, when used in addition to standard of care

RARITAN, N.J., July 16, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the Phase 3 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) clinical trial, evaluating the efficacy and safety of INVOKANA® (canagliflozin) versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

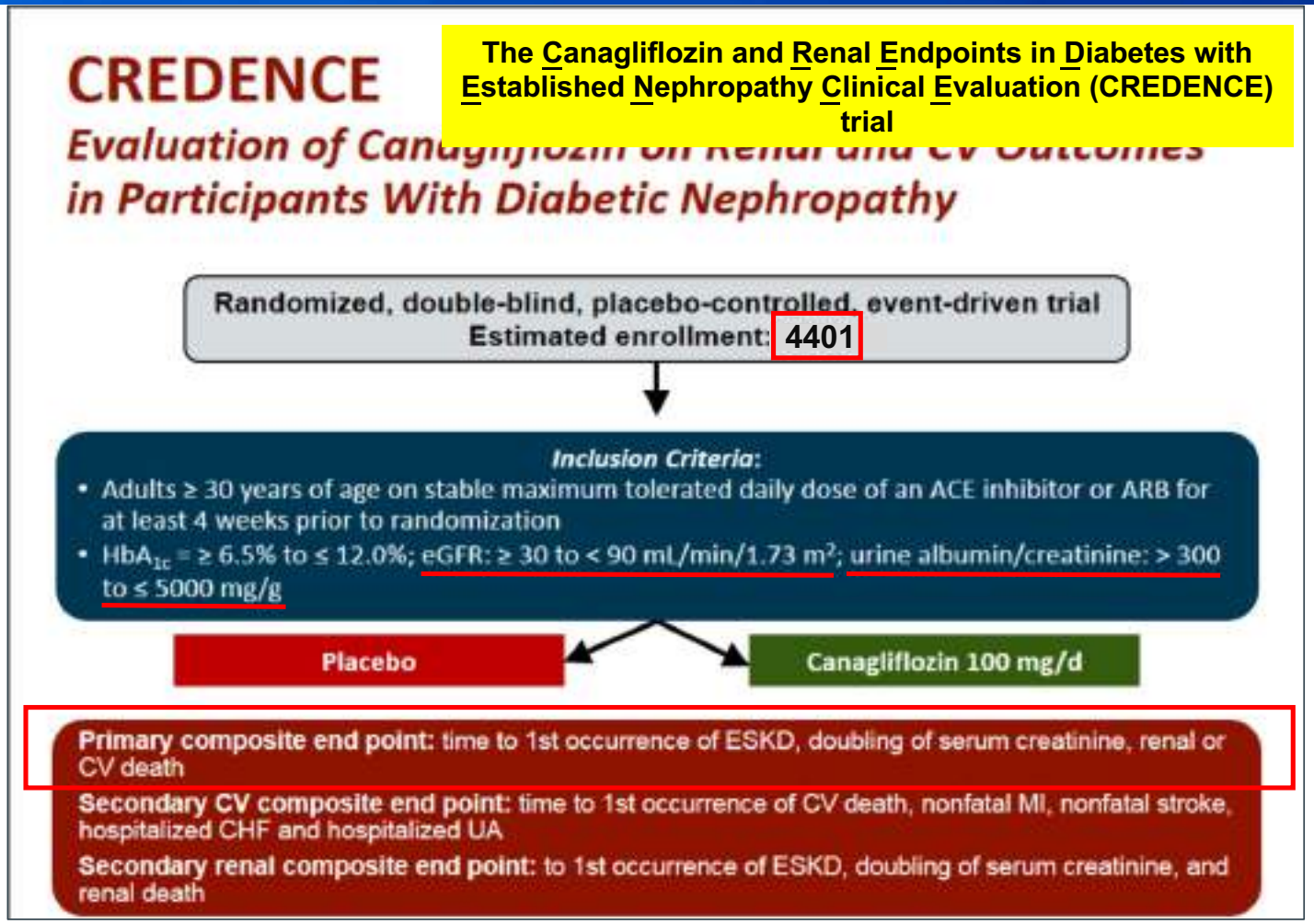
https://www.janssen.com/phase-3-credence-renal-outcomes-trial-invokanar-canagliflozin-being-stopped-early-positive-efficacy

CREDENCE Study Design



Am J Nephrol 2017;46:462–472

Patient Enrollment and End Points



https://www.medscape.org

Rationale, Design, and Expected Results

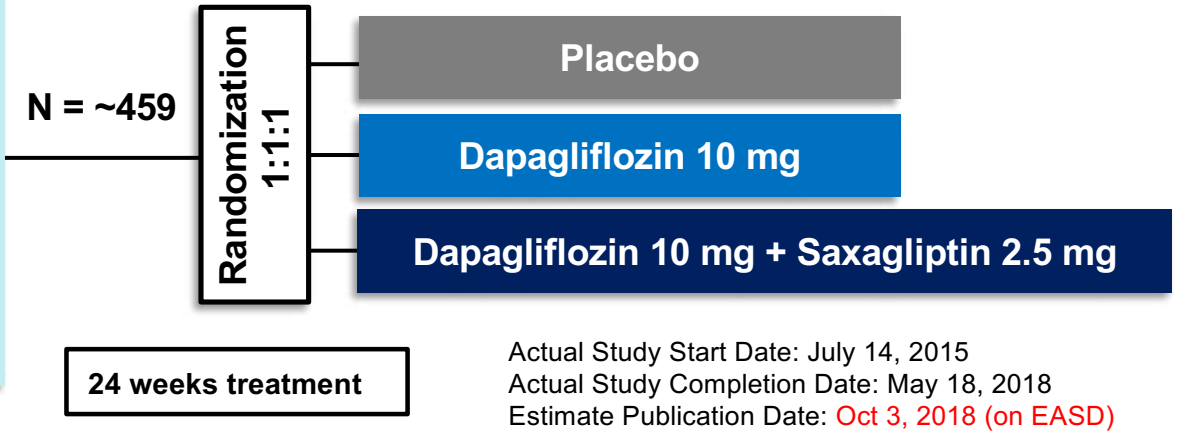
- **Background**
  - -The effects of canagliflozin on kidney and CV events have not been studied in T2DM patients with established kidney disease.
- **Objective**
  - -CREDENCE trial aims to compare the efficacy and safety of canagliflozin vs placebo at preventing kidney and CV outcomes in T2DM patients with kidney disease.
- **Methods**
  - - CREDENCE is a randomized, double-blind, event-driven, placebo-controlled trial set in in 34 countries with a projected duration of **~5.5 years** and enrolling **4,401** patients.
  - - **Primary outcome: the composite of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death.**
- **Conclusion**
  - - CREDENCE will provide definitive evidence about the effects of canagliflozin on renal (and cardiovascular) outcomes in patients with T2DM and established kidney disease.

Am J Nephrol 2017;46:462–472

DELIGHT: Study to Evaluate the Effect of Dapagliflozin With and Without Saxagliptin on Albuminuria, and to Investigate the Effect of Dapagliflozin and Saxagliptin on HbA1c in Patients With Type 2 Diabetes and CKD

Population:

- ≥18 years of age
- History of T2DM for more than 12 months
- HbA1c≥7.0% and ≤11.0%
- eGFR 25–75 mL/min/1.73m^2
- Micro or macroalbuminuria (UACR 30 - 3500 mg/g)
- Treatment with ACE inhibitor or an ARB for at least 3 months prior to screening



Actual Study Start Date: July 14, 2015
Actual Study Completion Date: May 18, 2018
Estimate Publication Date: Oct 3, 2018 (on EASD)

Primary endpoint:

- Change in HbA1c (dapagliflozin 10 mg + saxagliptin 2.5 mg) [Time Frame: From baseline up to 24 weeks of treatment]
- Percent change in Urine albumin to creatinine ratio (UACR)

(dapagliflozin 10 mg + saxagliptin 2.5 mg) [Time Frame: From baseline up to 24 weeks of treatment]
(dapagliflozin 10 mg) [Time Frame: From baseline up to 24 weeks of treatment]

Secondary endpoints:

- Percent change in total body weight, FPG
- Proportion of patients that achieve 30% reduction in UACR, HbA1c<7%
- Change in seated SBP, HbA1c

原本預計發表的DELIGHT，因為還在進一步分析，EASD上沒有發表。

C
https://clinicaltrials.gov/show/NCT02544555

For the purpose of scientific medical exchange

CANVAS 試驗結論

14 降低14%的整體風險 (3-Point MACE)，包含因心血管疾病死亡(13%)、非致死性心肌梗塞(15%)、或非致死性中風(10%)

33 降低33% 因心臟衰竭住院風險

27 延緩27%蛋白尿惡化情形

N Engl J Med 2017; 377:644-657 (Ref. 9)

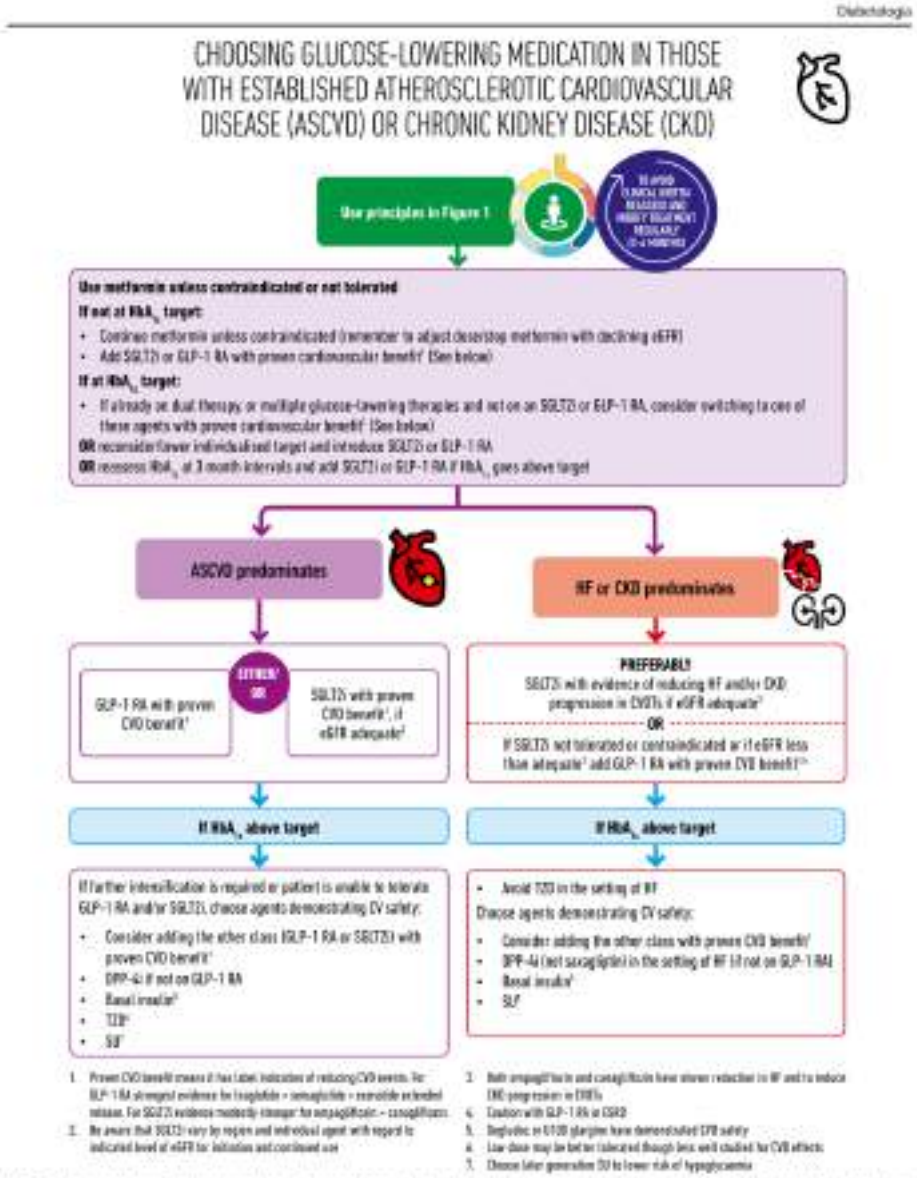


Fig. 3 Choosing glucose-lowering medication in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)

Consensus recommendation

- For patients with <u>type 2 diabetes and CKD</u>, <u>with or without CVD</u>, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression

Energy Balance after SGLT2 inhibition

RESULTS

At week 90, weight loss averaged −3.2 ± 4.2 kg (corresponding to a median calorie deficit of 51 kcal/day [interquartile range (IQR) 112]). However, the observed calorie loss through glycosuria (206 kcal/day [IQR 90]) was predicted to result in a weight loss of −11.3 ± 3.1 kg, assuming no compensatory changes in energy intake. Thus, patients lost only 29 ± 41% of the weight loss predicted by their glycosuria; the model indicated that this difference was accounted for by a

Body weight was stable after 24 weeks

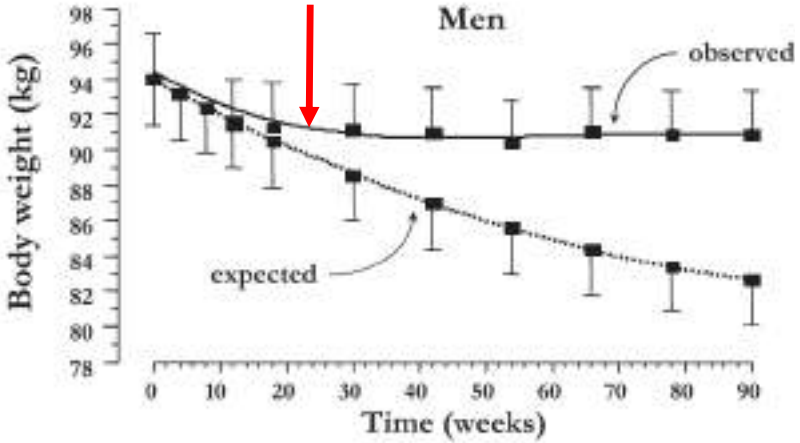


Figure 2—Time course of observed and predicted (by glycosuria) weight loss in men and women with T2DM treated with empagliflozin (25 mg/day) for 90 weeks. Plots are mean ± SEM.

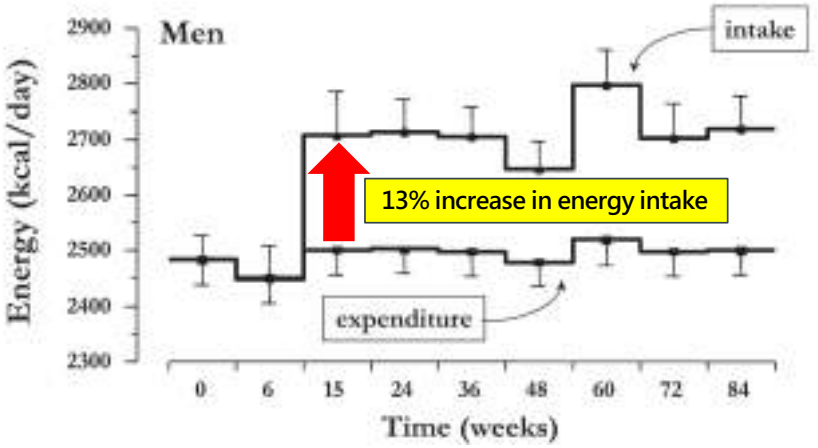


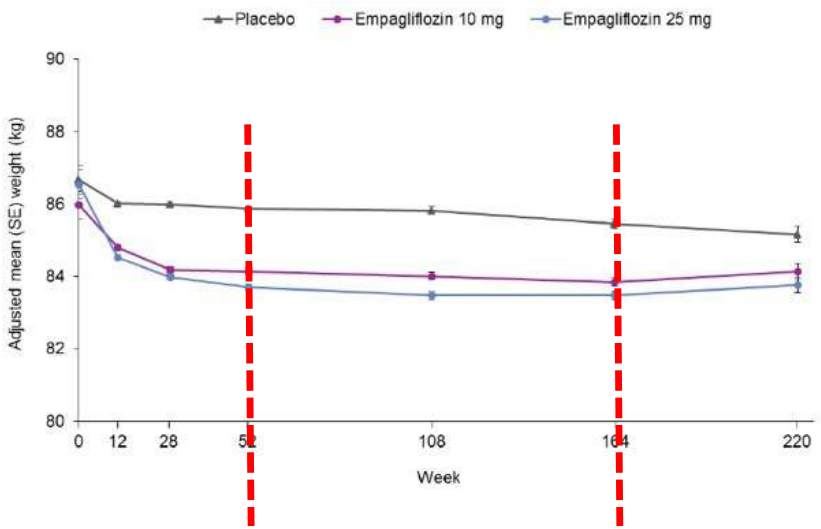
Figure 3—Calculated rates of energy intake and TDEE in men and women with T2DM treated with empagliflozin (25 mg/day) for 90 weeks. Plots are mean ± SEM averaged over the indicated time intervals.

Diabetes Care 38:1730–1735, 2015 (Ref. 19)

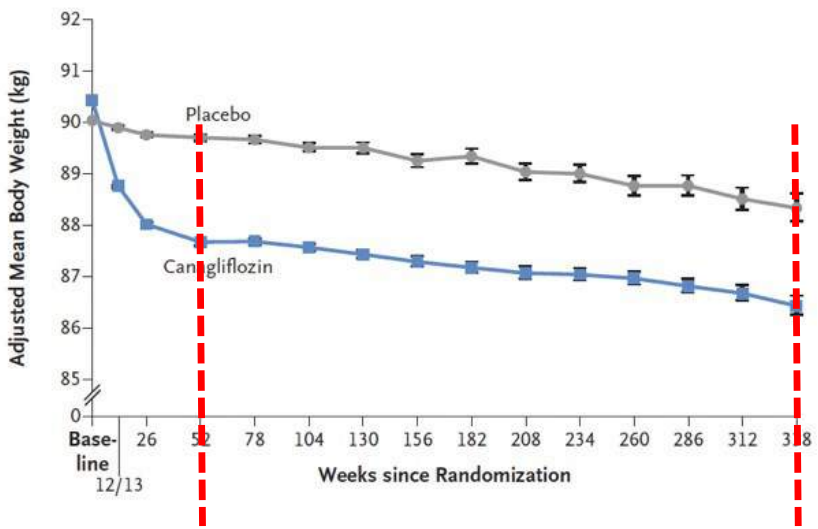
EMPA-REG vs CANVAS : Body Weight

Body weight

EMPA-REG

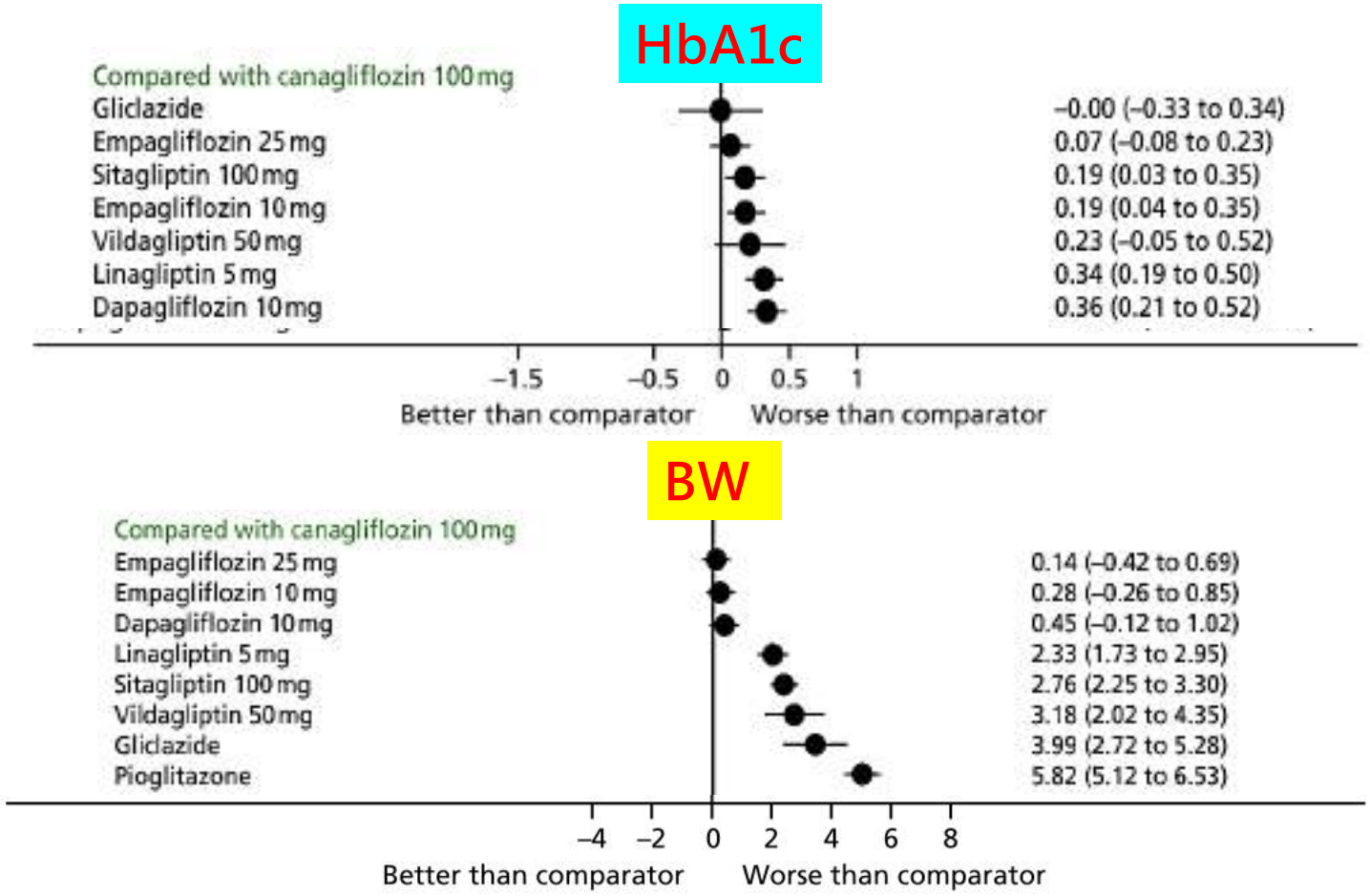


CANVAS



N Engl J Med 2017; 377:644-657 (Ref. 9)
N Engl J Med 2015; 373:2117-28 (Ref. 12)

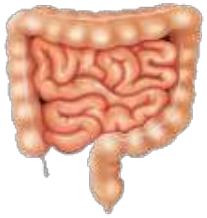
Canagliflozin, dapagliflozin and empagliflozin for treating type 2 diabetes: Network Meta-analysis



Health Technology Assessment, No. 21.2 (Ref. 6)

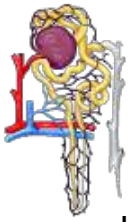
Effect of SGLT1 / SGLT2

Intestine SGLT1



- Main uptake mechanism for glucose and galactose in the intestine
- S2 and S3 segments of the proximal renal tubule are responsible for ~10% of the renal glucose re-absorption
- **High-affinity** (K_m = ~0.5 mM), low-capacity transporter which transfers glucose and sodium with a Na^+:glucose coupling ratio of 2

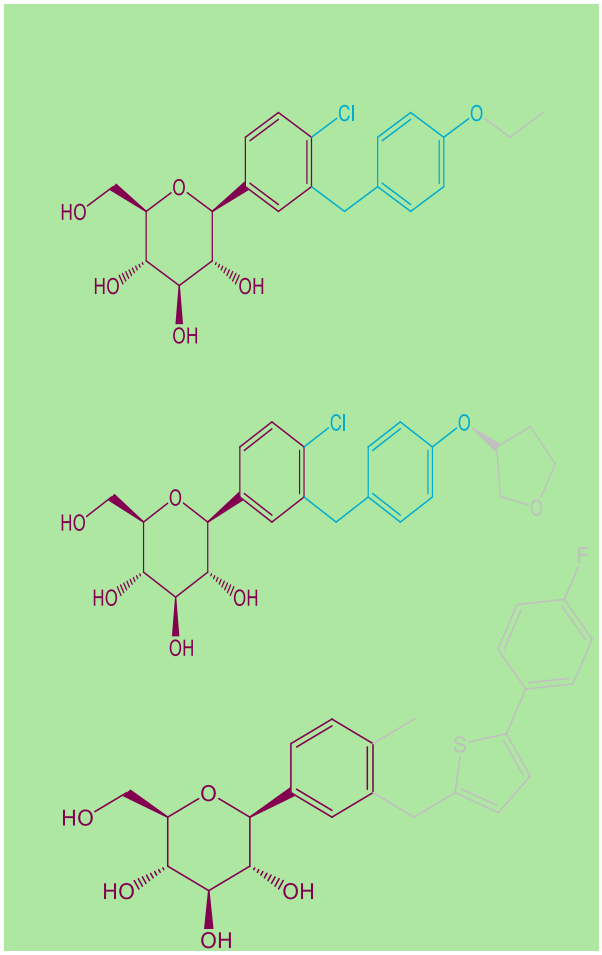
Kidney SGLT2



- Almost completely expressed in the brush-border membrane of proximal renal tubular cells in the S1 + S2 segment
- Responsible for ~90% of the total renal glucose re-absorption
- **Low-affinity** (K_m = ~2 mM), high-capacity transporter which transfers glucose and sodium with a Na^+:glucose coupling ratio of 1

1. Chao EC and Henry RR. *Nat Rev Drug Discov*. 2010;9:551–559;
2. Mather A and Pollock C. *Kidney Int Suppl.* 2011;(120):S1–6;
3. Wright EM, et al. *J Intern Med*. 2007;261:32–43.

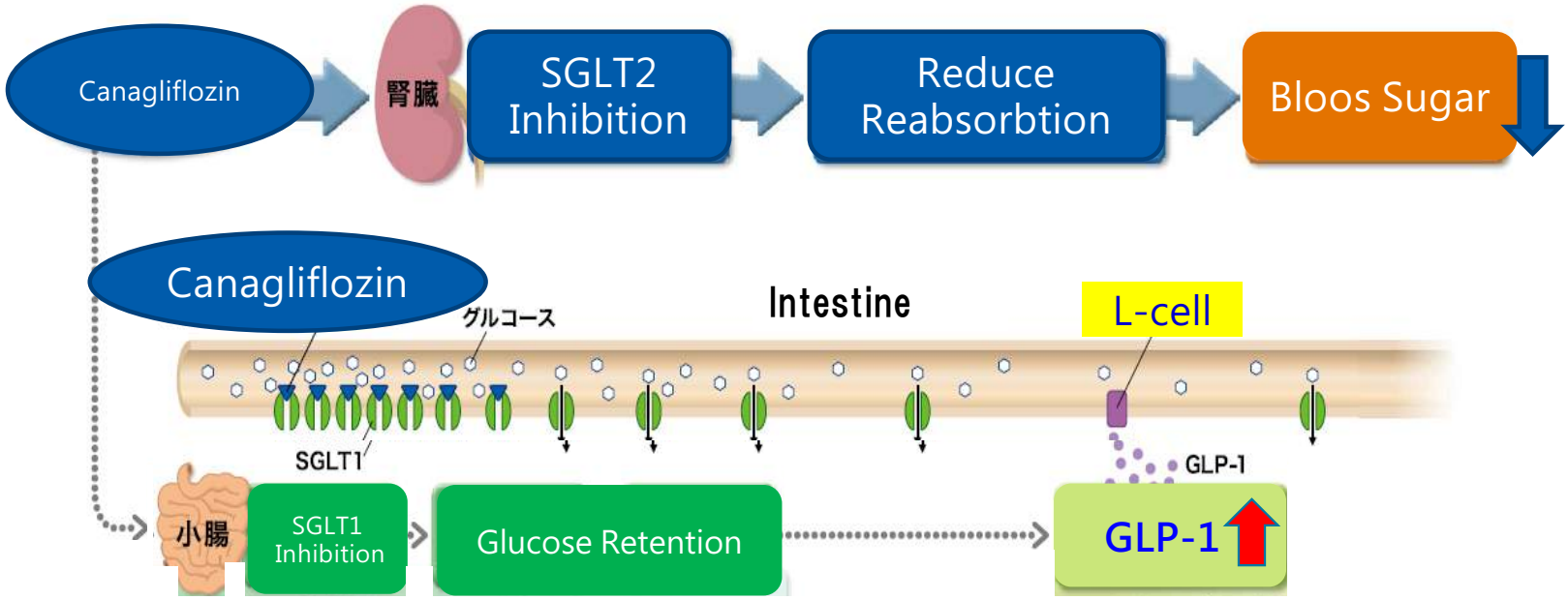
Structure and selectivity profiles for SGLT2 over SGLT1



	Selectivity SGLT-1 : SGLT-2
Dapagliflozin	1:1,200
Empagliflozin	1:2,500
Canagliflozin	1:414

Singh AK et al. Indian J Endocrinol Metab. 2015 Nov-Dec;19(6):722-30 (Ref. 16)

Canagliflozin increase aGLP-1 through SGLT1 inhibition



Canagliflozin Lowers Postprandial Glucose and Insulin by DelayingIntestinal Glucose Absorption in Addition to Increasing Urinary Glucose Excretion

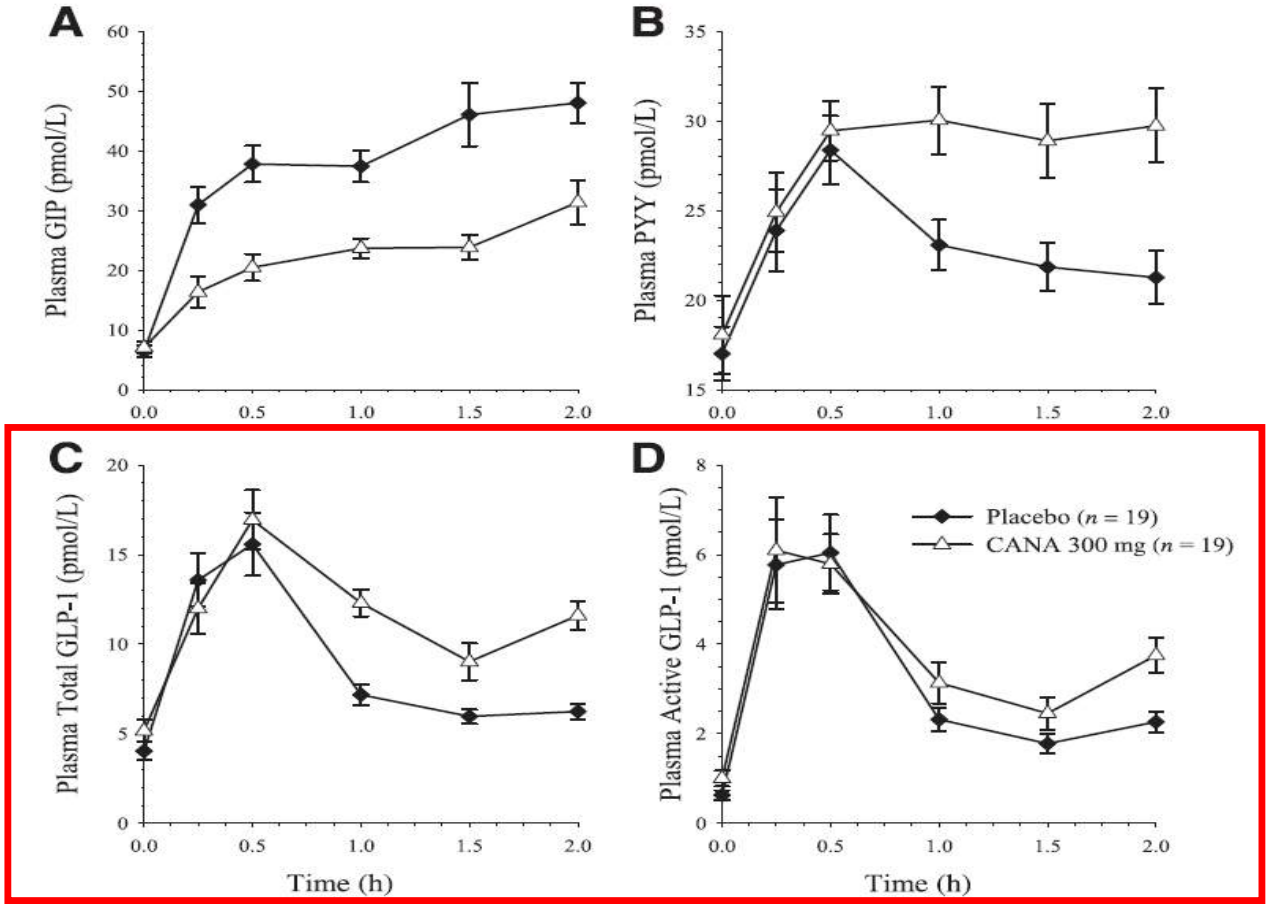
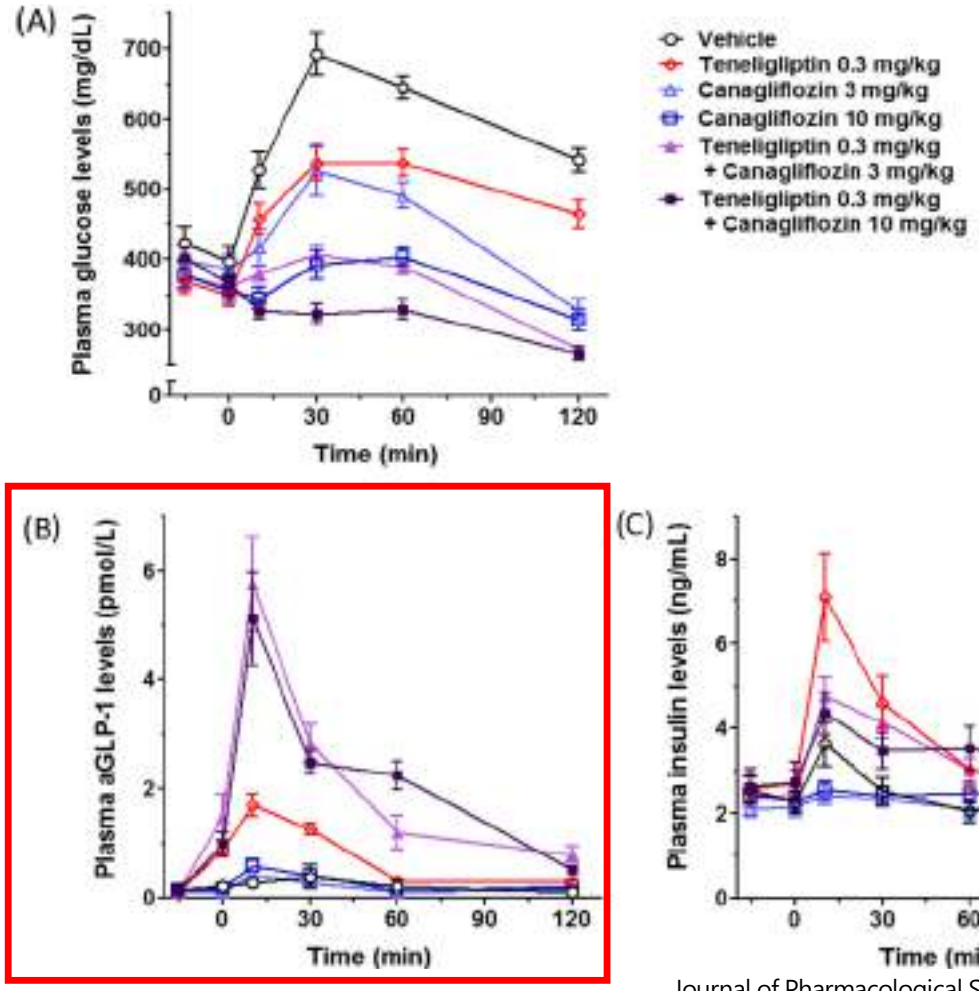


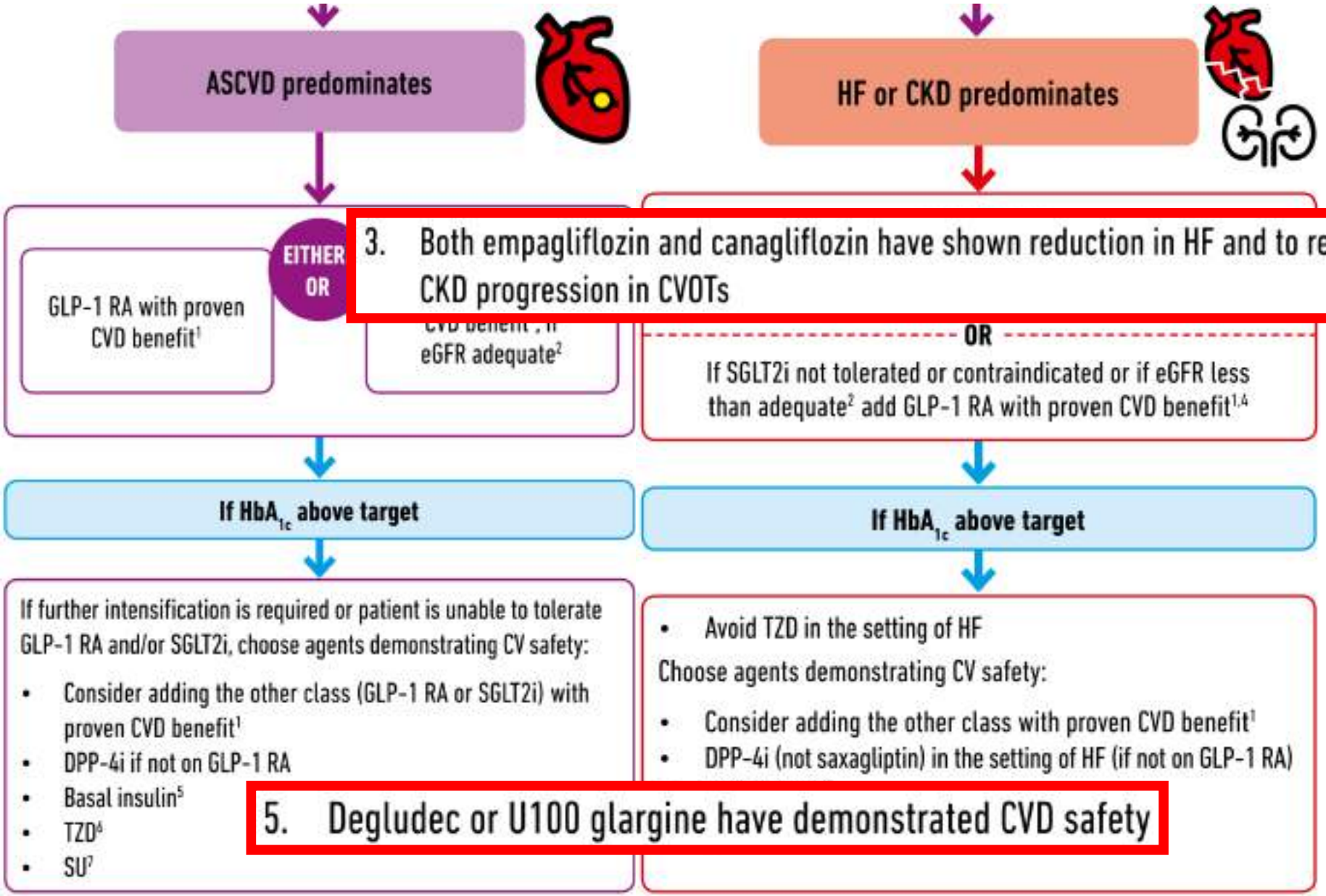
Figure 3—*Mean ± SEM plasma concentration-time profiles of GIP* (A), *PYY* (B), *total GLP-1* (C), *and active GLP-1* (D). *CANA, canagliflozin.*

Diabetes Care 36:2154–2161, 2013 (Ref. 17)

Effects of treatment with a combination of canagliflozin and teneligliptin during OGTT in ZDF rats



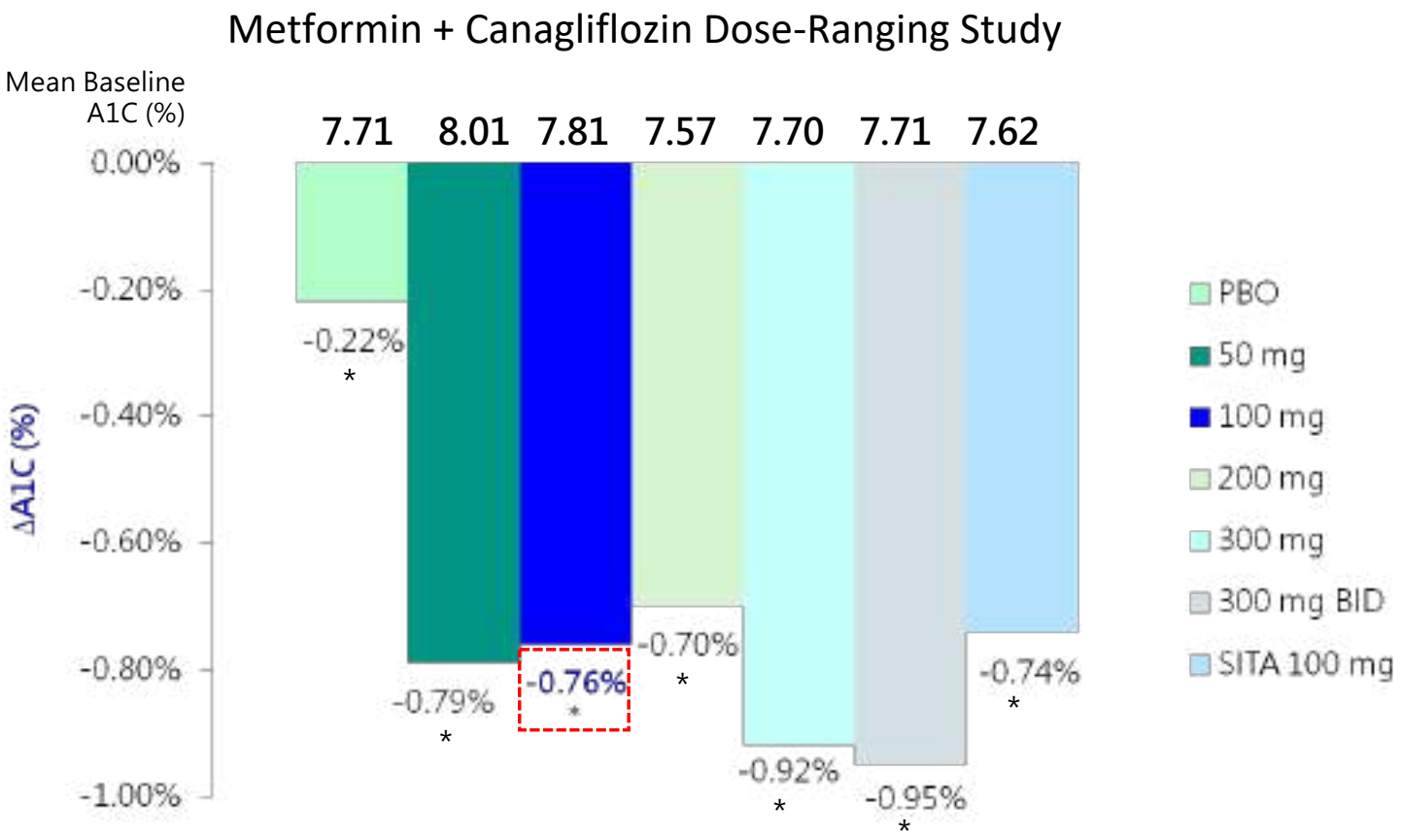
Journal of Pharmacological Sciences 127 (2015) 456-461 (Ref. 18)



3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs

5. Degludec or U100 glargine have demonstrated CVD safety

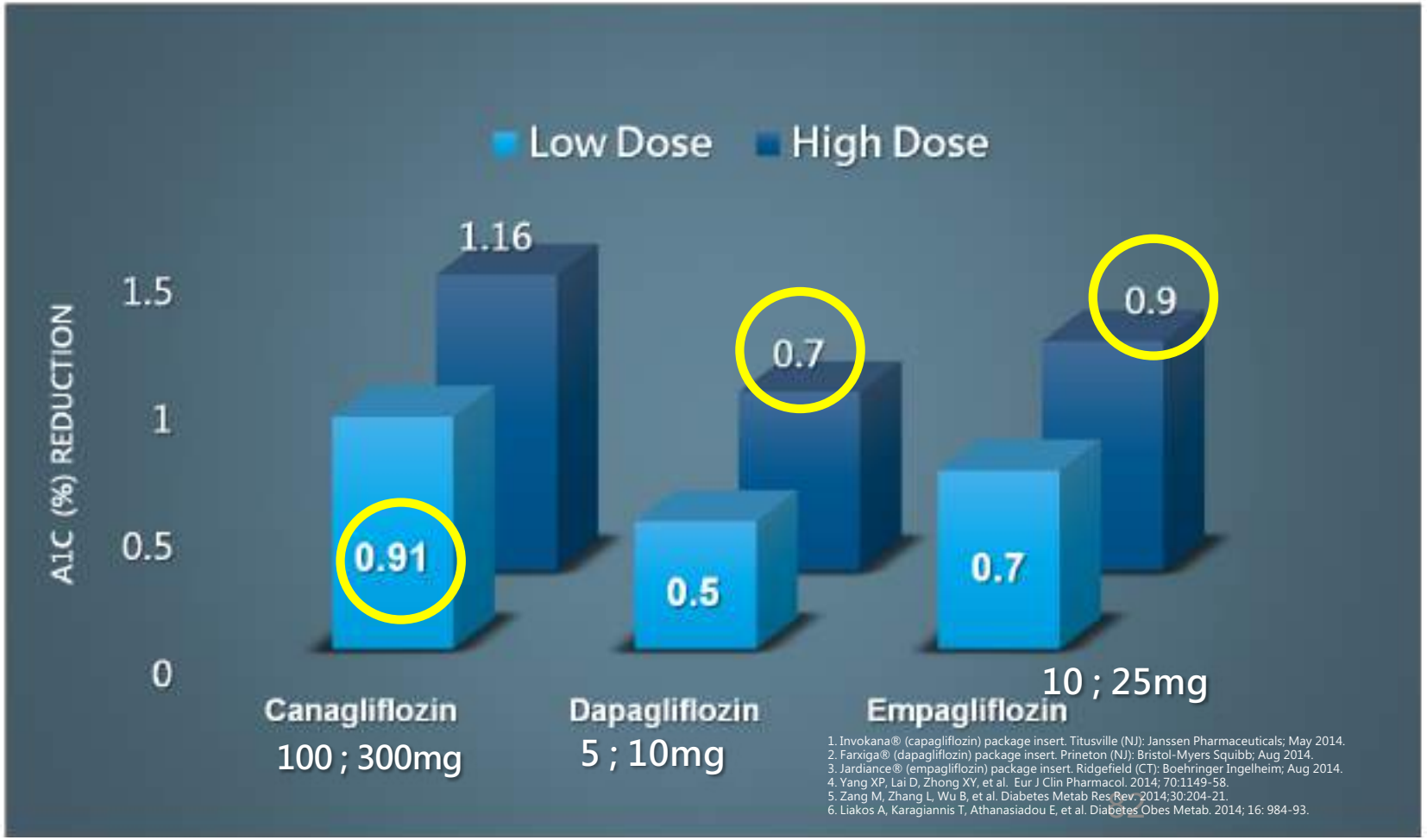
Efficacy of Canagliflozin



*P<.001 vs. placebo calculated using LS means

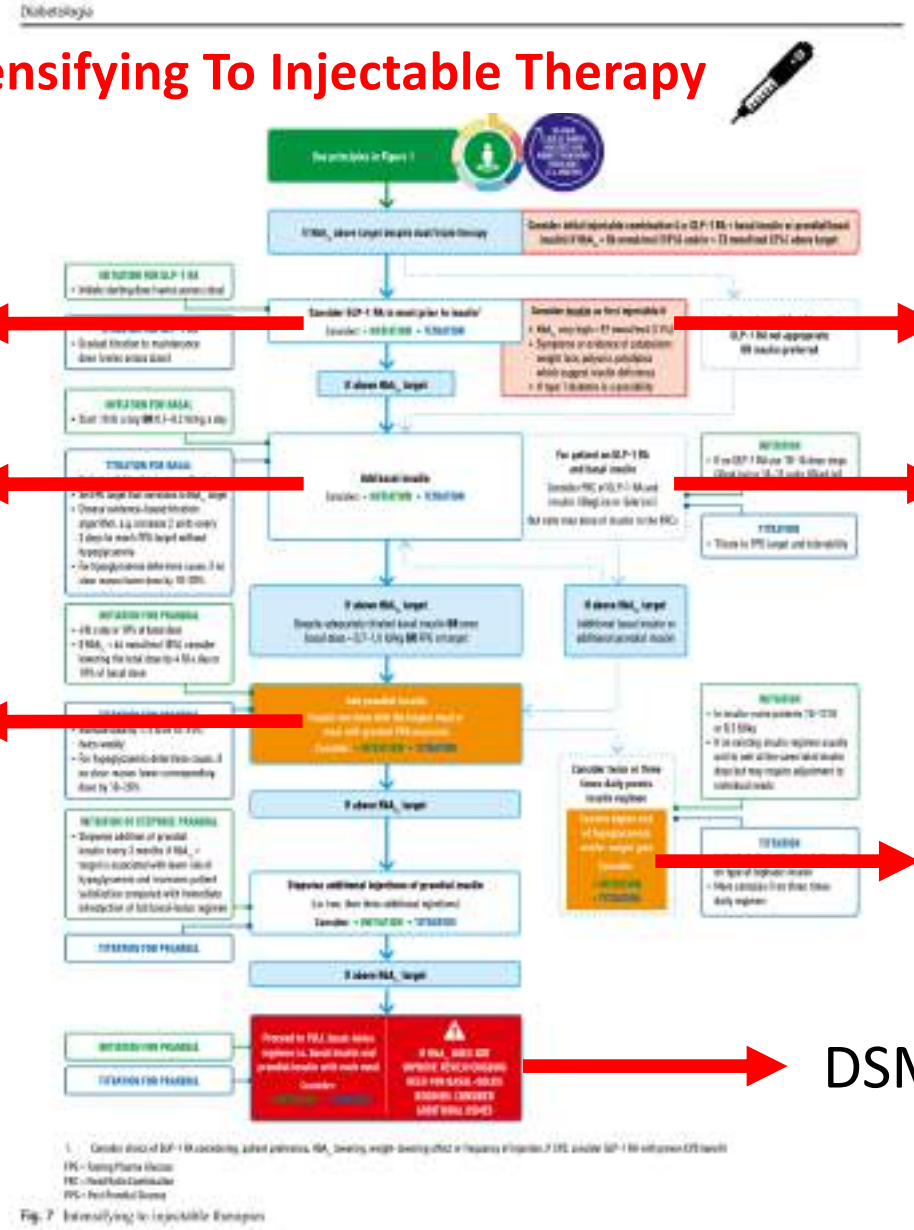
Diabetes Care 35:1232–1238, 2012 (Ref. 4)

Monotherapy : A1c Reductions



1. Invokana® (capagliflozin) package insert. Titusville (NJ): Janssen Pharmaceuticals; May 2014.
2. Farxiga® (dapagliflozin) package insert. Prineton (NJ): Bristol-Myers Squibb; Aug 2014.
3. Jardiance® (empagliflozin) package insert. Ridgefield (CT): Boehringer Ingelheim; Aug 2014.
4. Yang XP, Lai D, Zhong XY, et al. Eur J Clin Pharmacol. 2014; 70:1149-58.
5. Zang M, Zhang L, Wu B, et al. Diabetes Metab Res Rev. 2014;30:204-21.
6. Liakos A, Karagiannis T, Athanasiadou E, et al. Diabetes Obes Metab. 2014; 16: 984-93.

Intensifying To Injectable Therapy



GLP-1 receptor agonists

basal insulin

prandial insulin

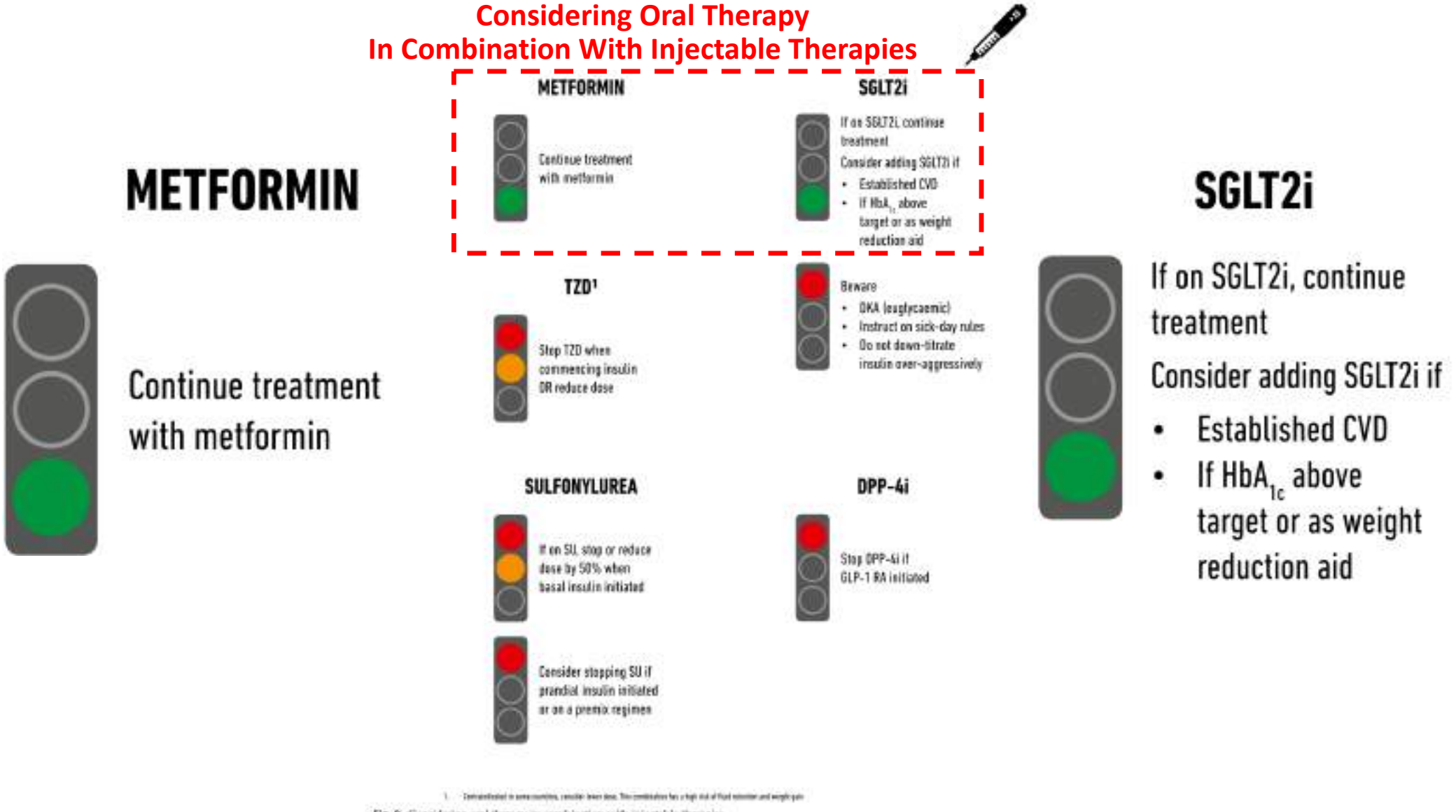
insulin

GLP-1 receptor agonists/basal insulin (fixed ratio combination)

premixed insulin

DSMES

Considering Oral Therapy In Combination With Injectable Therapies



1. Contraindicated in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain

Fig. 8 Considering oral therapy in combination with injectable therapies

Overall Summary

*The management of hyperglycaemia in type 2 diabetes has become complex with the number of glucose-lowering medications now available.
*Patient-centered decision-making and support and consistent efforts at improving diet and exercise remain the foundation of all glycaemic management.
*Initial use of metformin, follow by addition of glucose-lowering medications based on patient co-morbidities and concerns is recommended as we await answers to the many questions that remain.

Thank you