First line oral agents in the treatment of type 2 diabetes metformin vs. SGLT2-I

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APRIL 2021

OUTLINE

- Case scenario
- Where Does Metformin Stand in Modern Day Management of T2DM?
- Evidence for Metformin as first line monotherapy
- Evidence for SGLT2-I as first line monotherapy

First scenario

- A 46 – years- old overweight lady diagnosed with T2 DM since 6 months ago.
- Her BMI =27, she is otherwise healthy, advised for life style modification
- Her most recent HbA1c is 8%
- Lipid profile was normal, e-GFR= 85 ml/min
- Normotensive

What is the best next step treatment ?

Second scenario

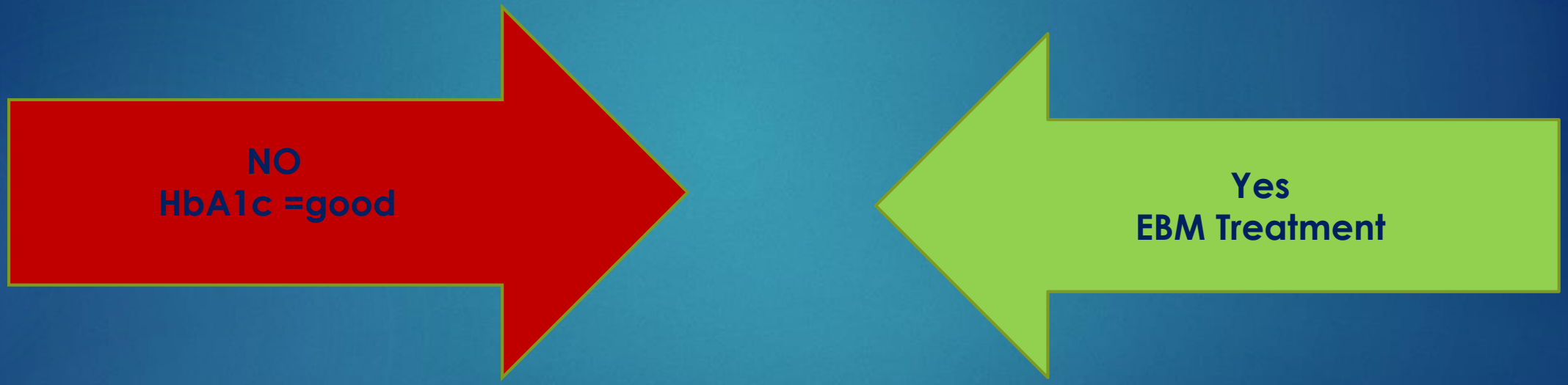
- 64 year old male
- DM2 since 2015
- Had ACS , Secondary PTCA in 2020

TX for diabetes

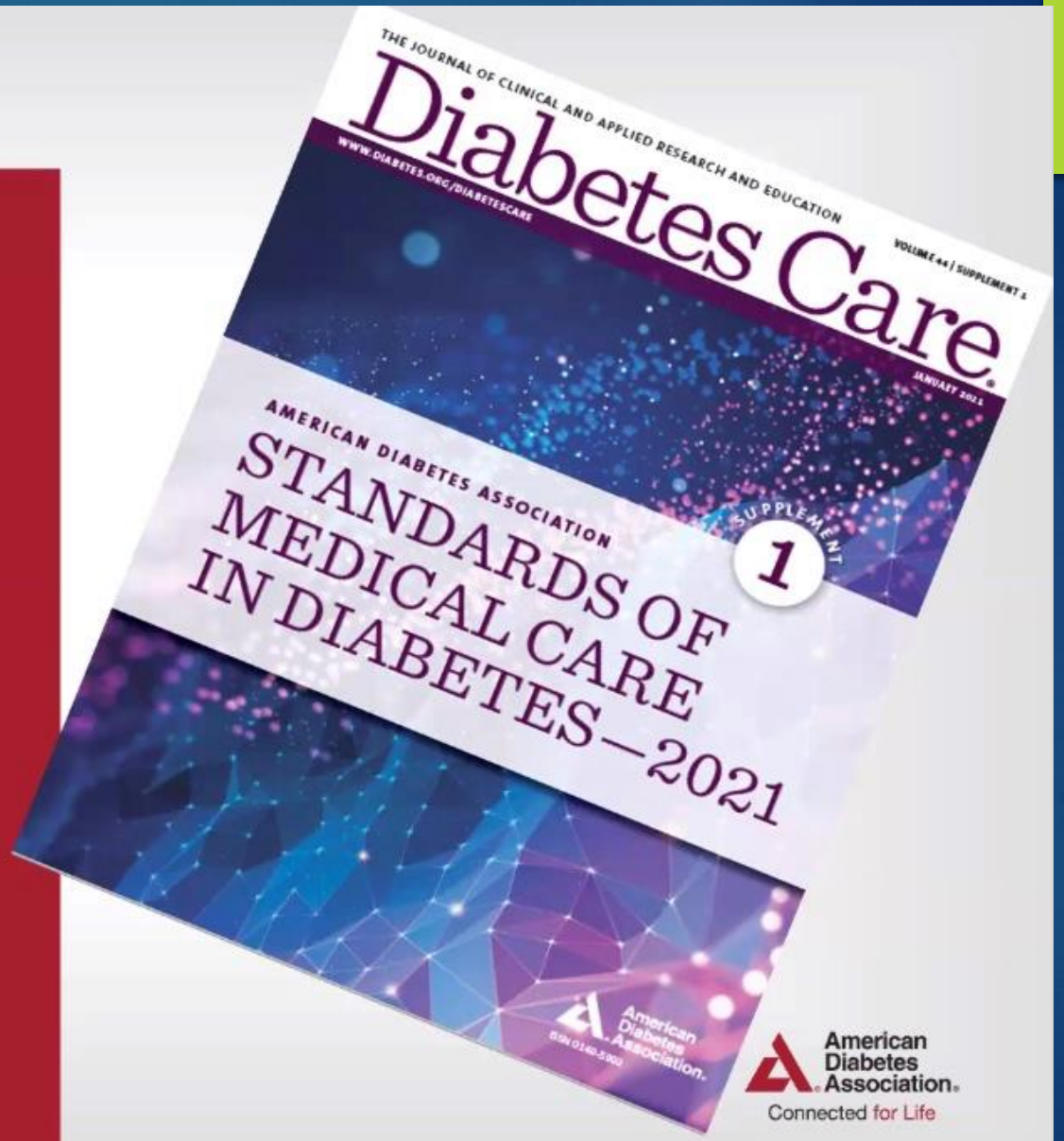
Metformin 1000 BD

HbA1c 6,9

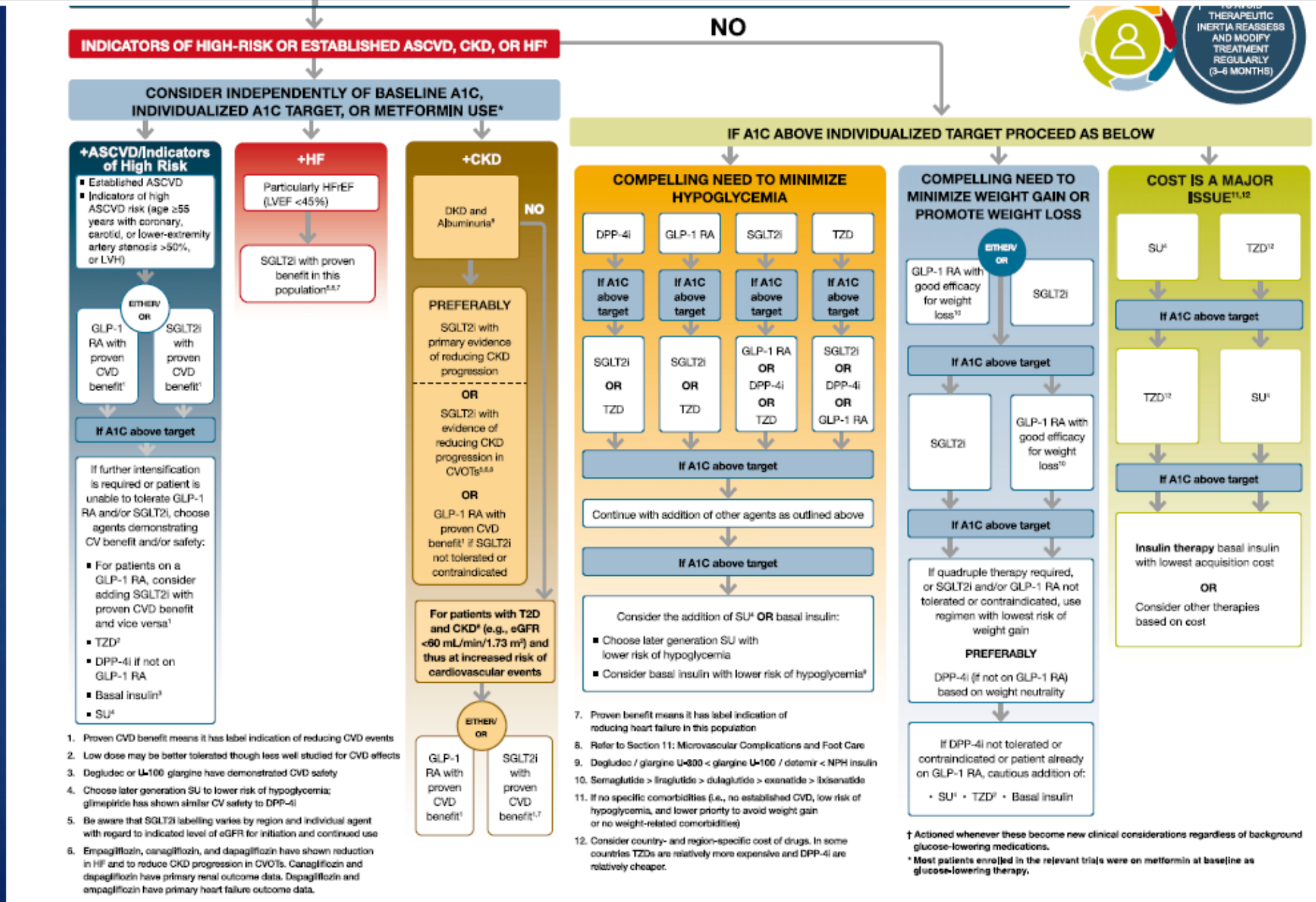
Should we modify the glucose lowering medication?



Standards of Medical Care in Diabetes—2021



FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)



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.

ADA 2021

Initial Therapy

1- Metformin should be started at the time T2DM is diagnosed unless there are contraindications; for many patients this will be monotherapy in combination with lifestyle modifications.

2- Additional and/or alternative agents may be considered in special circumstances, such as in individuals with established or increased risk of cardiovascular or renal complications

- Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death.

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

Initial Therapy

- Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and CV mortality

- There is little systematic data available for other oral agents as initial therapy of T2DM.

Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications As monotherapy or metformin based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751

Chemical structure of metformin

(a)

(b)

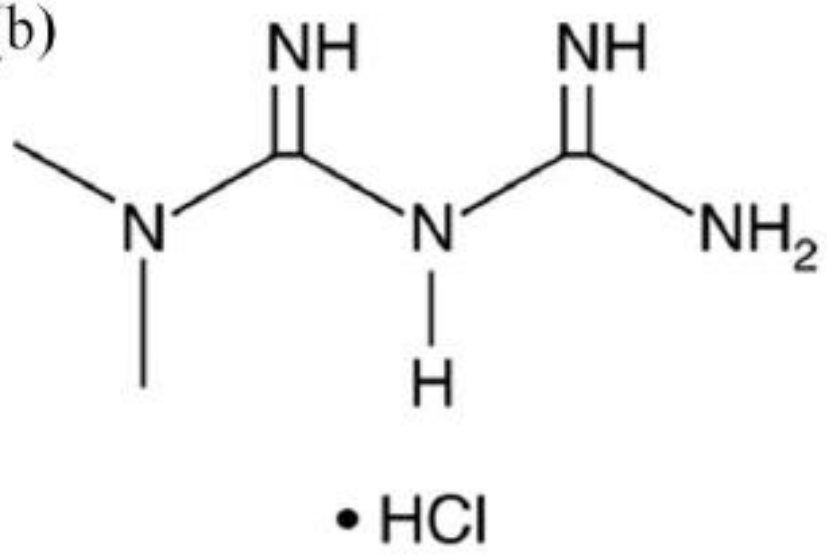
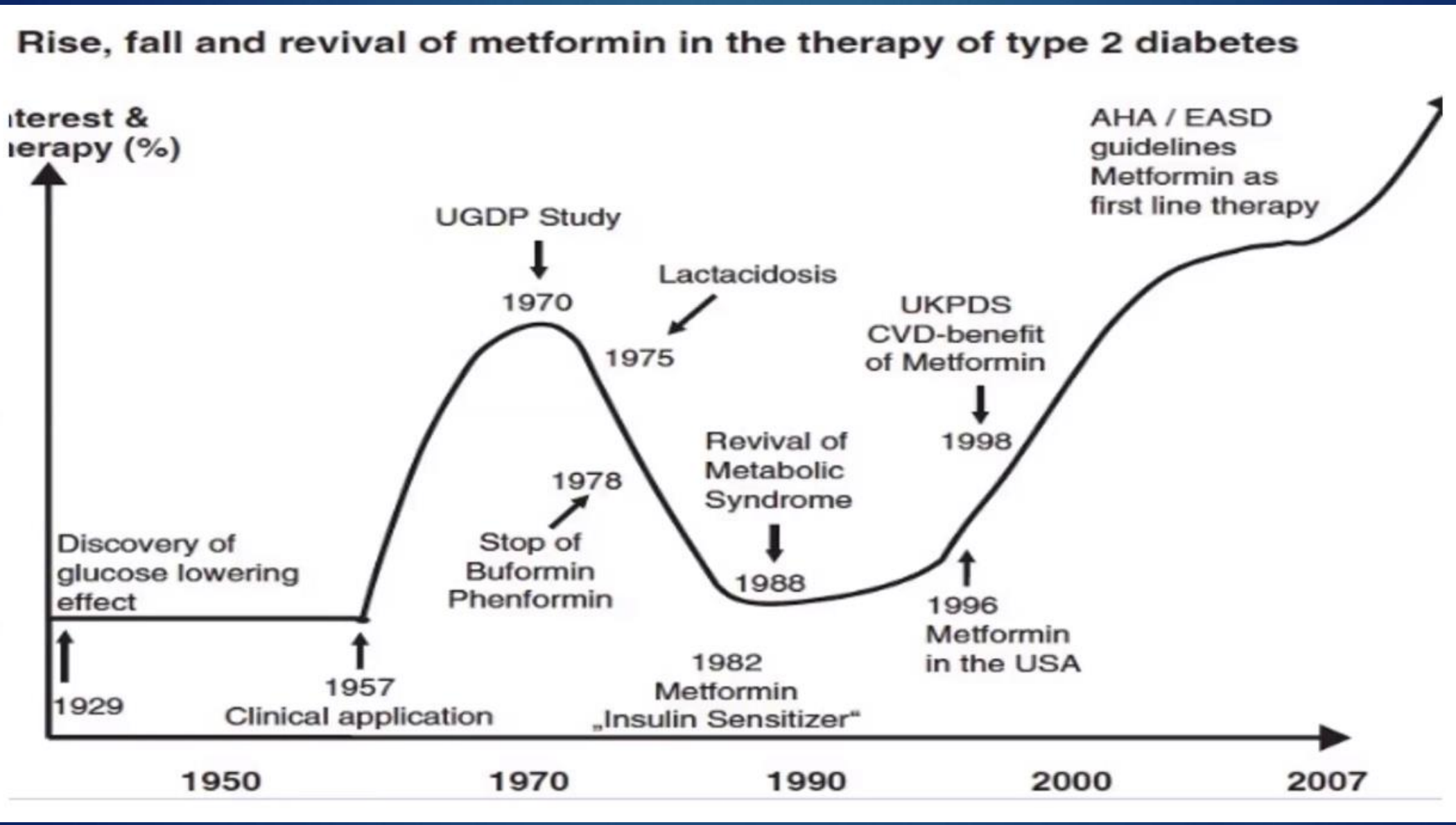
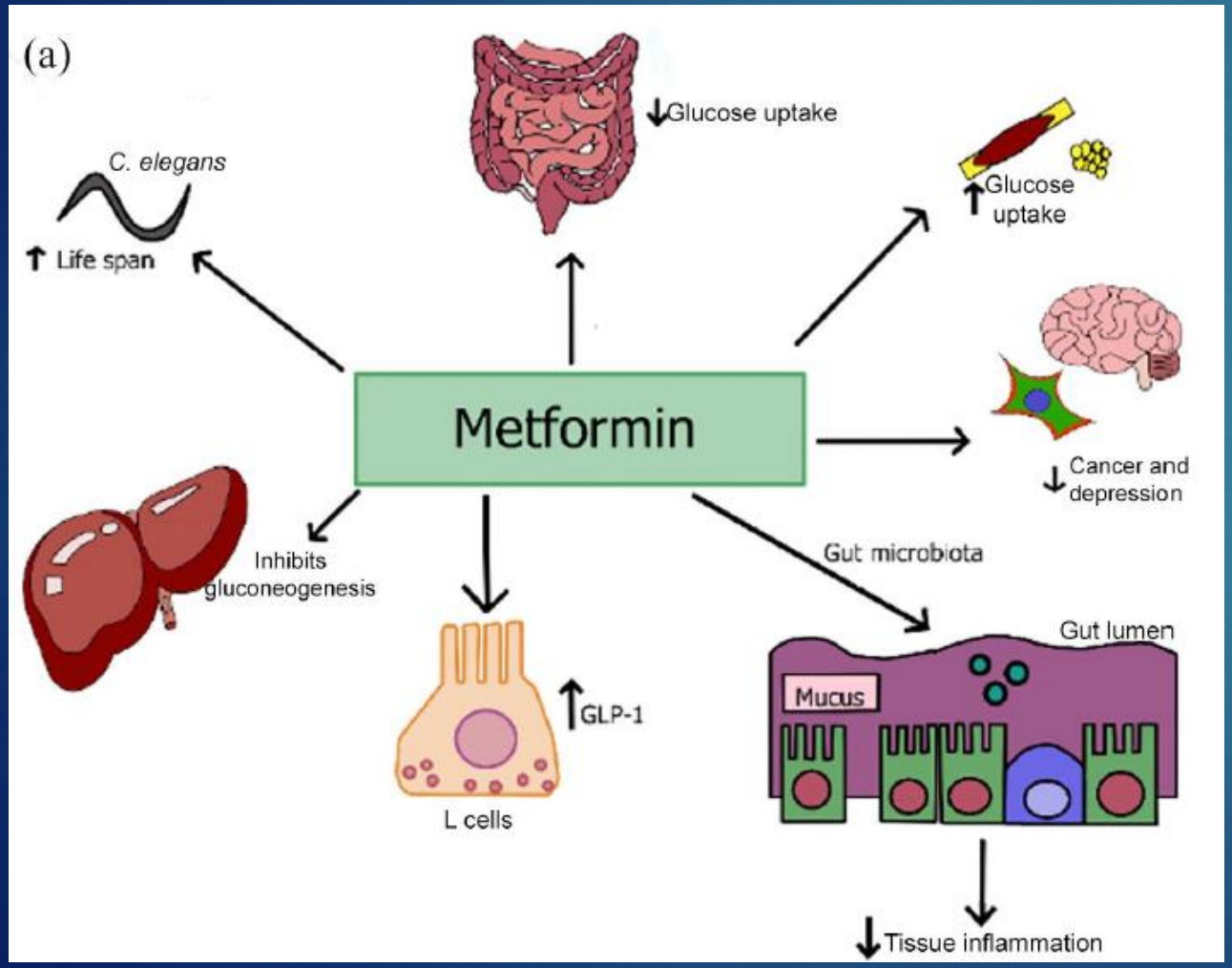


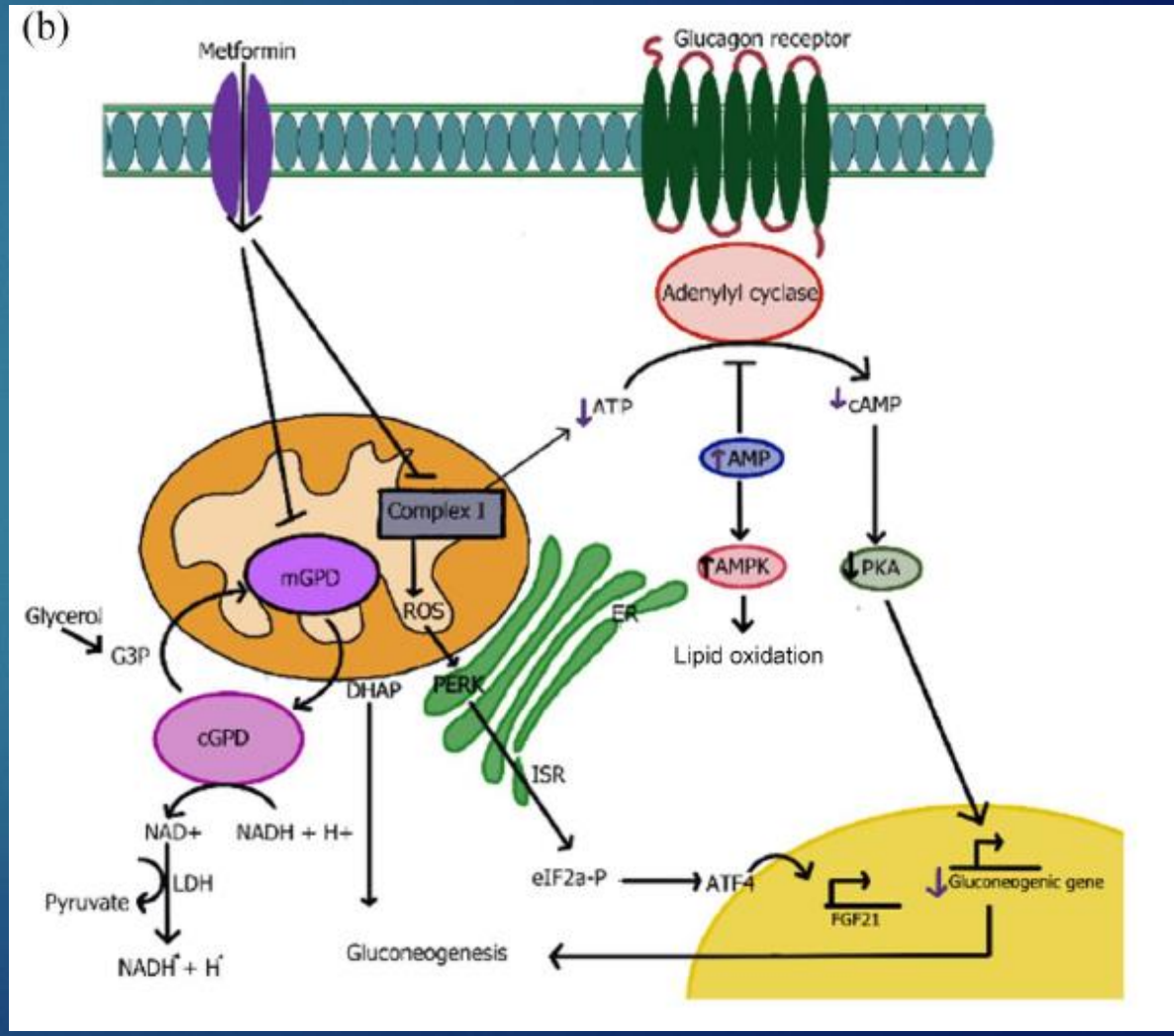
Figure 1. (A) *Galega officinalis*, commonly known as French lilac; it is rich in galegine, a substance with blood glucose-lowering activity and the foundation for the discovery of metformin. (B) The chemical structure of 1,1-dimethylbiguanide hydrochloride or metformin hydrochloride.

Almost ***60 years*** after first introduction for the treatment of T2D



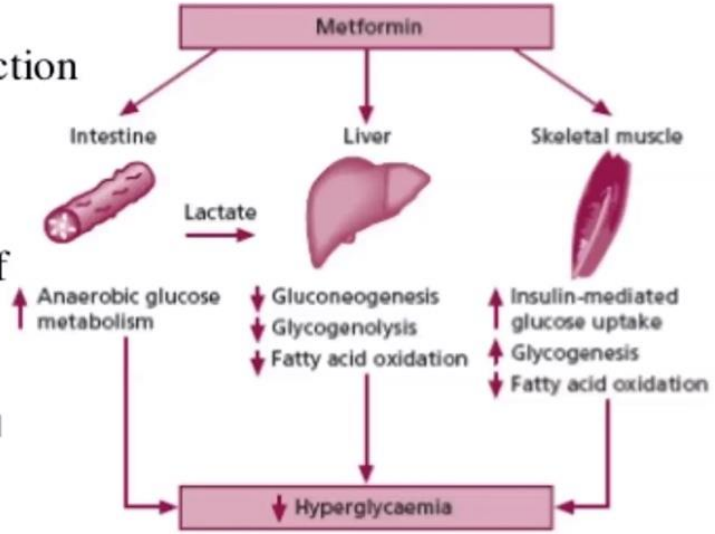
Metformin mechanism of action

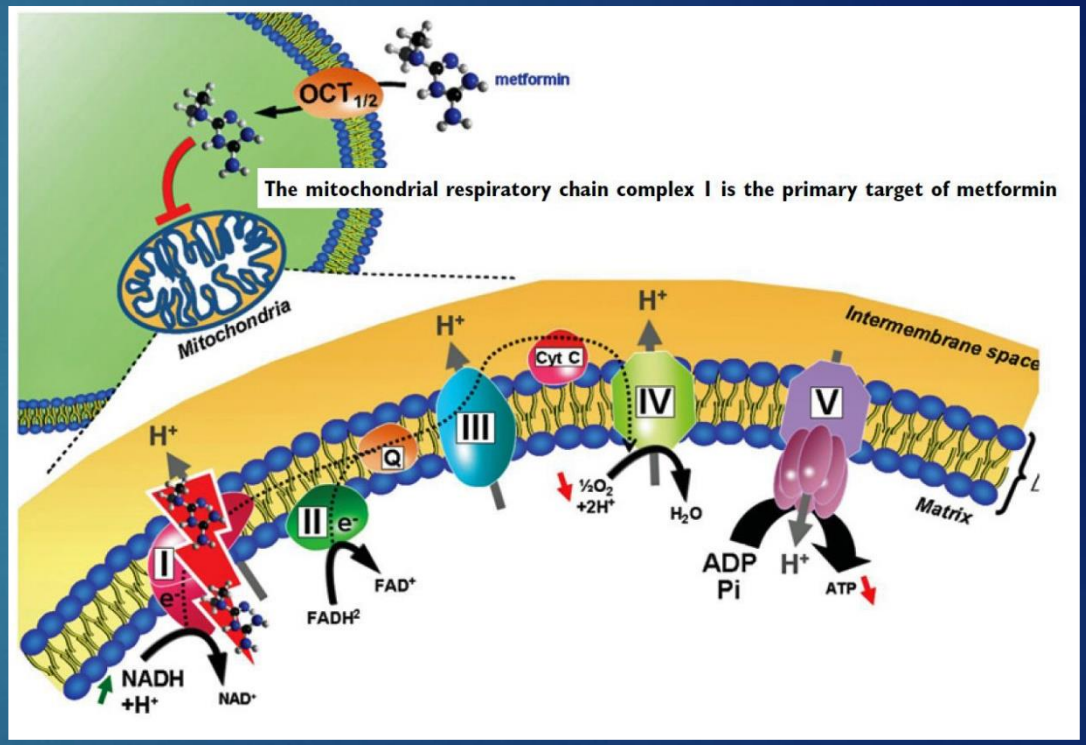




MECHANISM OF ACTION

- Decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex 1.[2]
- Decrease intestinal absorption of glucose
- anti-oxidative properties of metformin on endothelial cells[2]



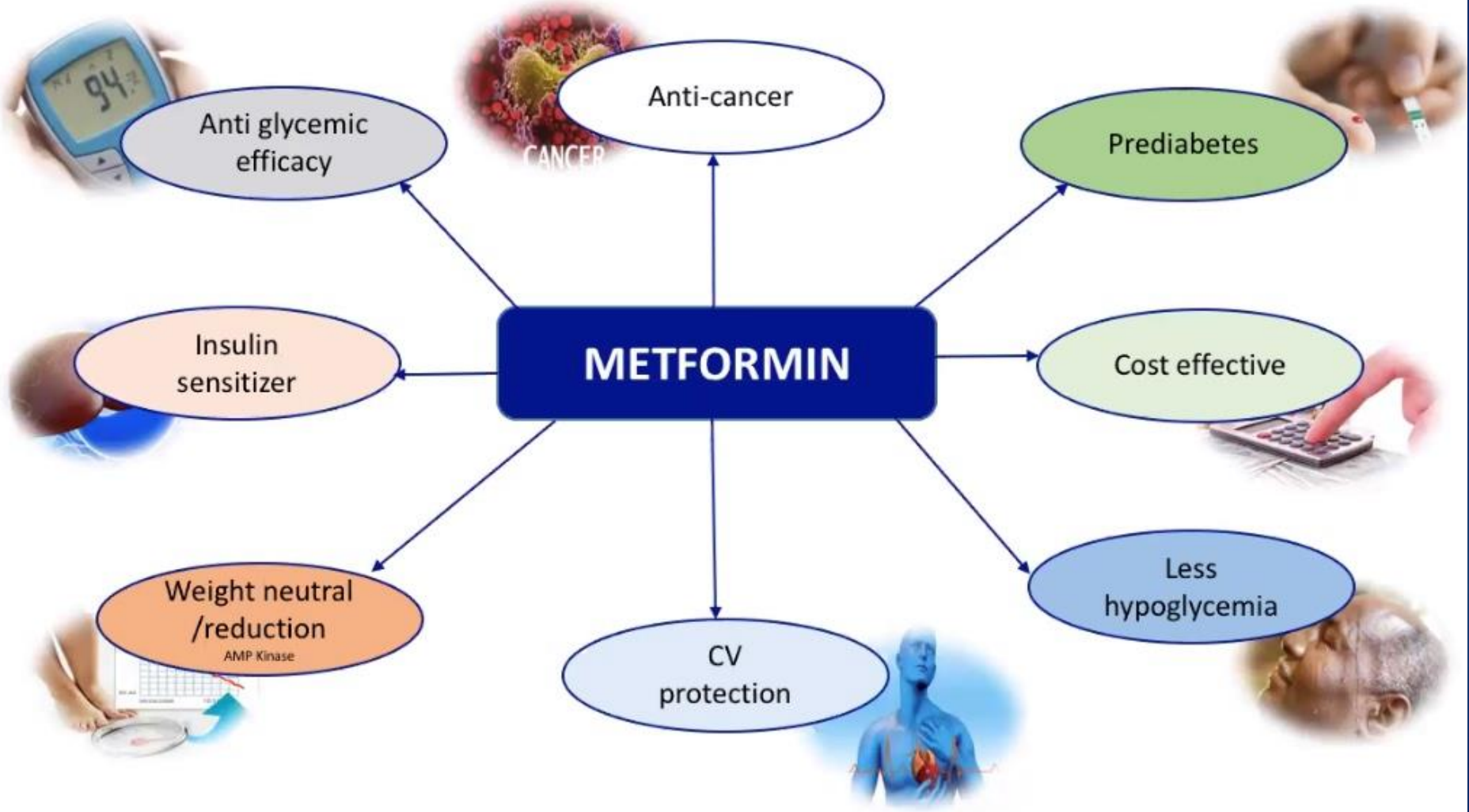


Metformin inhibits this complex

The consequence of *inhibition of the respiratory chain complex I by metformin* is a transient reduction in cellular energy status.

AMPK activation

Metformin clinical benefits



18.5.2 Oral hypoglycaemic agents	
☐ gliclazide*	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
metformin	**Tablet:** 500 mg (hydrochloride).
Complementary List	
metformin ***[c]***	***Tablet:*** *500 mg (hydrochloride).*
18.6 Medicines for hypoglycaemia	
glucagon	**Injection:** 1 mg/ mL.
Complementary List	
diazoxide ***[c]***	***Oral liquid:*** *50 mg/mL* ***Tablet:*** *50 mg*
18.7 Thyroid hormones and antithyroid medicines	
levothyroxine	**Tablet:** 25 micrograms **[c]**; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet:** 60 mg.
☐ methimazole*	**Tablet:** 5mg, 10mg, 20mg.

With the sulfonylurea gliclazide and insulin, metformin is part of the triad of antihyperglycemic agents on the 2019 WHO list of essential medications

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Check for updates

REVIEW ARTICLE

WILEY

Metformin and cardiorenal outcomes in diabetes: A reappraisal

John R. Petrie FRCP[1] | Peter R. Rossing MD[2,3] | Ian W. Campbell FRCP[4]

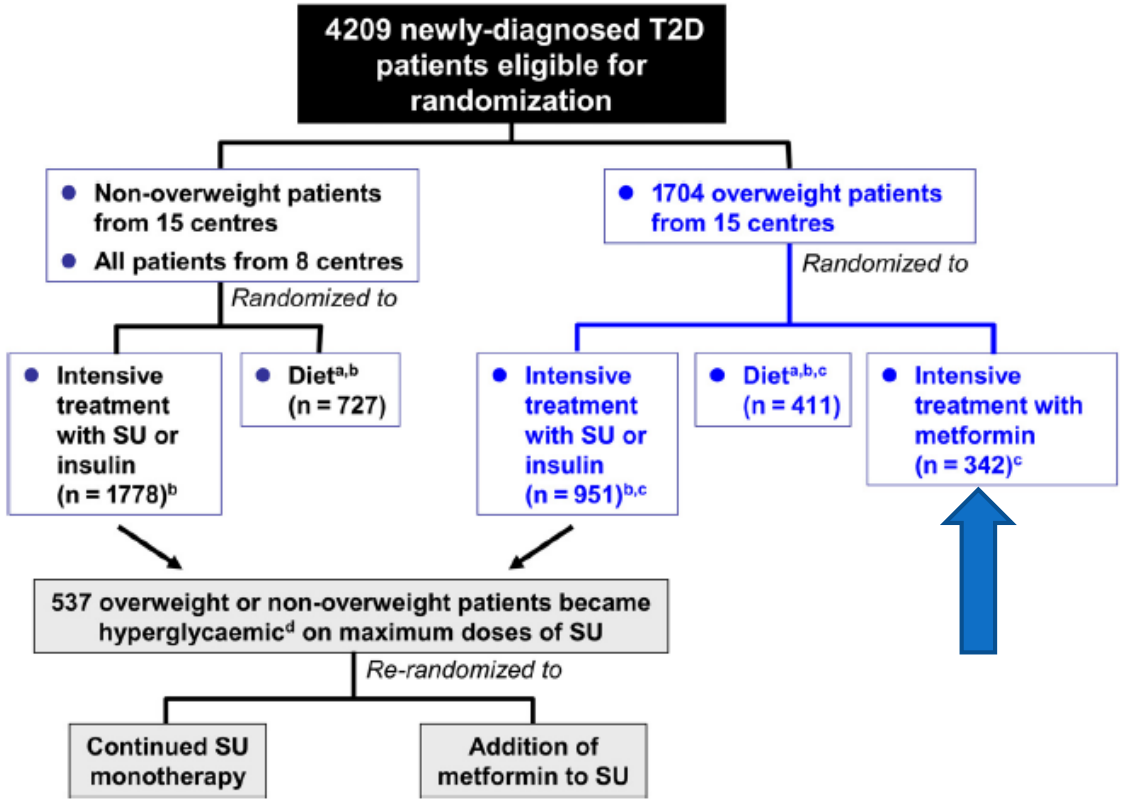
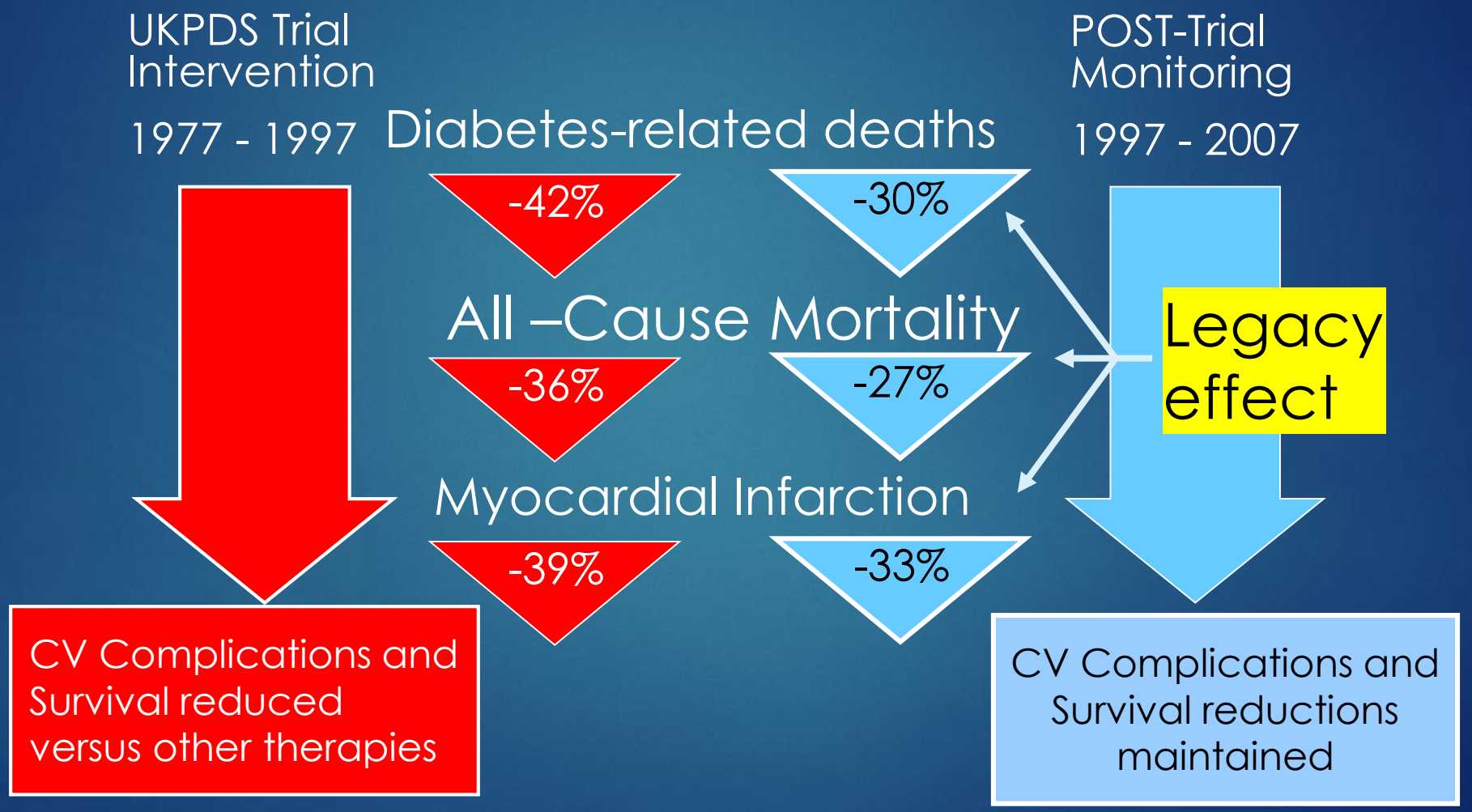


FIGURE 1 Summary of randomized allocation of patients to treatment in the UK Prospective diabetes study. SU, sulphonylurea; T2D, type 2 diabetes. [a]Conventional treatment policy in the UKPDS. [b]These patients were included in the main trial analysis (UKPDS 33). [c]UKPDS 34. [d]Defined as fasting plasma glucose 6.1–15 mmol/L (110–270 mg/dL) without symptoms of hyperglycaemia. Adapted from references[7,8] with permission from Elsevier

Metformin and the UKPDS, What Did It Tell Us?

- A sub-study of this large multicenter trial in newly diagnosed individuals with T2D showed that compared to SU and insulin, metformin was associated with a reduction in:
- Any diabetes-related endpoint including MI and HF ($p = 0.0034$)
- All-cause mortality ($p = 0.021$)
- Stroke ($p = 0.032$) over a mean duration of 10.7 years

Lessons from UKPDS: Legacy Effect of Metformin Therapy from diagnosis



UKPDS 34. Lancet 1998; 352: 854-65

UKPDS 80. NEJM 2008; 359: 1577-89

Randomized clinical trials involving metformin and CVD outcomes

Table 2—Randomized clinical trials involving metformin and CVD outcomes

Trial/year	Comparison	Study population	*N*	Main CVD outcome(s)	HR (95% CI)	*P*
UKPDS 34 (4) (1998)	Metformin vs. diet Metformin vs. SU/insulin	Overweight, newly diagnosed T2D patients	1,704	All-cause mortality Myocardial infarction	0.64 (0.45, 0.91) 0.61 (0.41, 0.89)	NR 0.010
HOME (6) (2009)	Metformin vs. placebo	T2D patients on insulin	390	Expanded MACE*	0.61 (0.40, 0.94)	0.02
SPREAD-DIMCAD (7) (2013)	Metformin vs. glipizide	T2D patients with CAD	304	Expanded MACE†	0.54 (0.30, 0.90)	0.026

CAD, coronary artery disease; MACE, major adverse cardiovascular events; NR, not reported; SU, sulfonylurea. *Myocardial infarction, acute coronary syndrome, coronary or peripheral revascularization, electrocardiogram changes, heart failure, stroke/transient ischemic attack. †Cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization.

Han et al. Cardiovasc Diabetol (2019) 18:96
https://doi.org/10.1186/s12933-019-0900-7

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis

Yechen Han[1,2], Hongzhi Xie[1,2], Yongtai Liu[1,2], Peng Gao[1,2], Xufei Yang[1,2] and Zhujun Shen[1,2*]

- A recent, very large meta-analysis included more than 1 million patients, who participated in 40 randomized or observational evaluations of metformin.

- Treatment with metformin versus no metformin therapy was associated with reduced risk of CV death (adjusted HR 0.81 [95% CI 0.79 to 0.84]).

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia.6–930:(5)49;2006

Cardiovascular mortality metformin Vs non metformin

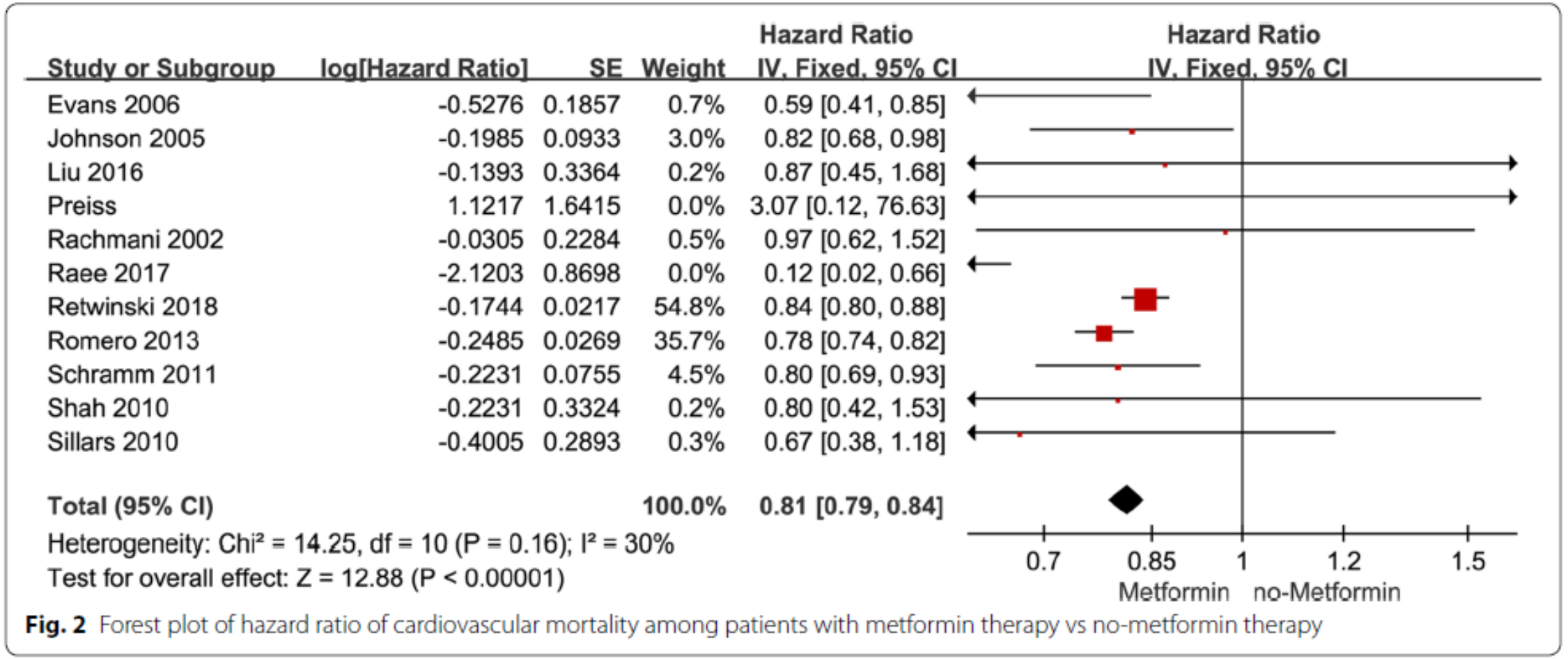
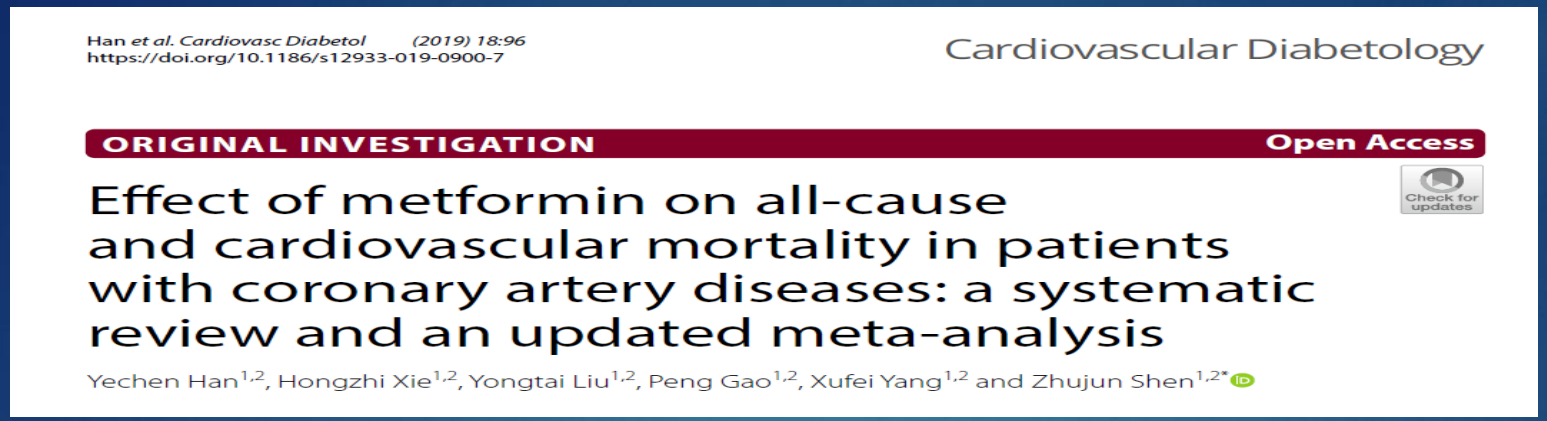


Fig. 2 Forest plot of hazard ratio of cardiovascular mortality among patients with metformin therapy vs no-metformin therapy



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- All-cause mortality was reduced in the overall population (adjusted HR 0.67 [95% CI 0.60 to 0.75])
- in those with prior MI (adjusted HR 0.79 [95% CI 0.68 to 0.92])
- in those with prior CHF (adjusted HR 0.84 [95% CI 0.81 to 0.87])

- The frequency of CV events was also reduced, although interestingly no significant effect was observed in the absence of type 2 diabetes.

DIABETES RESEARCH AND CLINICAL PRACTICE 160 (2020) 108001

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journal homepage: www.elsevier.com/locate/diabres

Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: Results from meta-analysis

Kui Zhang [a,1], *Wenxing Yang* [b,1], *Hao Dai* [a], *Zhenhua Deng* [a,*]

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701,843 patients of T2DM on metformin treatment

Following metformin treatment in patients with T2DM was associated with decreased cardiovascular risk, both with the mortality and incidence.

Heterogeneity among studies may potentially affect the final results.

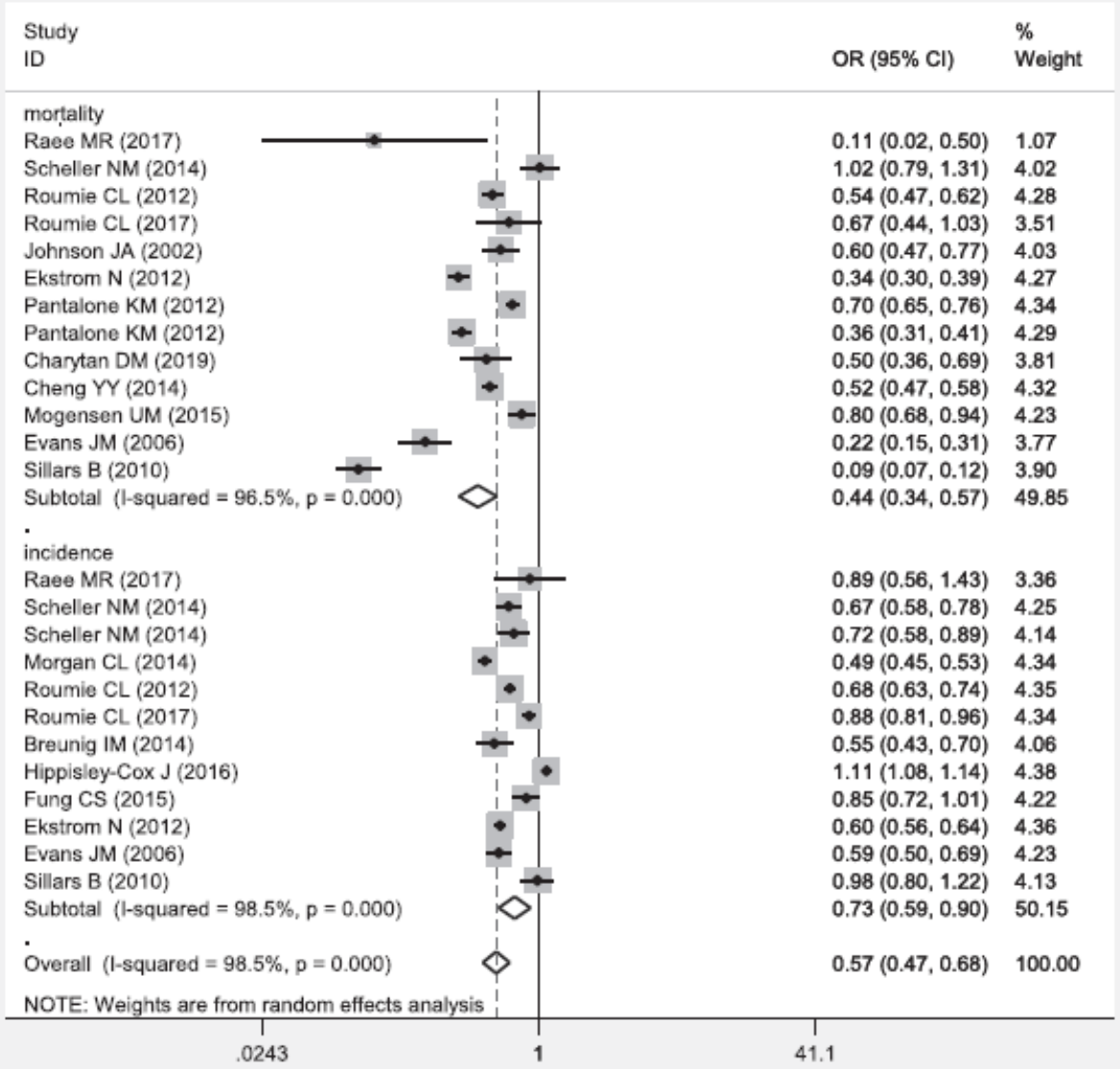

Fig. 2 – Forest plot of cardiovascular diseases risk following treatment with metformin in patients with T2DM.

Key Questions on the Current Role of Metformin

Should Metformin be the First-Line Treatment in T2D?

- In order to answer this question, let us first **define an ideal glucose-lowering agent.**

An ideal glucose-lowering agent

1. Safe
2. Effective
3. Durable
4. Suitable for use at all stages of diabetes
5. across a range of individuals with range of co-morbidities
6. Simple to administer with good adherence
7. Suitable for use in combination with other agents

Single agent, which fills most of these criteria above, is metformin

Safety and Tolerability in Elderly Population

- The age range for MACE outcome trials of GLP-1RA and SGLT2i have been around 60 to 65 years and does not include frail individuals who form a large cohort of T2D.

- For such individuals, metformin with convenient dosing schedule, low risk of hypoglycemia and good tolerability requiring little monitoring appears to be a safe and effective option .

Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care **2012**, 35, 731–737.

Is There is a Clear Evidence in Head-to-head Trials of a Benefit of Other Agents Over Metformin

Either in Cardiovascular Benefit or

Cost-Effectiveness?

SGLT2i and GLP-1RA

1- We do not have any direct head-to-head primary CVOTs comparing metformin against either SGLT2i or GLP-1RA

2- Cost will remain a consideration even if either SGLT2i or GLP-1RA were found to be superior.

3- There are significant intra-class differences in terms of the CV outcomes within both SGLT2i and GLP-1RA, and not all agents are equally potent or effective.

SU

- A multicenter randomized, double-blind, placebo controlled trial of metformin and glipizide on CV outcomes in T2D and CAD found that:

Treatment with metformin for 3 years substantially reduced MACE compared with glipizide (HR of 0.54, 95% CI 0.30, 0.90; p = 0.026).

Cardiovascular outcome trials of glucose-lowering therapies. Expert Rev. Pharm. Outcomes Res. **2020**, 20, 237–249

DDP4 Inhibitors

- In a longitudinal study of 123,050 individuals with T2D followed over several years

Adjusted HR for a composite of CVD events including hospitalizations for ischemic stroke, MI and HF, and hypoglycemia were all found to be statistically lower for metformin compared to DPP4 inhibitors as a class (0.87, 95% CI 0.79, 0.94)

Risks of cardiovascular diseases associated with dipeptidyl peptidase-4 inhibitors and other antidiabetic drugs in patients with type 2 diabetes: A nation-wide longitudinal study. Cardiovasc. Diabetol. **2016**, 15, 41.

DDP4 Inhibitors

- Even in major CVOTs of DPP4- I, baseline metformin use was associated with a trend towards improved CV outcomes (HR 0.92, 95% CI 0.84, 1.01) compared to baseline metformin nonusers (HR 1.10, 95% CI 0.97, 1.26)

- Baseline metformin status may have a moderating effect on CVOTs of DPP4 inhibitors.

Metformin Use May Moderate the Effect of DPP-4 Inhibitors on Cardiovascular Outcomes. Diabetes Care **2017**, 40, dc171528

COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

Does Metformin Interfere With the Cardiovascular Benefits of SGLT2 Inhibitors? Questions About Its Role as the Cornerstone of Diabetes Treatment

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[b]*Imperial College, London, UK*

https://doi.org/10.1016/j.amjmed.2020.01.016

Dose metformin interfere with CV benefits of SGLT2-I

1- In one large-scale trial, empagliflozin reduced the risk of CV death by:

- 54% in metformin nonusers
- 29% in metformin users (interaction P = 0.07)

2- The interaction between metformin and Canagliflozin was even more striking in which risk of cardiovascular death or hospitalization for heart failure reduced by

- 36% in patients not receiving metformin
- 12% in those receiving metformin (interaction P = 0.03)

3- Information regarding the interaction between metformin and dapagliflozin has not yet been presented.

Dose metformin interfere with CV benefits of SGLT2-I

- Therefore, the findings with empagliflozin and Canagliflozin represent all available evidence concerning the influence of metformin pretreatment on the heart failure benefits of SGLT2 inhibitors.

- If metformin does exert an effect to attenuate the effects of SGLT2 inhibitors, it may be time to reconsider the wisdom of using metformin as a first-line treatment for patients with type 2 diabetes

Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy?

Silvio E. Inzucchi MD[1] | David Fitchett MD[2] | Dubravka Jurišić-Eržen MD[3] | Vincent Woo MD[4] | Stefan Hantel PhD[5] | Christina Janista PhD[5] | Stefan Kaspers MD[5] | Jyothis T. George MBBS, PhD, FRCP[5] | Bernard Zinman MD[6] on behalf of the EMPA-REG OUTCOME® Investigators

Results: Of 7020 eligible patients, 74% were receiving metformin, 43% SU and 48% insulin at baseline (each alone or in combination); the most common regimens were metformin plus SU (20%) and metformin plus insulin (20%). Empagliflozin reduced the risk of CV death irrespective of the use of: metformin [with: hazard ratio (HR) 0.71 (95% confidence interval, CI, 0.54–0.94); without: 0.46 (0.32–0.68); $P_{interaction}$ = 0.07]; SU [with: HR 0.64 (0.44–0.92); without: 0.61 (0.46–0.81); $P_{interaction}$ = 0.85]; or insulin [with: HR 0.63 (0.46–0.85); without: 0.61 (0.44–0.85); $P_{interaction}$ = 0.92]. Reductions in three-point major adverse CV events, hospitalizations for heart failure, and all-cause mortality were consistent across subgroups of baseline therapies. Empagliflozin reduced the risks of incident or worsening nephropathy versus placebo irrespective of the use of SU or insulin at baseline ($P_{interaction}$ > 0.05), but there was a greater reduction in this risk for patients not using metformin [HR 0.47 (95% CI 0.37–0.59)] versus those using metformin [HR 0.68 (95% CI 0.58–0.79)] at baseline ($P_{interaction}$ = 0.01).

Conclusions: The addition of empagliflozin to antihyperglycaemic regimens of patients with type 2 diabetes and CV disease consistently reduced their risks of adverse CV outcomes and mortality irrespective of baseline use of metformin, SU or insulin. For chronic kidney disease progression, there may be a larger benefit from empagliflozin in those patients who are not using metformin.

FIGURE 1 Cardiovascular outcomes, all-cause mortality, and incident or worsening nephropathy in patients by use of metformin, sulphonylurea or insulin at baseline. Cox regression analysis in patients treated with ≥1 dose of study drug

(A)

	Empagliflozin *n* with events/*N* (%)	Placebo *n* with events/*N* (%)	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
CV death					
All patients	172/4,687 (3.7)	137/2,333 (5.9)		0.62 (0.49, 0.77)	
Metformin at baseline					
Yes	118/3,459 (3.4)	84/1,734 (4.8)	11.5 vs 16.4	0.71 (0.54, 0.94)	*P*=0.07
No	54/1,228 (4.4)	53/599 (8.8)	15.2 vs 31.5	0.46 (0.32, 0.68)	
SU at baseline					
Yes	67/2,014 (3.3)	51/992 (5.1)	11.1 vs 17.4	0.64 (0.44, 0.92)	*P*=0.85
No	105/2,673 (3.9)	86/1,341 (6.4)	13.4 vs 22.2	0.61 (0.46, 0.81)	
Insulin at baseline					
Yes	93/2,252 (4.1)	74/1,135 (6.5)	14.2 vs 22.8	0.63 (0.46, 0.85)	*P*=0.92
No	79/2,435 (3.2)	63/1,198 (5.3)	10.8 vs 17.7	0.61 (0.44, 0.85)	

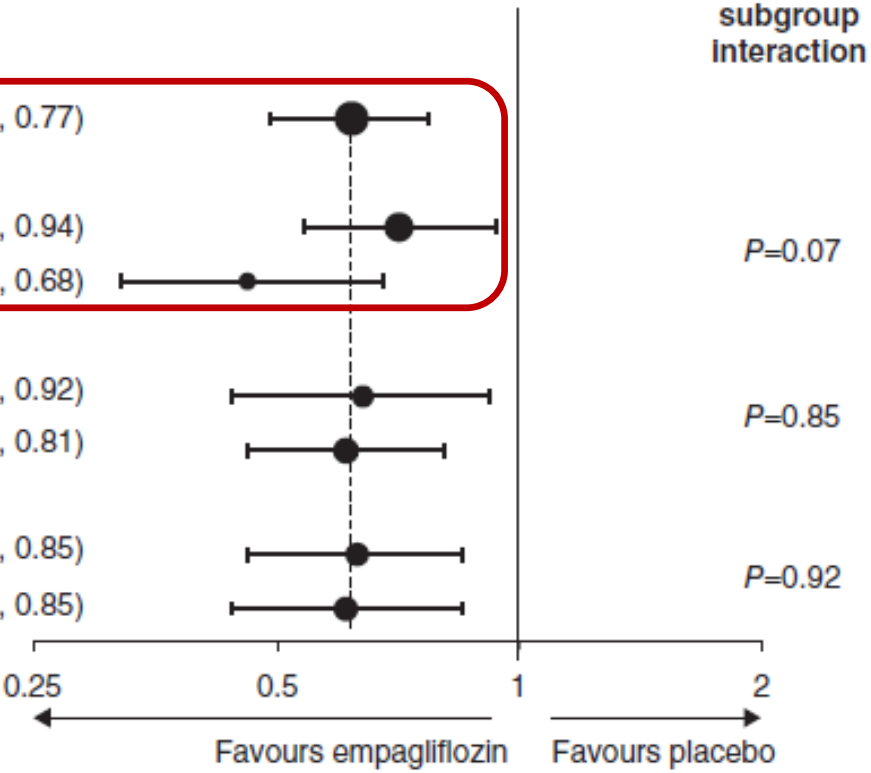


FIGURE 1 Cardiovascular outcomes, all-cause mortality, and incident or worsening nephropathy in patients by use of metformin, sulphonylurea or insulin at baseline. Cox regression analysis in patients treated with ≥1 dose of study drug

(B)

	Empagliflozin *n* with events/*N* (%)	Placebo *n* with events/*N* (%)	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
Hospitalization for heart failure					
All patients	126/4,687 (2.7)	95/2,333 (4.1)		0.65 (0.5, 0.85)	
Metformin at baseline					
Yes	79/3,459 (2.3)	59/1,734 (3.4)	7.9 vs 11.9	0.68 (0.49. 0.95)	*P*=0.61
No	47/1,228 (3.8)	36/599 (6.0)	13.6 vs 22.6	0.59 (0.38, 0.91)	
SU at baseline					
Yes	40/2,014 (2.0)	30/992 (3.0)	6.8 vs 10.5	0.65 (0.40, 1.04)	*P*=0.95
No	86/2,673 (3.2)	65/1,341 (4.8)	11.4 vs 17.5	0.66 (0.48, 0.91)	
Insulin at baseline					
Yes	84/2,252 (3.7)	61/1,135 (5.4)	13.2 vs 19.6	0.68 (0.49, 0.94)	*P*=0.72
No	42/2,435 (1.7)	34/1,198 (2.8)	5.9 vs 9.8	0.61 (0.39, 0.96)	

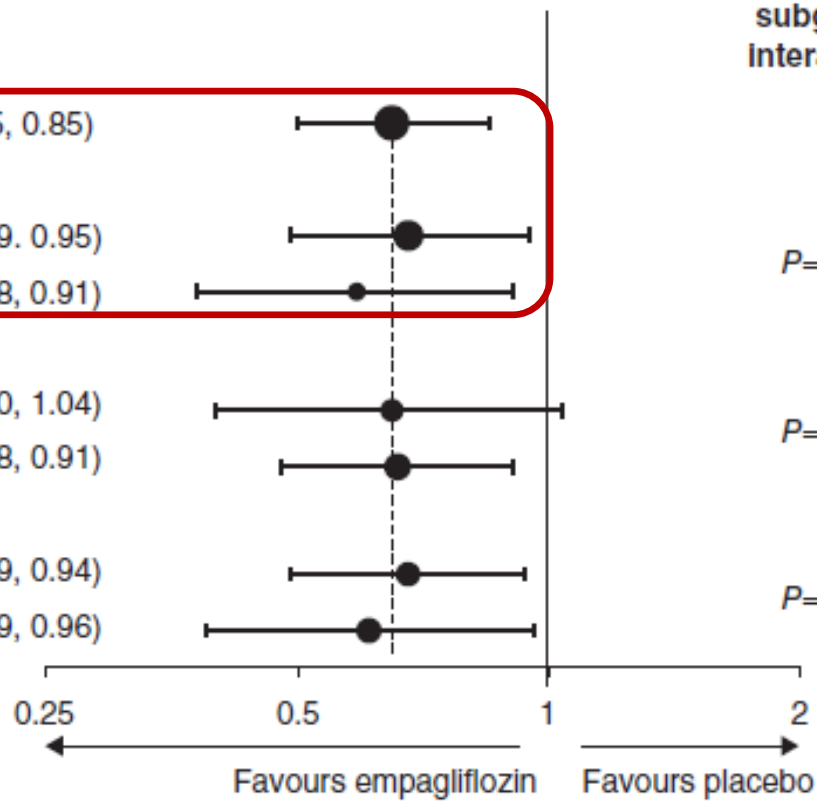
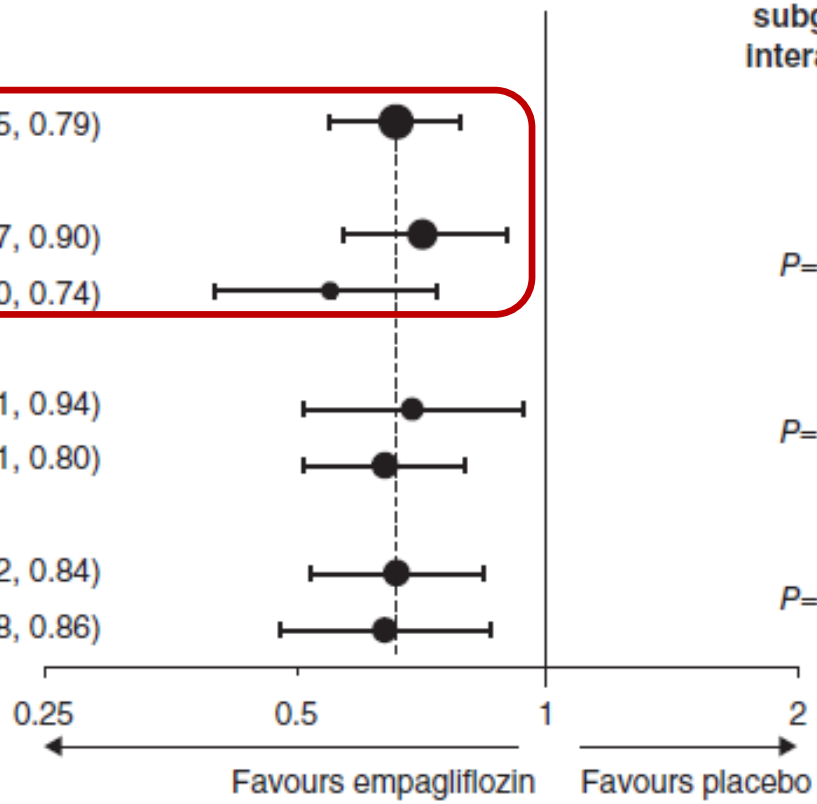


FIGURE 1 Cardiovascular outcomes, all-cause mortality, and incident or worsening nephropathy in patients by use of metformin, sulphonylurea or insulin at baseline. Cox regression analysis in patients treated with ≥1 dose of study drug

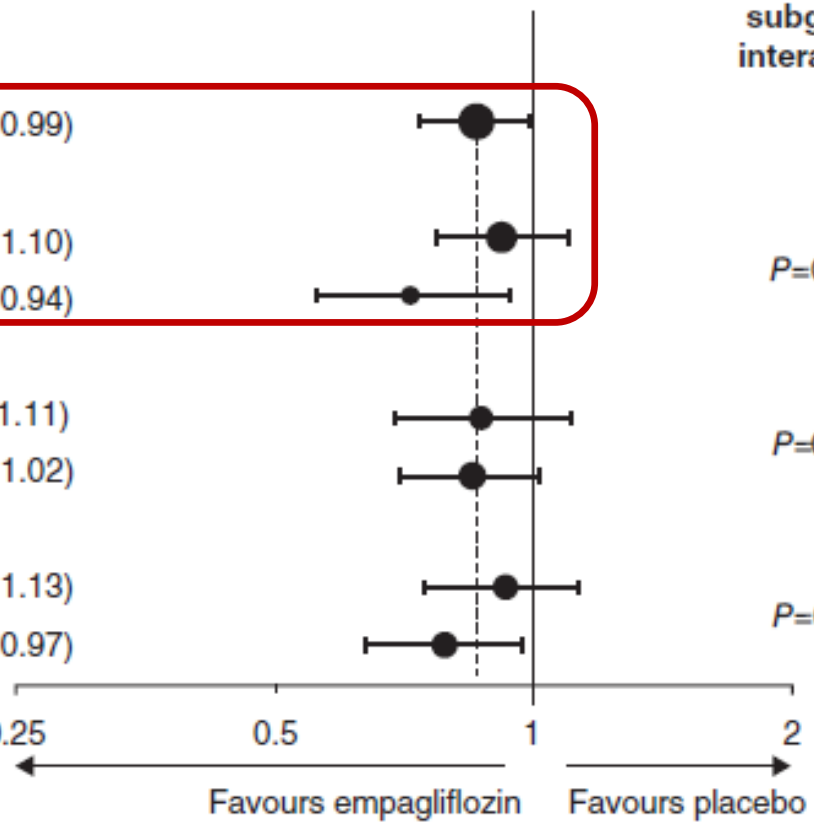
(C)

	Empagliflozin *n* with events/*N* (%)	Placebo *n* with events/*N* (%)	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
Heart failure hospitalization or CV death					
All patients	265/4,687 (5.7)	198/2,333 (8.5)		0.66 (0.55, 0.79)	
Metformin at baseline					
Yes	173/3,459 (5.0)	123/1,734 (7.1)	17.3 vs 24.7	0.71 (0.57, 0.90)	*P*=0.18
No	92/1,228 (7.5)	75/599 (12.5)	26.6 vs 47.2	0.55 (0.40, 0.74)	
SU at baseline					
Yes	96/2,014 (4.8)	67/992 (6.8)	16.3 vs 23.5	0.69 (0.51, 0.94)	*P*=0.69
No	169/2,673 (6.3)	131/1,341 (9.8)	22.4 vs 35.3	0.64 (0.51, 0.80)	
Insulin at baseline					
Yes	160/2,252 (7.1)	118/1,135 (10.4)	25.2 vs 38.0	0.66 (0.52, 0.84)	*P*=0.87
No	105/2,435 (4.3)	80/1,198 (6.7)	14.8 vs 23.1	0.64 (0.48, 0.86)	



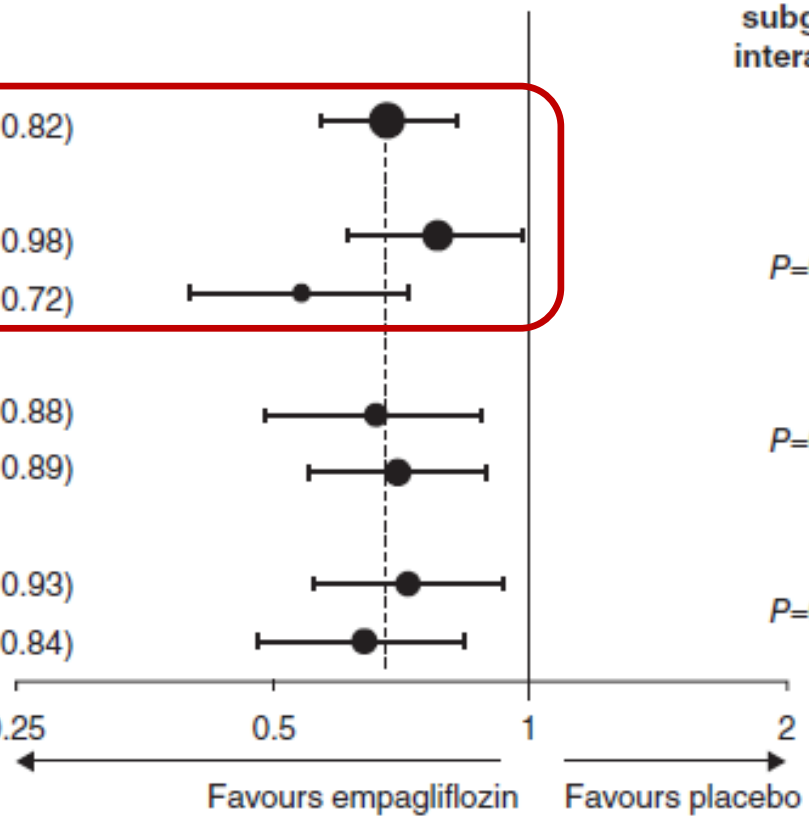
(D)

	Empagliflozin *n* with events/*N* (%)	Placebo *n* with events/*N* (%)	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
3-point MACE					
All patients	490/4,687 (10.5)	282/2,333 (12.1)		0.86 (0.74, 0.99)	
Metformin at baseline					
Yes	344/3,459 (9.9)	189/1,734 (10.9)	43.3 vs 59.3	0.92 (0.77, 1.10)	*P*=0.14
No	146/1,228 (11.9)	93/599 (15.5)	35.3 vs 38.9	0.72 (0.56, 0.94)	
SU at baseline					
Yes	195/2,014 (9.7)	109/992 (11.0)	34.1 vs 39.1	0.87 (0.69, 1.11)	*P*=0.83
No	295/2,673 (11.0)	173/1,341 (12.9)	40.0 vs 47.5	0.85 (0.70, 1.02)	
Insulin at baseline					
Yes	265/2,252 (11.8)	142/1,135 (12.5)	42.8 vs 46.3	0.93 (0.75, 1.13)	*P*=0.28
No	225/2,435 (9.2)	140/1,198 (11.7)	32.6 vs 41.6	0.79 (0.64, 0.97)	



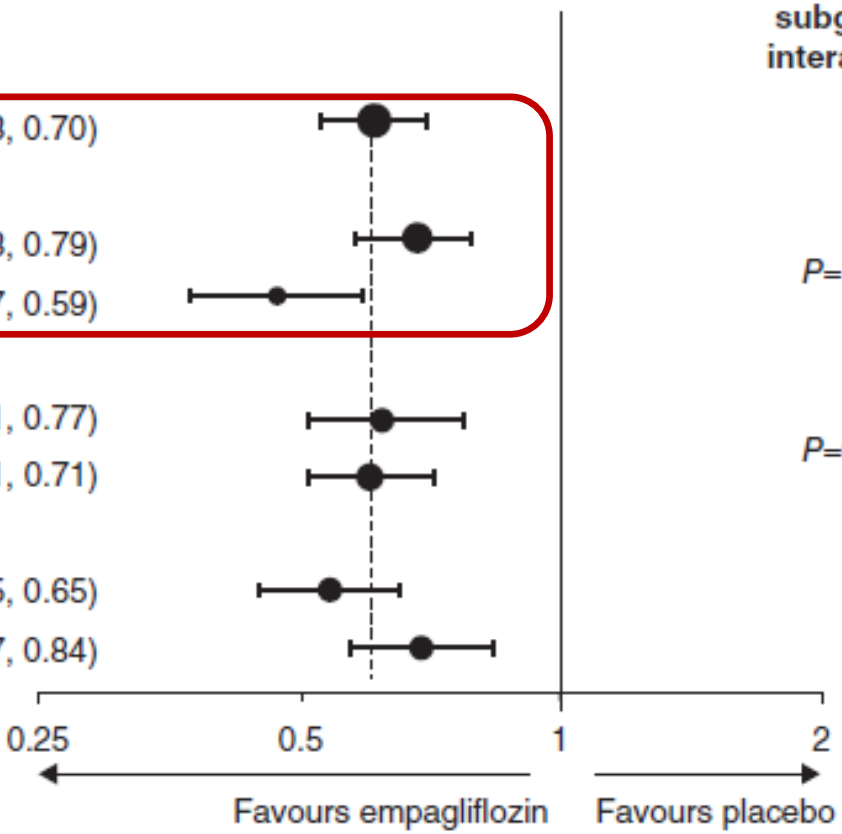
(E)

	Empagliflozin *n* with events/*N* (%)	Placebo	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
All-cause mortality					
All patients	269/4,687 (5.7)	194/2,333 (8.3)		0.68 (0.57, 0.82)	
Metformin at baseline					
Yes	176/3,459 (5.1)	115/1,734 (6.6)	26.1 vs 47.0	0.78 (0.61, 0.98)	*P*=0.06
No	93/1,228 (7.6)	79/599 (13.2)	17.1 vs 22.5	0.54 (0.40, 0.72)	
SU at baseline					
Yes	102/2,014 (5.1)	76/992 (7.7)	16.9 vs 26.0	0.66 (0.49, 0.88)	*P*=0.73
No	167/2,673 (6.2)	118/1,341 (8.8)	21.4 vs 30.5	0.70 (0.55, 0.89)	
Insulin at baseline					
Yes	155/2,252 (6.9)	106/1,135 (9.3)	23.7 vs 32.7	0.72 (0.56, 0.93)	*P*=0.50
No	114/2,435 (4.7)	88/1,198 (7.3)	15.6 vs 24.8	0.64 (0.48, 0.84)	



(F)

	Empagliflozin *n* with events/*N* (%)	Placebo *n* with events/*N* (%)	Empagliflozin vs Placebo Events per 100 pt-years	HR (95% CI)	Treatment by subgroup interaction
Incident or worsening nephropathy					
All patients	525/4,124 (12.7)	388/2,061 (18.8)		0.61 (0.53, 0.70)	
Metformin at baseline					
Yes	382/3,080 (12.4)	263/1,552 (16.9)	52.7 vs 109.0	0.68 (0.58, 0.79)	*P*=0.01
No	143/1,044 (13.7)	125/509 (24.6)	46.1 vs 66.5	0.47 (0.37, 0.59)	
SU at baseline					
Yes	220/1,799 (12.2)	159/895 (17.8)	44.9 vs 70.0	0.62 (0.51, 0.77)	*P*=0.78
No	305/2,325 (13.1)	229/1,166 (19.6)	50.1 vs 80.8	0.60 (0.51, 0.71)	
Insulin at baseline					
Yes	267/1,921 (13.9)	216/963 (22.4)	53.3 vs 94.4	0.54 (0.45, 0.65)	
No	258/2,203 (11.7)	172/1,098 (15.7)	43.1 vs 61.1	0.69 (0.57, 0.84)	



Metformin and DPP4 Inhibitors

- Meta-analysis of the three major CVOTs examining DPP4 inhibitors , showed that baseline metformin users experienced a trend towards improved CV outcomes when combined with DPP4 inhibitors (HR 0.92, 95% CI 0.84, 1.01)

- Compared to baseline metformin non-users who in fact showed a trend towards harm (HR1.10, 95% CI 0.97, 1.26) .

Metformin Use May Moderate the Effect of DPP-4 Inhibitors on Cardiovascular Outcomes. Diabetes Care **2017**, 40, dc171528

Metformin and GLP-1RA

- In the Harmony outcomes trial, those on baseline metformin therapy did slightly better (HR 0.77, 95% CI 0.65–09.2) than those who were not on metformin (HR 0.79, 95% CI 0.62, 1.00).

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): A double-blind, randomized placebo-controlled trial. Lancet **2018**, 392, 1519–1529.

First-line treatment for type 2 diabetes: is it too early to abandon metformin?

First-line treatment for type 2 diabetes: is it too early to abandon metformin?

- In CVOT s most participants were on at least one OAD at baseline
- Therefore, the CV benefit of SGLT2 i- or GLP-1 RA remains uncertain for treatment-naive individuals
- Making difficult any comparison with previous evidence of first-line metformin treatment on CV events.

Gnesin F, Thuesen AC, Kähler LK, Madsbad S, Hemmingsen B. Metformin monotherapy for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2020; **6:** CD012906.

Is it too early to abandon metformin?

A reduced efficacy of SGLT2 inhibitors in individuals taking metformin was reported in subgroup analyses of cardiovascular outcome trials, with inconsistent findings across agents and outcomes.

Packer M. Does metformin interfere with the cardiovascular benefits of SGLT2 inhibitors? Questions about its role as the cornerstone of diabetes treatment. *Am J Med* 2020; **133:** 781–82.

Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab* 2020; **22:** 631–39.

Neuen BL, Heerspink HL, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin in people with type 2 diabetes according to baseline use of metformin. American Association of Clinical Endocrinologists 28th Annual Scientific & Clinical Congress; Los Angeles, CA, USA; April 24–28, 2019,

Is it too early to abandon metformin?

For example, in the EMPA-REG:

1. Empagliflozin reduced the risk of admission to hospital for heart failure to a similar extent irrespective of metformin use at baseline

2. Conversely, **the reduction in renal outcomes was greater in individuals not on metformin.**

Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? *Diabetes Obes Metab* 2020; **22:** 631–39.

Is it too early to abandon metformin?

The CANVAS , showed:

1. Greater effect for admission to hospital for heart failure in participants not on metformin
2. similar effect for renal outcomes.

Caution is needed when interpreting such results

These CVOT S were primarily planned to investigate the safety of SGLT2 inhibitors and GLP-1 receptor agonists on primary outcomes

Neuen BL, Heerspink HL, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin in people with type 2 diabetes according to baseline use of metformin. American Association of Clinical Endocrinologists 28th Annual Scientific & Clinical Congress; Los Angeles, CA, USA; April 24–28, 2019,

Kent DM, van Klaveren D, Paulus JK, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) statement: explanation and elaboration. *Ann Intern Med* 2020; **172:** W1–25.

Is it too early to abandon metformin? Points to be considered

1- Analyses looking for differential effects (interactions) should be considered exploratory and at best hypothesis-generating

2- in view of their low statistical power, lack of multiple testing adjustment, and no evidence of interaction for the primary outcome

- As has been the case for all trials reporting heterogeneity of treatment effect with metformin (LEADER, Harmony, EMPA-REG, CANVAS, DECLARE-TIMI, VERTIS CV).

3- Moreover, participants not on metformin at baseline are not necessarily treatment-naive.

- Furthermore, exploring interaction with one-factor at a time is prone to confounding bias due to potential systematic differences between individuals with and without metformin (ie, diabetes duration or previous history of heart failure), which are reported in LEADER,EMPA-REG,CANVAS, and DECLARE-TIMI .

Is it too early to abandon metformin?

This observation tallies with the distinction between

- heterogeneity of treatment effect
- and causal interaction.

VanderWeele TJ, Knol MJ. Interpretation of subgroup analyses in randomized trials: heterogeneity versus secondary interventions. *Ann Intern Med* 2011; **154:** 680–83.

Is it too early to abandon metformin?

Whether trialists

- aim to predict the effect of the treatment in relation to concomitant use of metformin

- or aim to establish whether metformin is the cause of a reduced SGLT2 inhibitor (or GLP-1 RA) effect (causal interaction)

has relevant implications.

Kent DM, van Klaveren D, Paulus JK, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) statement: explanation and elaboration. *Ann Intern Med* 2020; **172:** W1–25.

Is it too early to abandon metformin?

What is the aim of the study

1- If the aim is to predict the effect of starting a treatment, controlling for factors that are different between participants with and without metformin is not required.

1- To clarify whether metformin is the cause of the reduced effect, trialists must account for factors that could be causally related to the reduced treatment effect and associated with metformin use, unless metformin is randomly assigned (as in a factorial design)

VanderWeele TJ, Knol MJ. Interpretation of subgroup analyses in randomized trials: heterogeneity versus secondary interventions. *Ann Intern Med* 2011; **154:** 680–83.

Is it too early to abandon metformin?

- Among these factors, **a possible candidate is kidney function**, because it is an established risk factor for CVD and death, and prescription of metformin should be carefully considered in patients with a reduced kidney function.

- Differences in e GFR according to baseline metformin were present in EMPA-REG ,CANVAS , and DECLARE-TIMI 58.

Is it too early to abandon metformin?

- Unfortunately, the studies published to date have adjusted for these factors variably for both primary and other outcomes.

- Post-hoc analyses, with standardized methodological approaches across different treatments and outcomes, would be a valuable source of evidence to differentiate a causal interaction from a heterogeneity of treatment effect.

Is it too early to abandon metformin?

The results of CVOT s have generated important evidence on treatment strategies to reduce the risk of cardiovascular disease in people with T2DM

but the contribution of these findings to the knowledge about the optimal first-line agent for treatment of type 2 diabetes is far more limited.

Is it too early to abandon metformin?

1- RCT comparing metformin with an SGLT2 –I or a GLP-1 RA as first-line agent would help to settle this controversy.

2- Not only the efficacy but also the cost and the long-term safety profile of competing medications should guide decisions in clinical practice.

- 3- The question of which first-line agent is best for individuals with type 2 diabetes should not detract from use of SGLT2 inhibitors and GLP-1 RA in patients with established cardiovascular diseases, for whom their efficacy is uncontroversial.

Diabetes Care

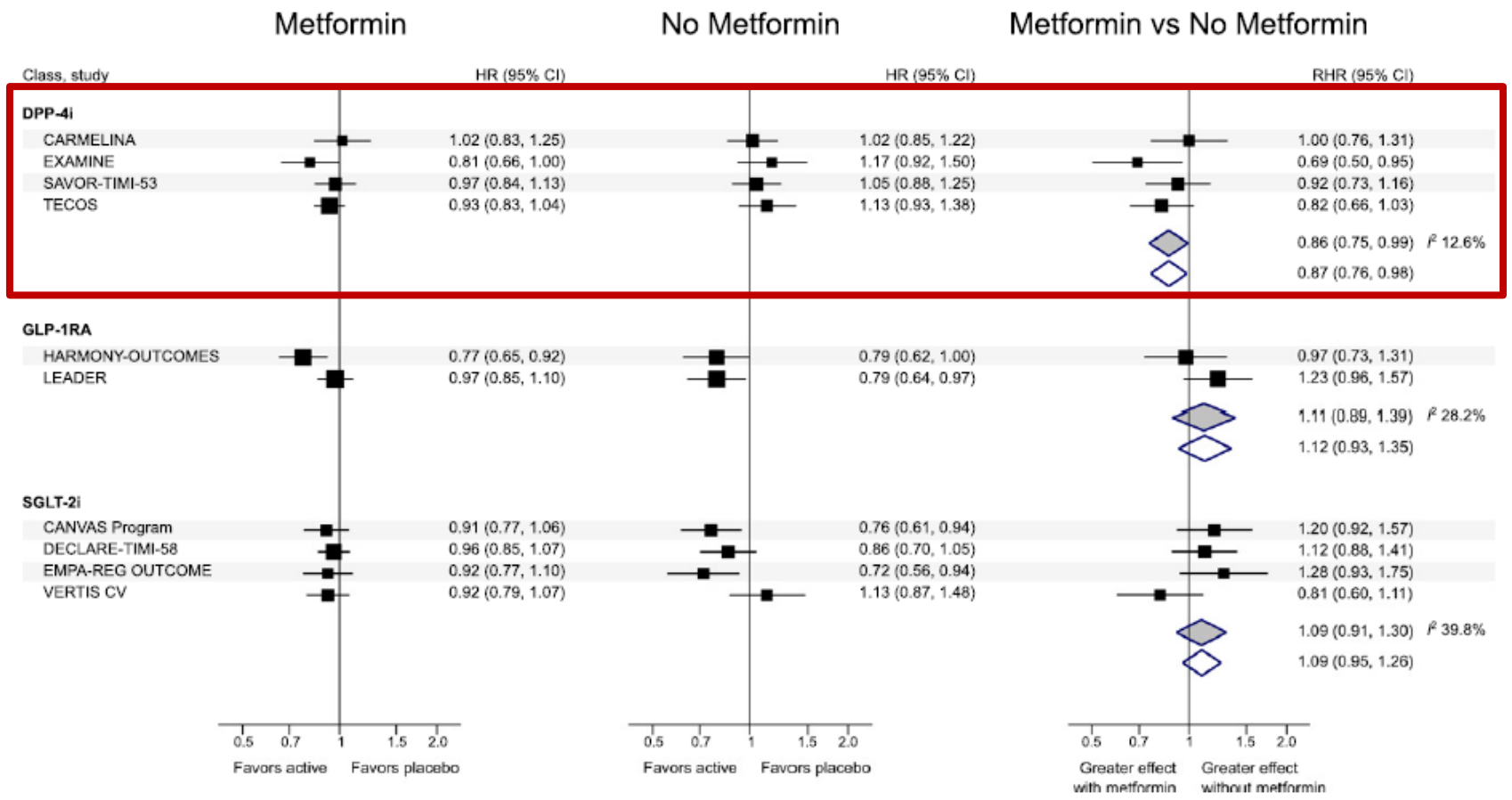
Use of Metformin and Cardiovascular Effects of New Classes of Glucose-Lowering Agents: A Meta-analysis of Cardiovascular Outcome Trials in Type 2 Diabetes

https://doi.org/10.2337/dc20-2080

Francesco Zaccardi,[1,2] David E. Kloecker,[1,2] John B. Buse,[3] Chantal Mathieu,[4] Kamlesh Khunti,[1,2] and Melanie J. Davies[2,5]

These results suggested a larger effect of DPP-4i in patients on metformin at baseline

conversely,
there was no statistical evidence that baseline metformin modified the cardio vascular effects of GLP-1RA and SGLT-2i.



Ann Intern Med. 2020;173:278-286. doi:10.7326/M20-0864

REVIEW

Annals of Internal Medicine

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes

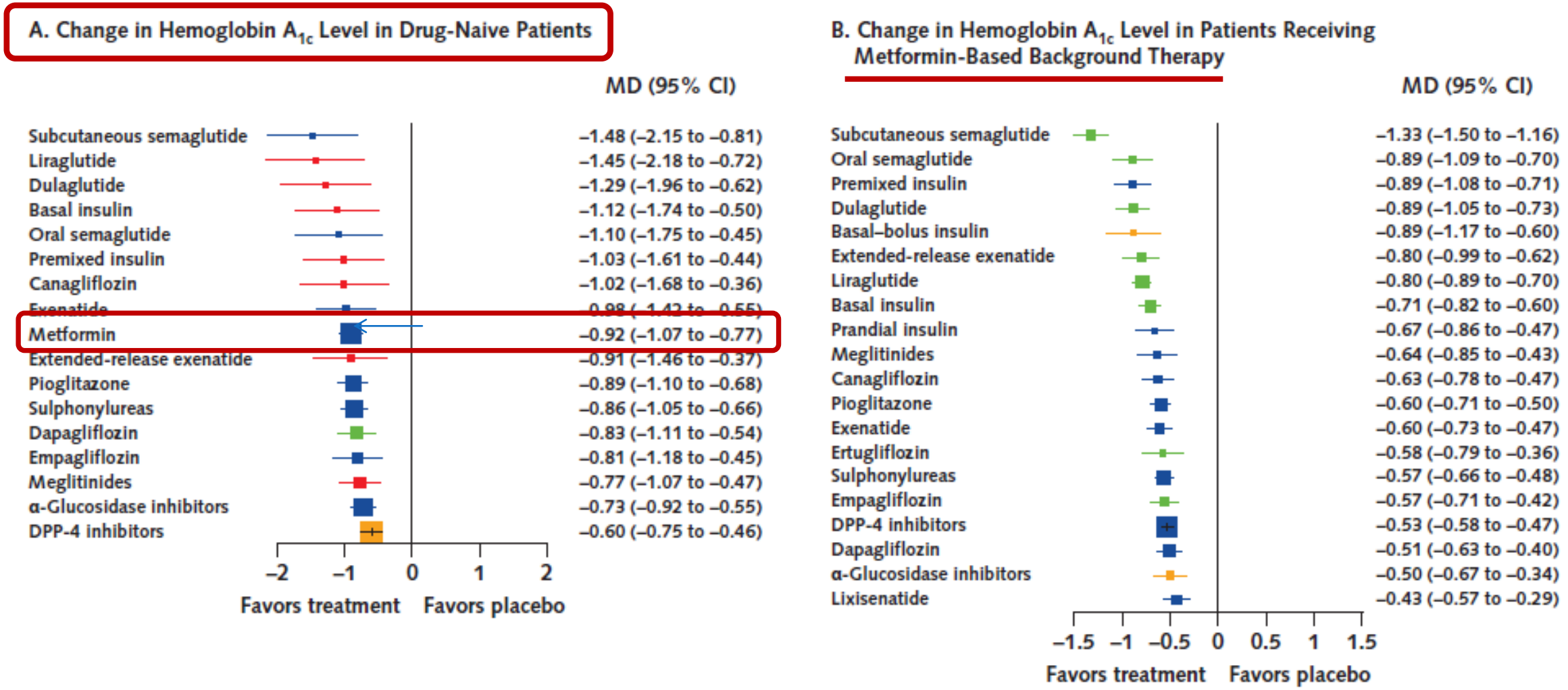
A Systematic Review and Network Meta-analysis

Apostolos Tsapas, MD, MSc (Oxon), PhD*; Ioannis Avgerinos, MD, MSc*; Thomas Karagiannis, MD, MSc, PhD*; Konstantinos Malandris, MD, MSc; Apostolos Manolopoulos, MD, MSc; Panagiotis Andreadis, MD, MSc; Aris Liakos, MD, MSc, PhD; David R. Matthews, MD, DPhil; and Eleni Bekiari, MD, MSc, PhD

453 trials assessing 21 antidiabetic interventions from 9 drug classes were included.
Interventions included monotherapies (134 trials)
add-on to metformin-based therapies (296 trials)
monotherapies versus add-on to metformin therapies (23 trials).

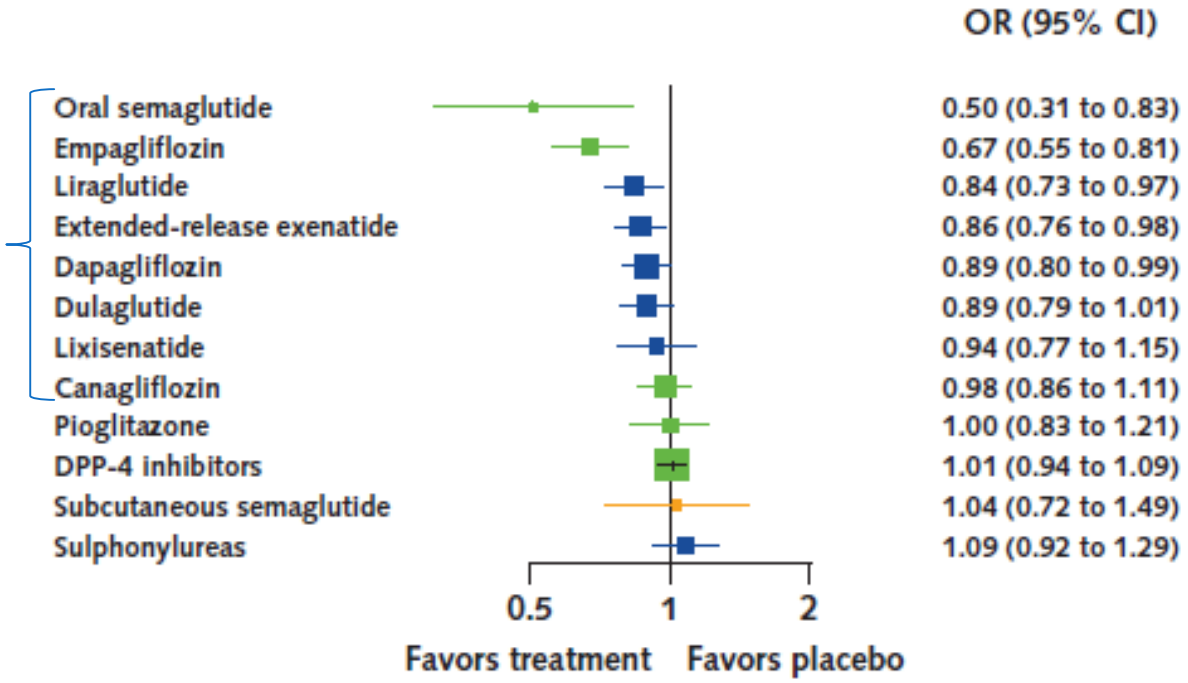
Comparative effectiveness of GLD for T2DM **A1c change**

Figure 2. Network meta-analysis results for the primary outcomes compared with placebo.

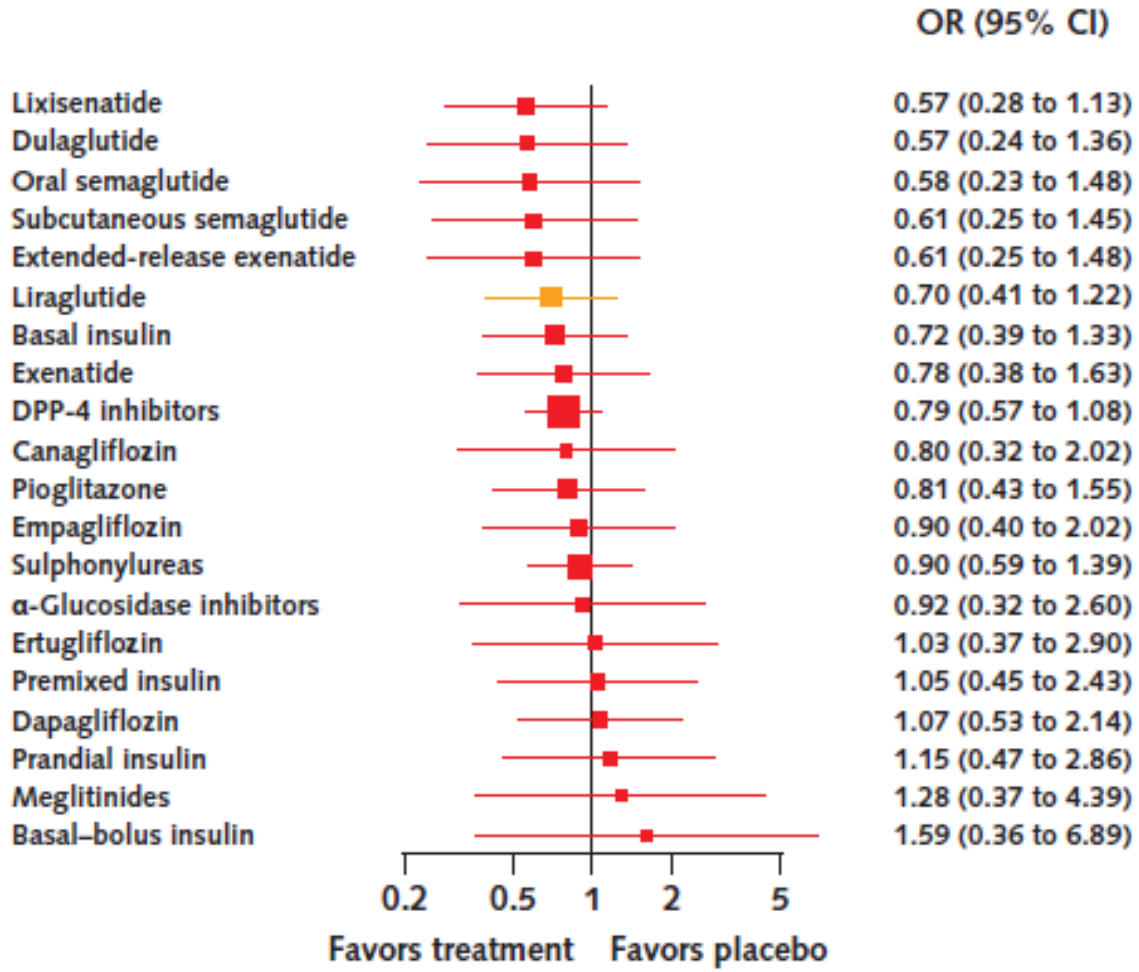


Comparative effectiveness of GLD for T2DM all cause mortality

C. All-Cause Mortality in Patients at Increased Cardiovascular Risk Receiving Metformin-Based Background Therapy



D. All-Cause Mortality in Patients at Low Cardiovascular Risk Receiving Metformin-Based Background Therapy



Conclusion

1- The use of metformin as first-line treatment of drug-naive patients at low cardiovascular risk seems justified.

2- Given the lack of pertinent evidence, we could not reach a conclusion about the optimal initial treatment of drug-naive patients at increased cardiovascular risk.

Conclusion

3- In patients at low cardiovascular risk receiving metformin-based background therapy, choice among available agents should be based on their effect on other efficacy and safety outcomes because of lack of difference in vascular outcomes

4- For patients at increased cardiovascular risk receiving metformin-based background therapy, the optimal choice between specific GLP-1 RAs and SGLT-2 inhibitors should be based on the cardiovascular profile of individual agents and guided by patients' personal preferences and therapeutic priorities.

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DOI: 10.1111/dom.14226

ORIGINAL ARTICLE

WILEY

Sodium-glucose co-transporter-2 inhibitors with and without metformin: A meta-analysis of cardiovascular, kidney and mortality outcomes

Brendon L. Neuen MBBS(Hons)[1] | Clare Arnott PhD[1,2,3,4] | Vlado Perkovic PhD[1,2] | Gemma Figtree DPhil[5] | Dick de Zeeuw PhD[6] | Greg Fulcher MD[7] | Min Jun PhD[1,2] | Meg J. Jardine PhD[1] | Sophia Zoungas PhD[8] | Carol Pollock PhD[5] | Kenneth W. Mahaffey MD[9] | Bruce Neal PhD[1] | Hiddo J. L. Heerspink PhD[1,2,6]

To assess whether the effects of SGLT2 inhibitors on cardiovascular, kidney and mortality outcomes are consistent with and without concomitant metformin use.

Results

- Six trials of four SGLT2 inhibitors that enrolled a total of 51743 participants.

- Baseline metformin use varied from 21% in DAPA-HF to 82% in DECLARE-TIMI 58.

SGLT2 inhibitors reduced the risk of MACE, with and without concomitant metformin use (HR 0.93, 95% CI 0.87–1.00 and HR 0.82, 95% CI 0.71–0.86, respectively; P-heterogeneity = 0.14).

Results

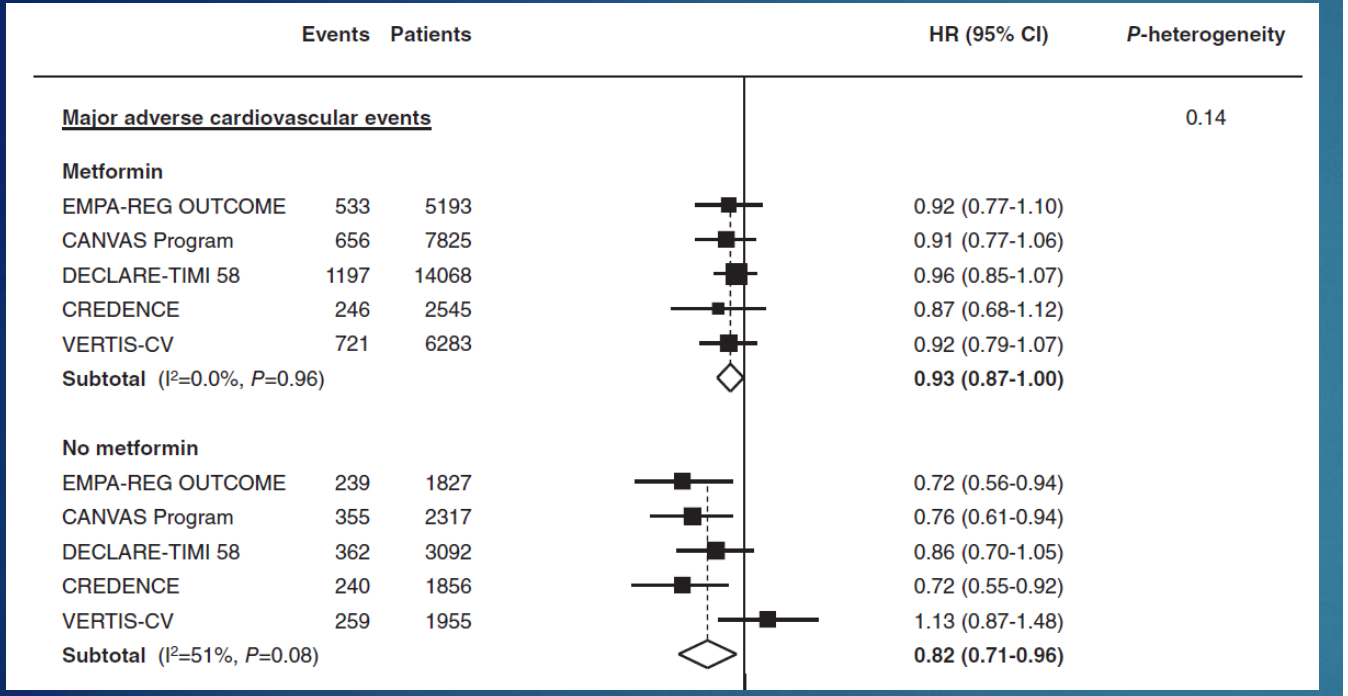
There were also clear and separate reductions in:

1. HHF or CV death with SGLT2 inhibitors, irrespective of metformin use (HR 0.79, 95% CI 0.73–0.86 and HR 0.74, 95% CI 0.63–0.87, respectively; P-heterogeneity = 0.48),

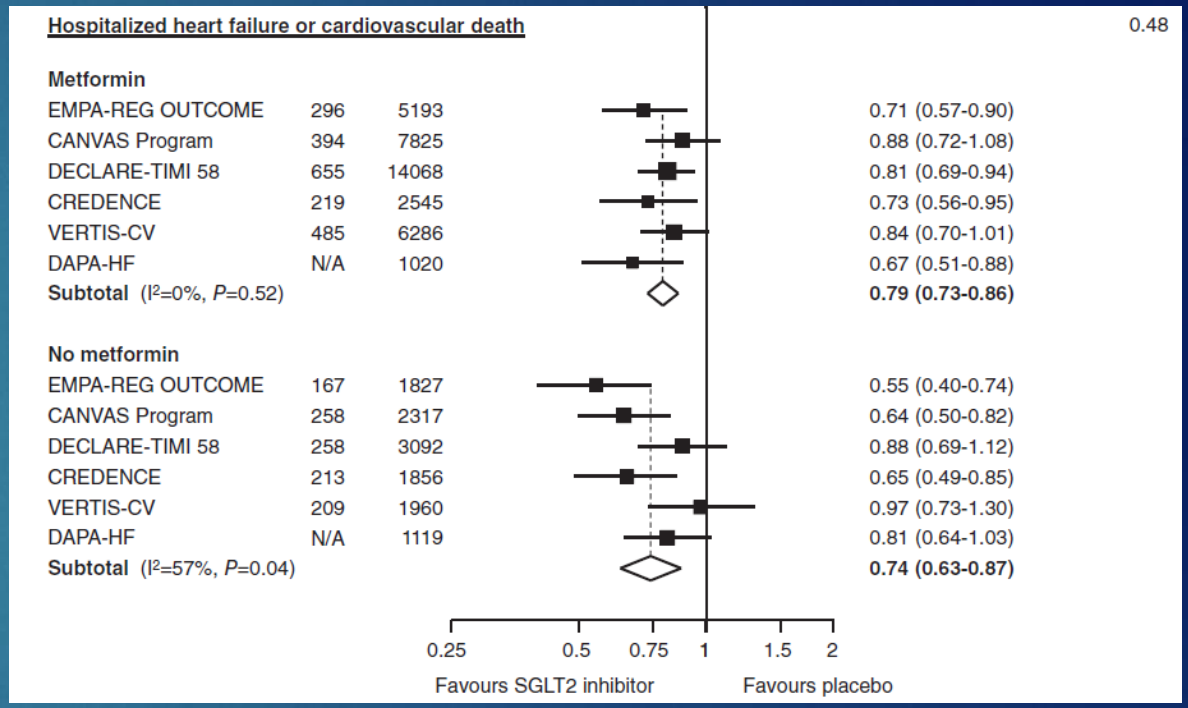
2. as well as for major kidney outcomes and all-cause mortality (all P-heterogeneity > 0.40).

SGLT2-I with or without metformin

MACE



MACE & HHF



SGLT2-I with or without metformin

HHF

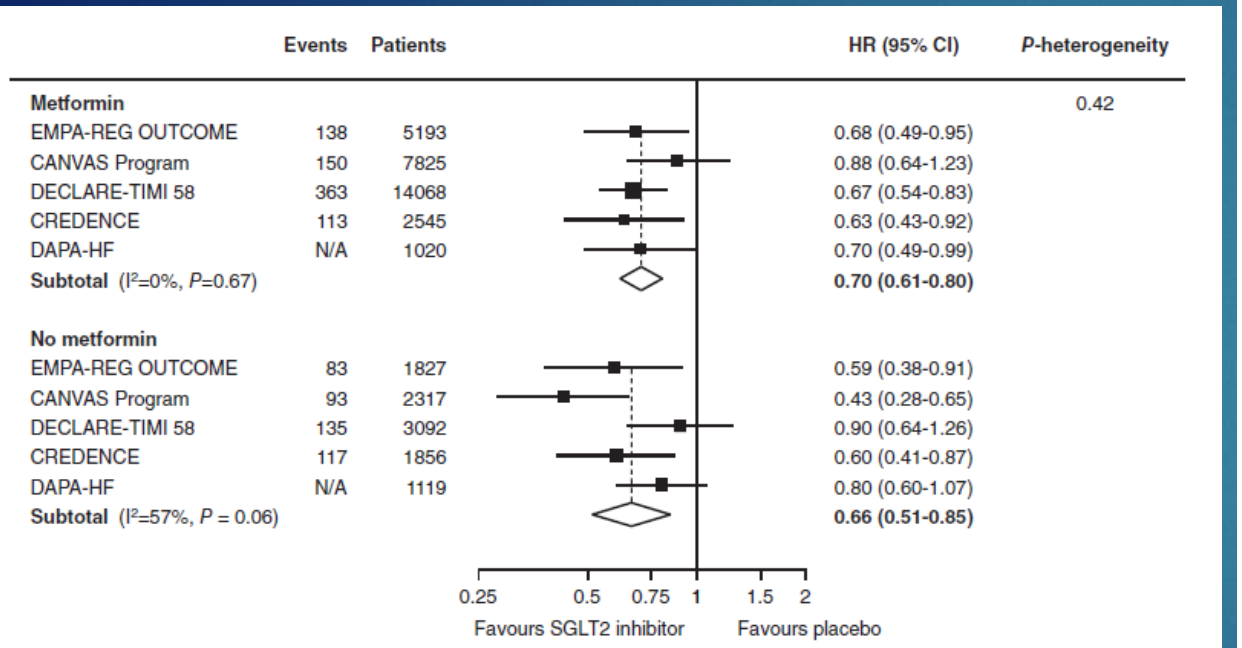


FIGURE 2 Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on hospitalization for heart failure by baseline metformin use. N/A, not available; CI, confidence interval

CV DEATH

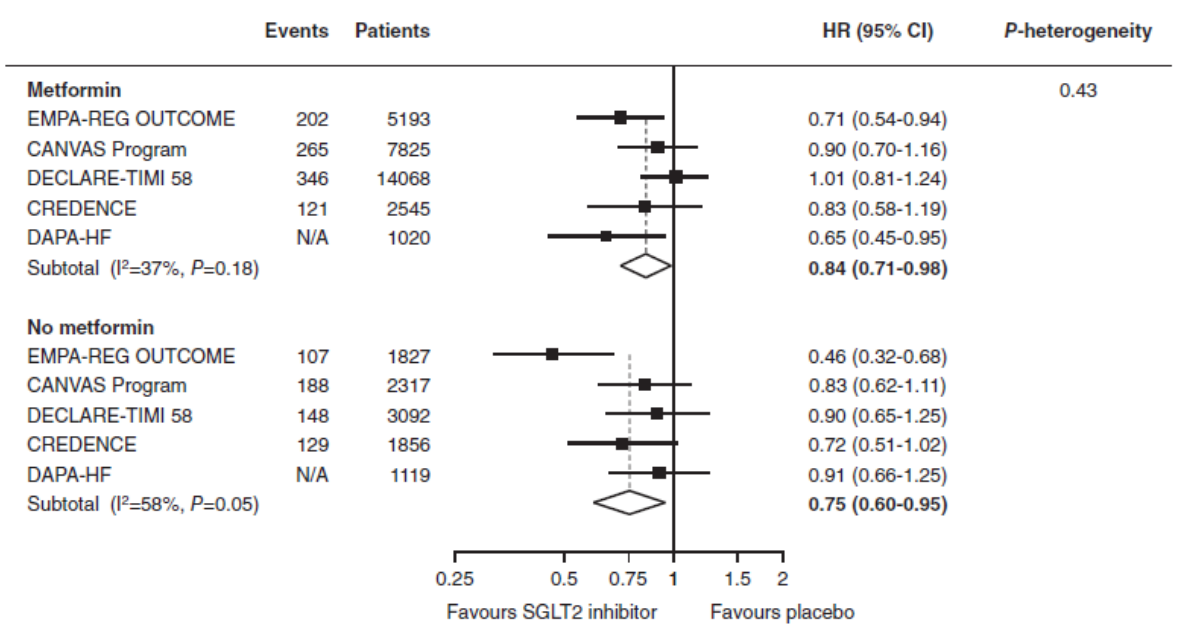
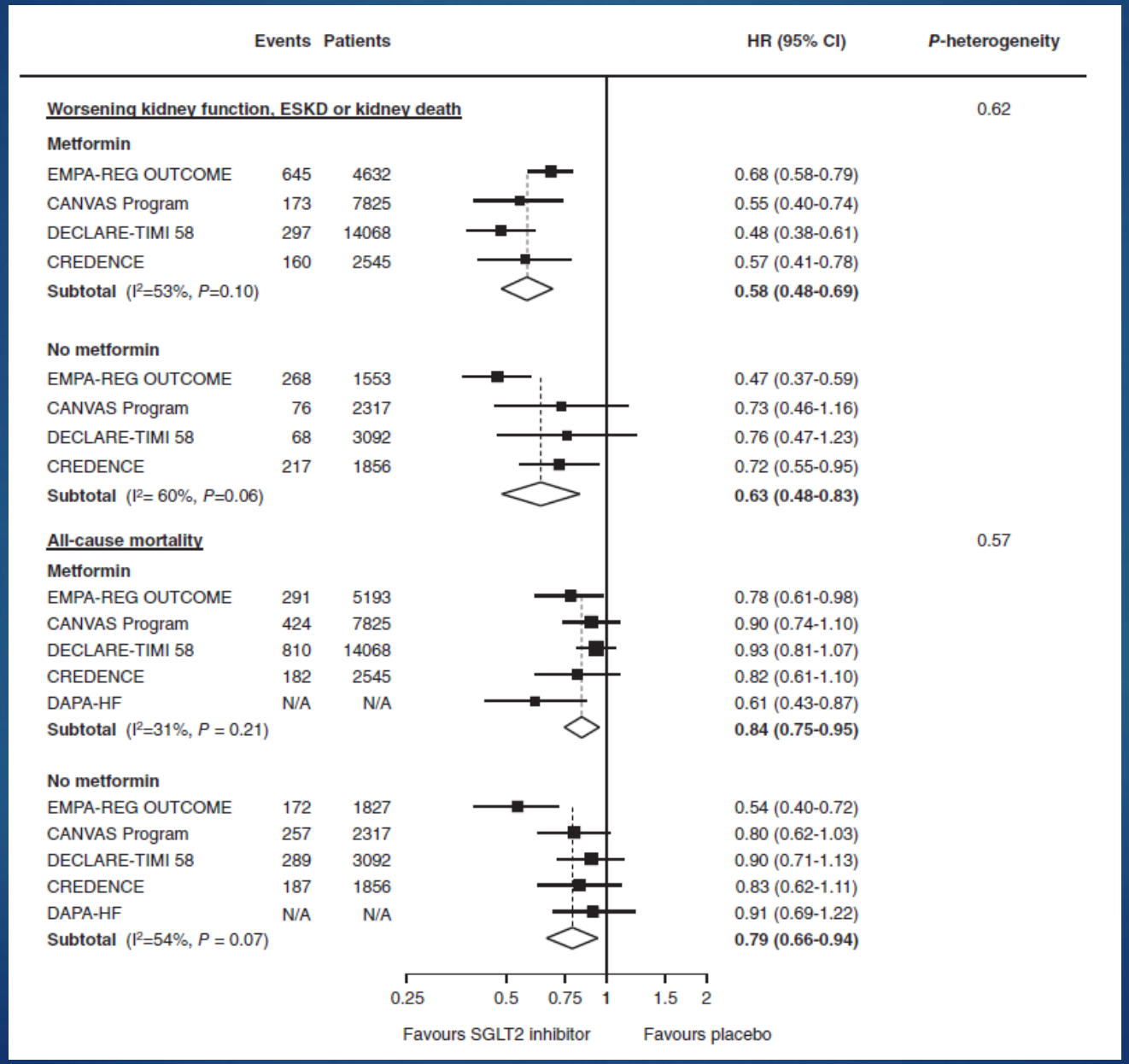


FIGURE 3 Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on cardiovascular death by baseline metformin use. CI, confidence interval; NA, not available

SGLT2-I with or without metformin



Conclusion

Treatment with SGLT2 inhibitors results in clear and consistent reductions in cardiovascular, kidney and mortality outcomes regardless of whether patients are receiving or not receiving metformin.

Escalation of therapy

It is crucial to escalate therapy after metformin as:

- within 2-years of initiating metformin monotherapy, over 30% of patients require an additional agent
- within 3-years over 50% require combination therapy.

Turner, R.C.; Cull, C.A.; Frighi, V.; Holman, R.R. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA **1999**, 281, 2005–2012

Paradigm shift

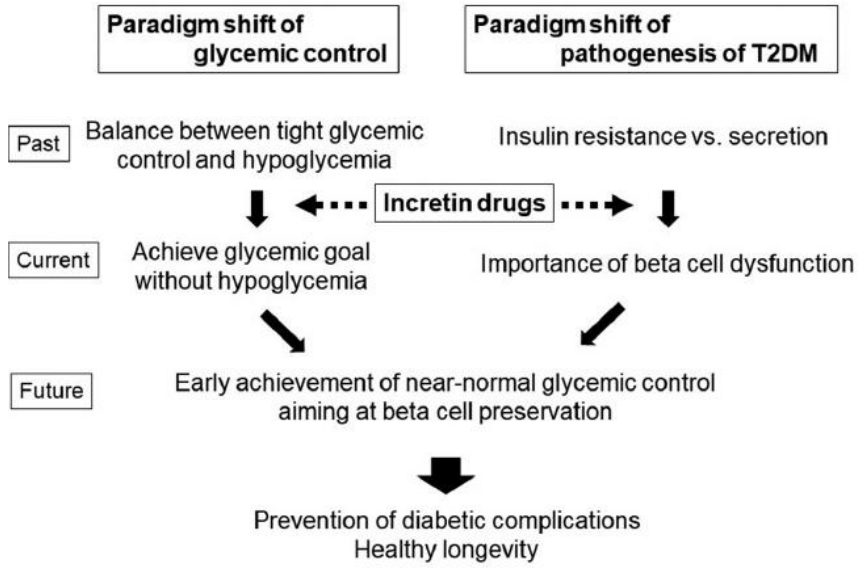
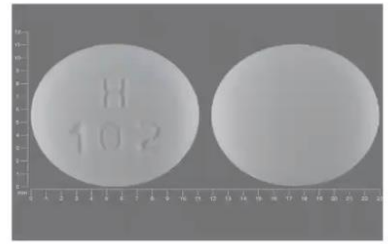


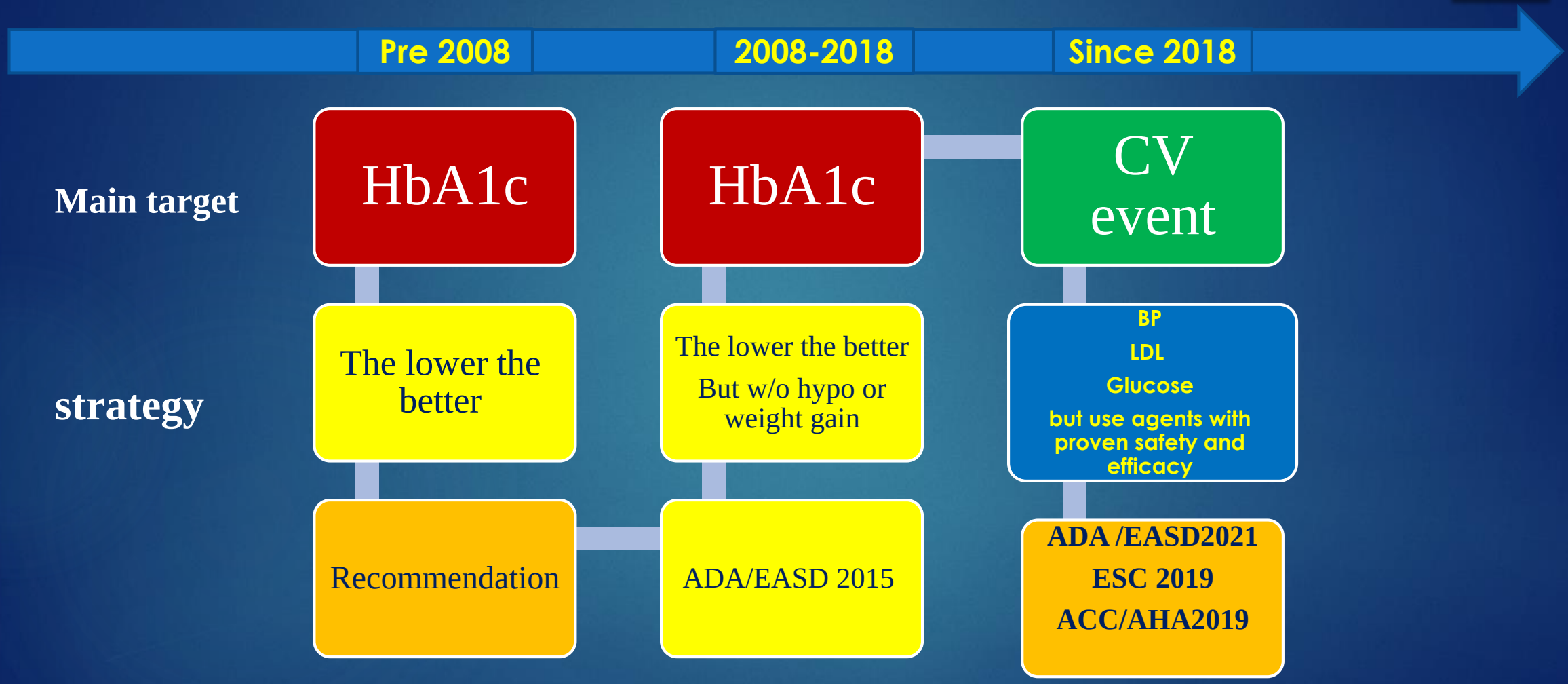
Figure 3. Paradigm shift in therapeutic strategy and pathophysiology of T2DM promoted by the development and launch of incretin drugs.

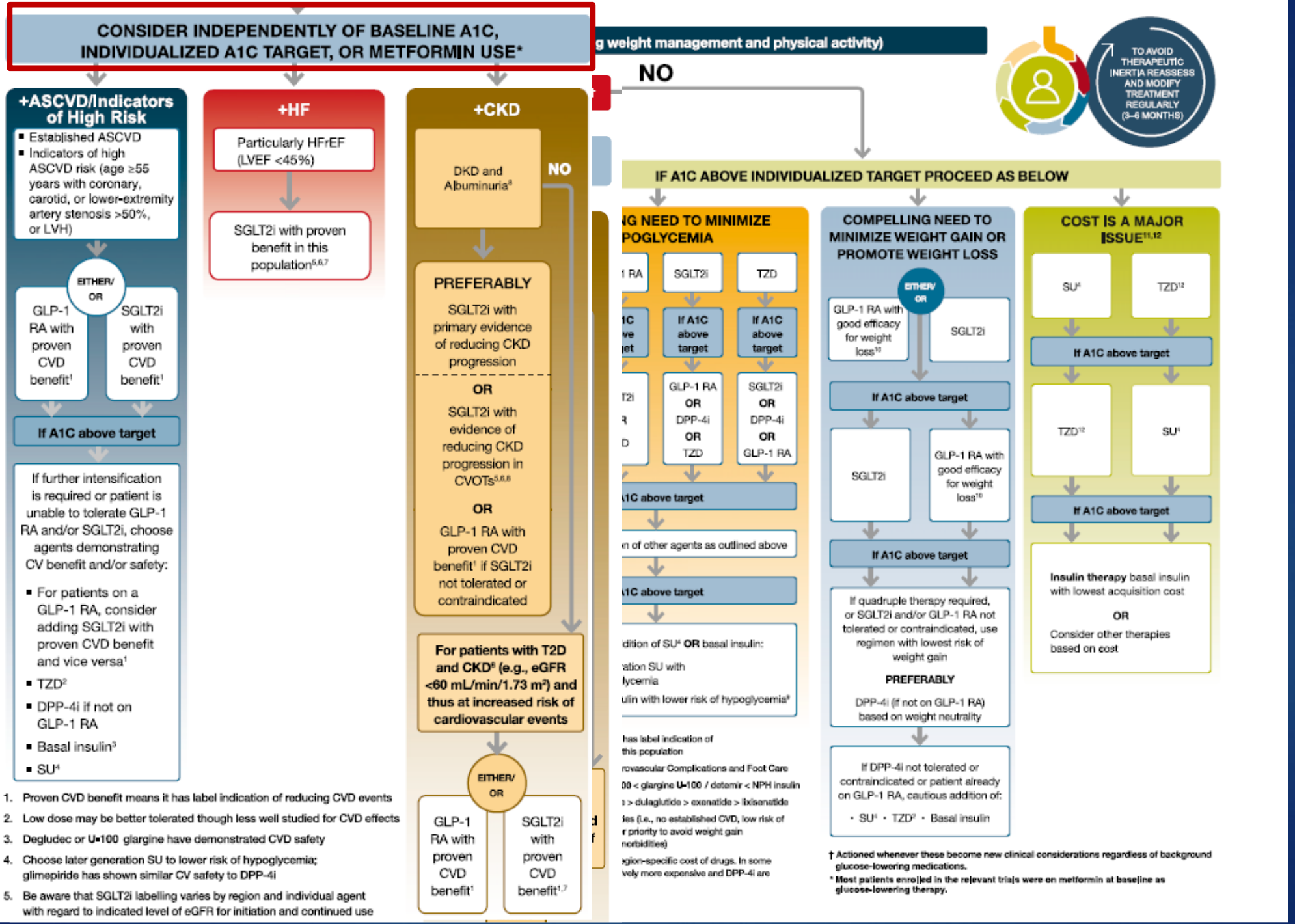
1995



2020

Evolution of treatment recommendations in type 2 DM management



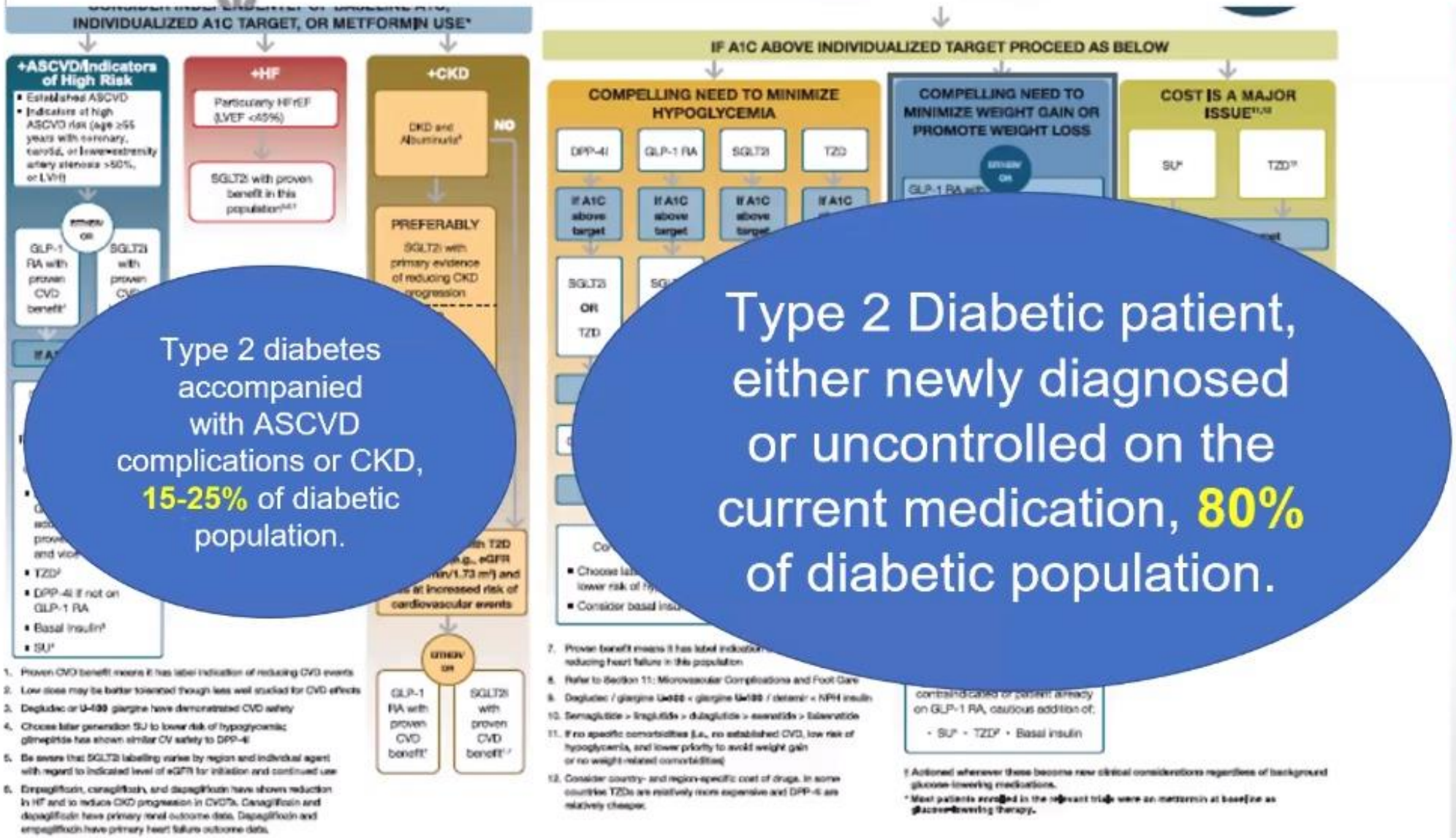


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar 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

† 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 (including weight management and physical activity)



2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021. Diabetes Care* 2021;44(Suppl. 1):S111-S124

American Diabetes Association.
Connected for Life

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

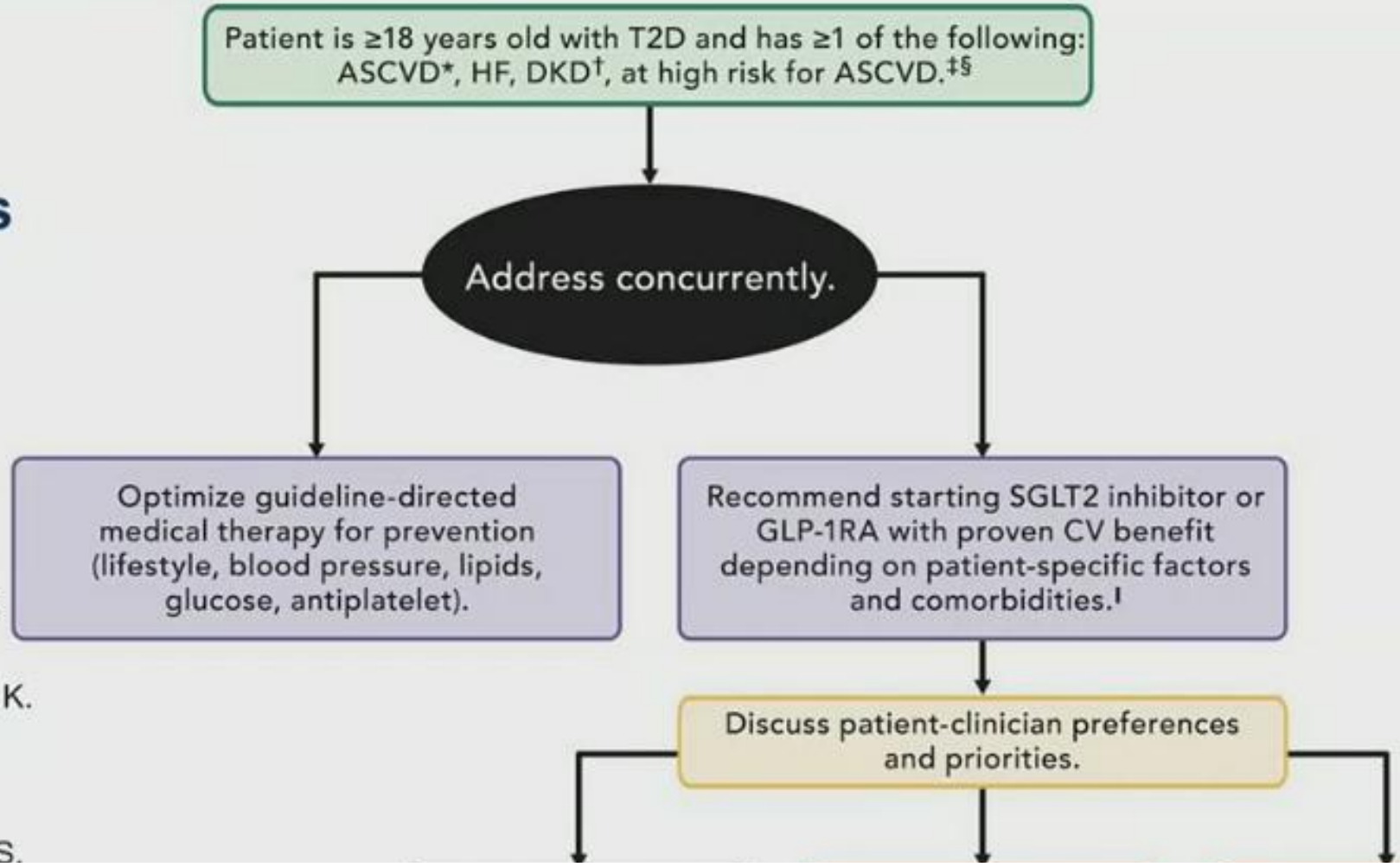
A Report of the American College of Cardiology Solution Set Oversight Committee
Endorsed by the American Diabetes Association

AMERICAN COLLEGE of CARDIOLOGY

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

A Report of the ACC Solution Set Oversight Committee

Sandeep R. Das, Brendan M. Everett, Kim K. Birtcher, Jenifer M. Brown, James L. Januzzi Jr., Rita R. Kalyani, Mikhail Kosiborod, Melissa Magwire, Pamela B. Morris, Joshua J. Neumiller and Laurence S.



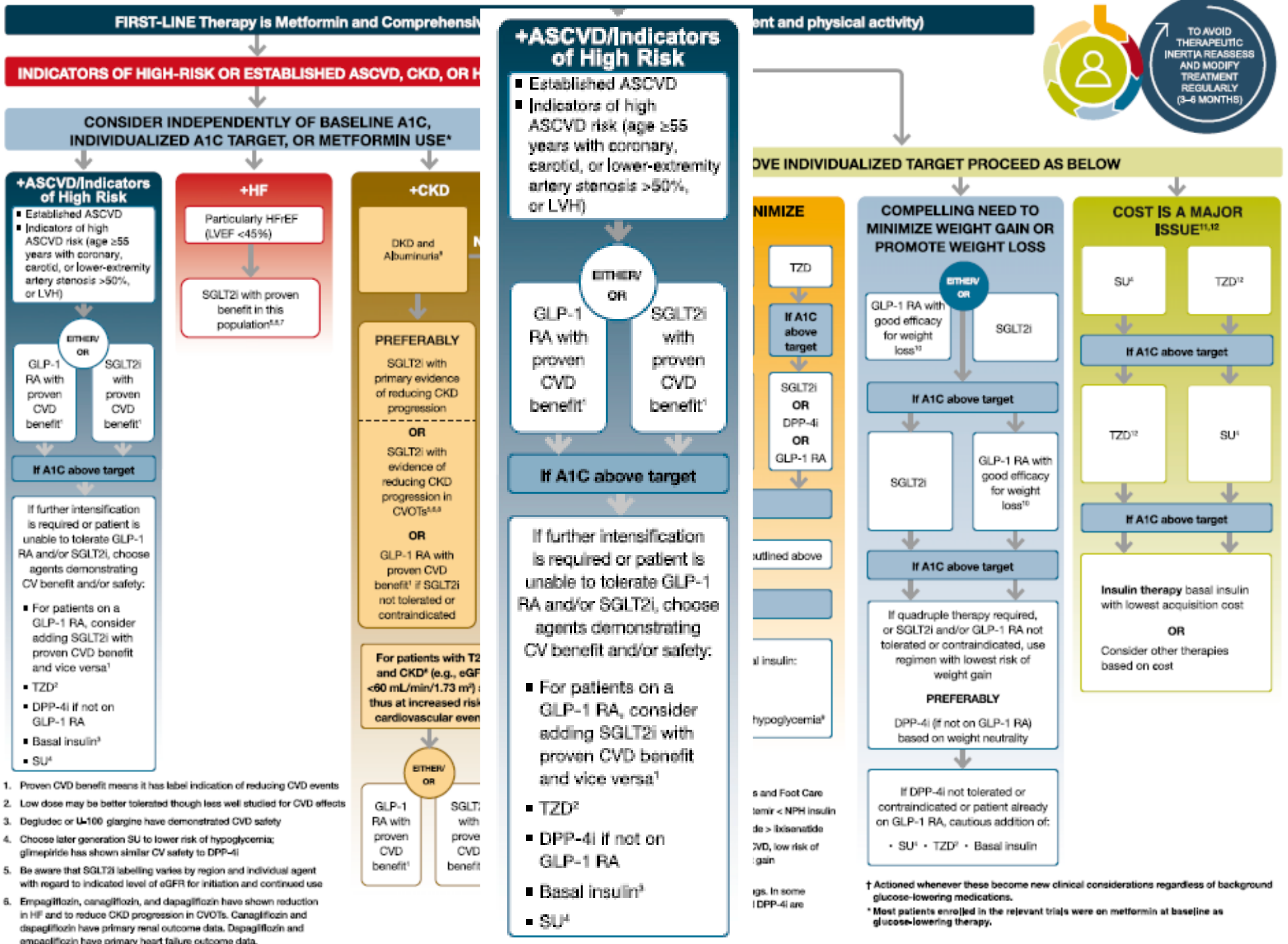
*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

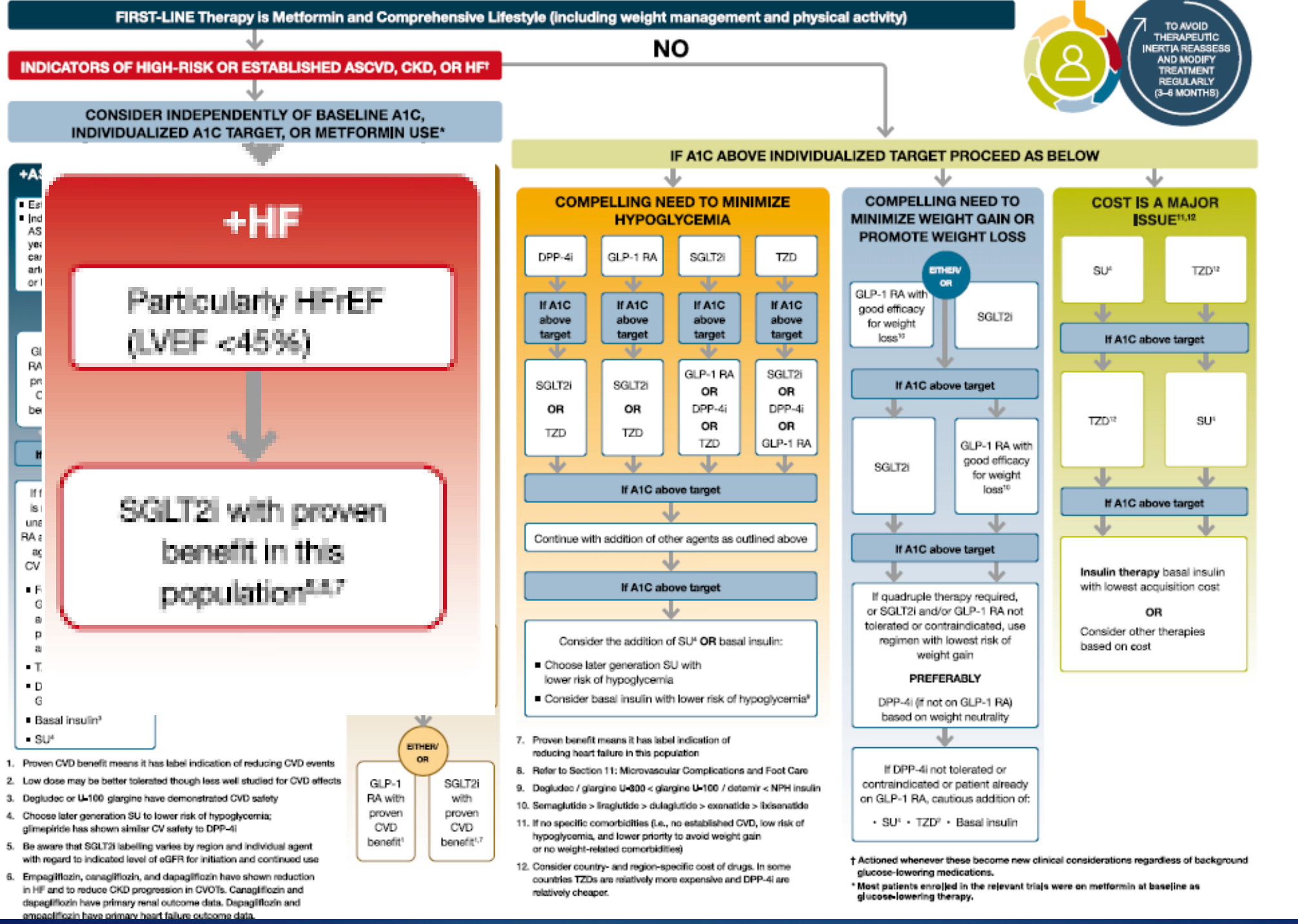
T2D = type 2 diabetes



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.

† 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.



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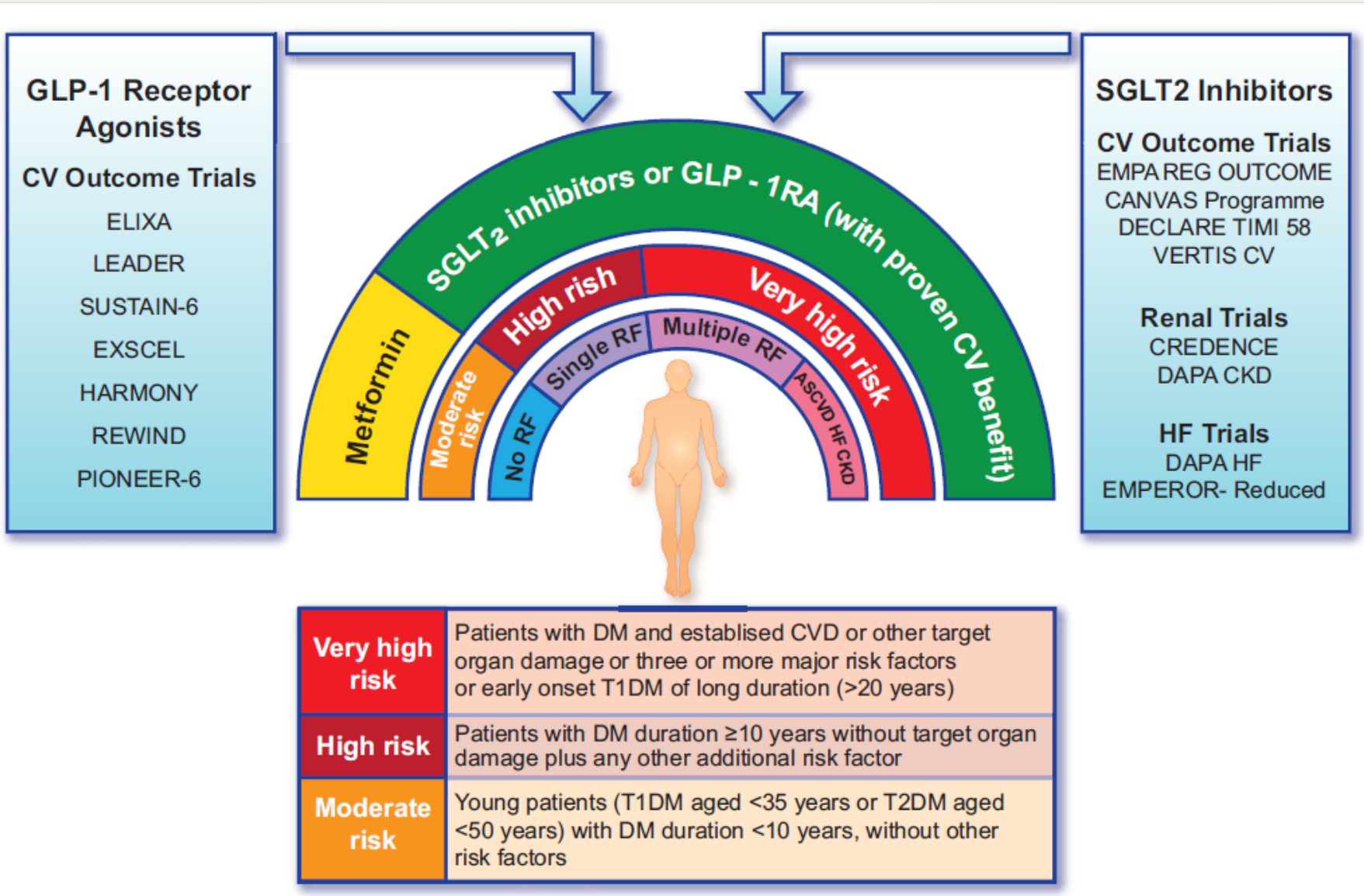
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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.

Figure 2 Cardiovascular risk classification and treatment recommendation to reduce cardiovascular outcomes in patients with T2D according to the 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; green, Class I/A recommendation; RF, risk factor; yellow, Class IIa/C recommendation (modified from Marx N, Eur Heart J 2020. doi:10.1093/eurheartj/ehaa174).



COMMENTARY

Should sodium-glucose cotransporter-2 inhibitors be first-line treatment for patients with type 2 diabetes?

Carl van Walraven MD MSc

■ Cite as: *CMAJ* 2020 April 6;192:E375-6. doi: 10.1503/cmaj.200426

See related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.191283

Does the SGLT2 inhibitors should become our first choice for treatment of type 2 diabetes?

A 2019 meta analysis involving 34 322 patients from 3 placebo-controlled RCTs found:

In patients on SGLT2 -I significant reductions in the risk of :

- Heart failure and CV death (OR 0.77, 95% CI 0.71–0.84)
- Renal disease progression (OR 0.55, 95% CI 0.48–0.64)
- In those with established atherosclerosis, MACE (OR 0.89, 95% CI 0.83–0.96)

Does the SGLT2 inhibitors should become our first choice for treatment of type 2 diabetes?

- Regardless of its comparator drug class, metformin achieved equivalent or better intermediate outcomes (including glucose control, patient weight and hypoglycemic events) compared with sulfonylureas and moderate evidence exists for reduced cardiovascular mortality with metformin.

- Furthermore, no RCT has directly compared long-term outcomes for metformin versus SGLT2 inhibitors

Does the SGLT2 inhibitors should become our first choice for treatment of type 2 diabetes?

- Despite these encouraging findings, SGLT2 inhibitors should not become first-line pharmacologic treatment for type 2 diabetes.

Our patient

No

6 months

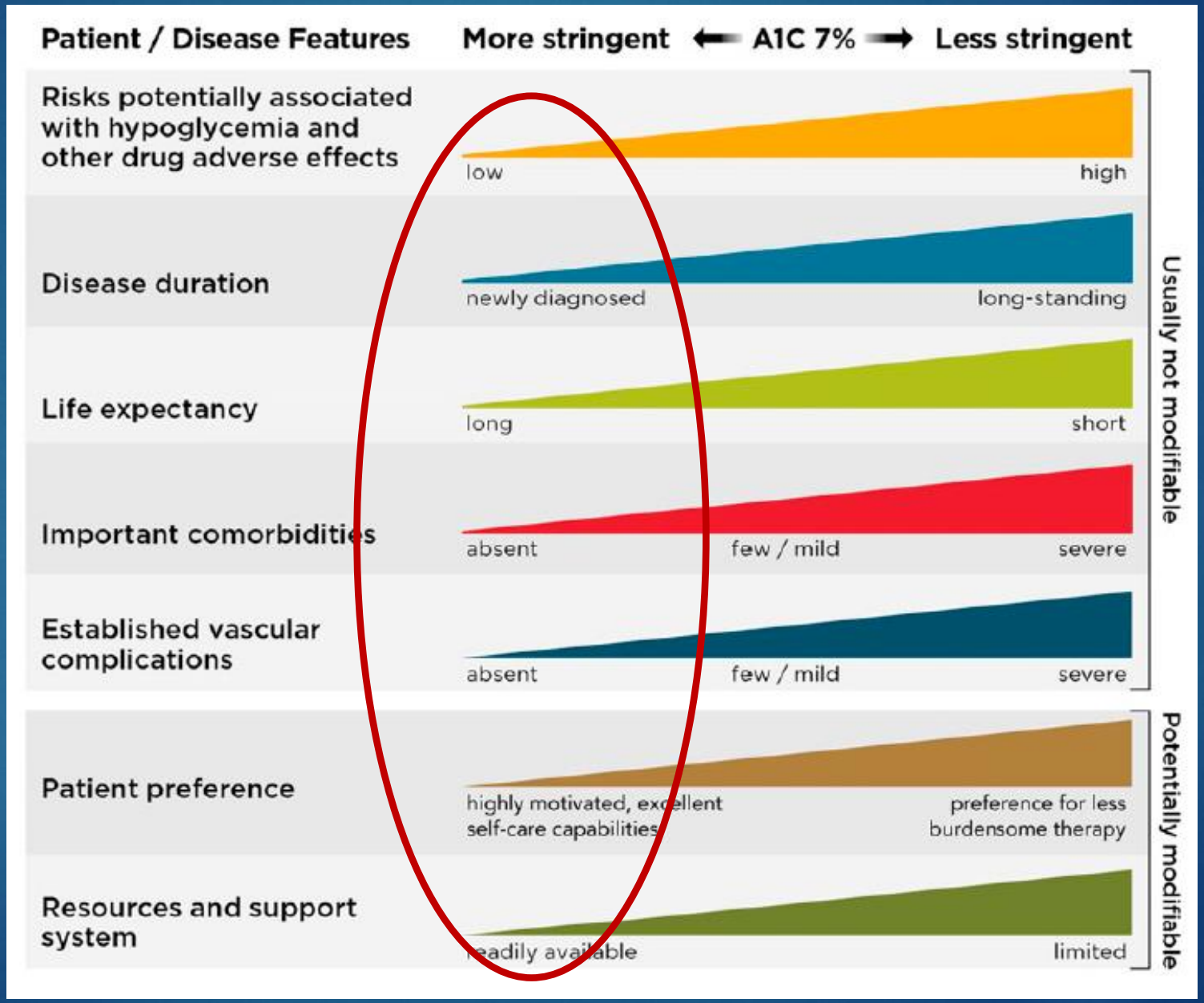
45 yrs old

Overweight only

absent

?

?



Choice of treatment

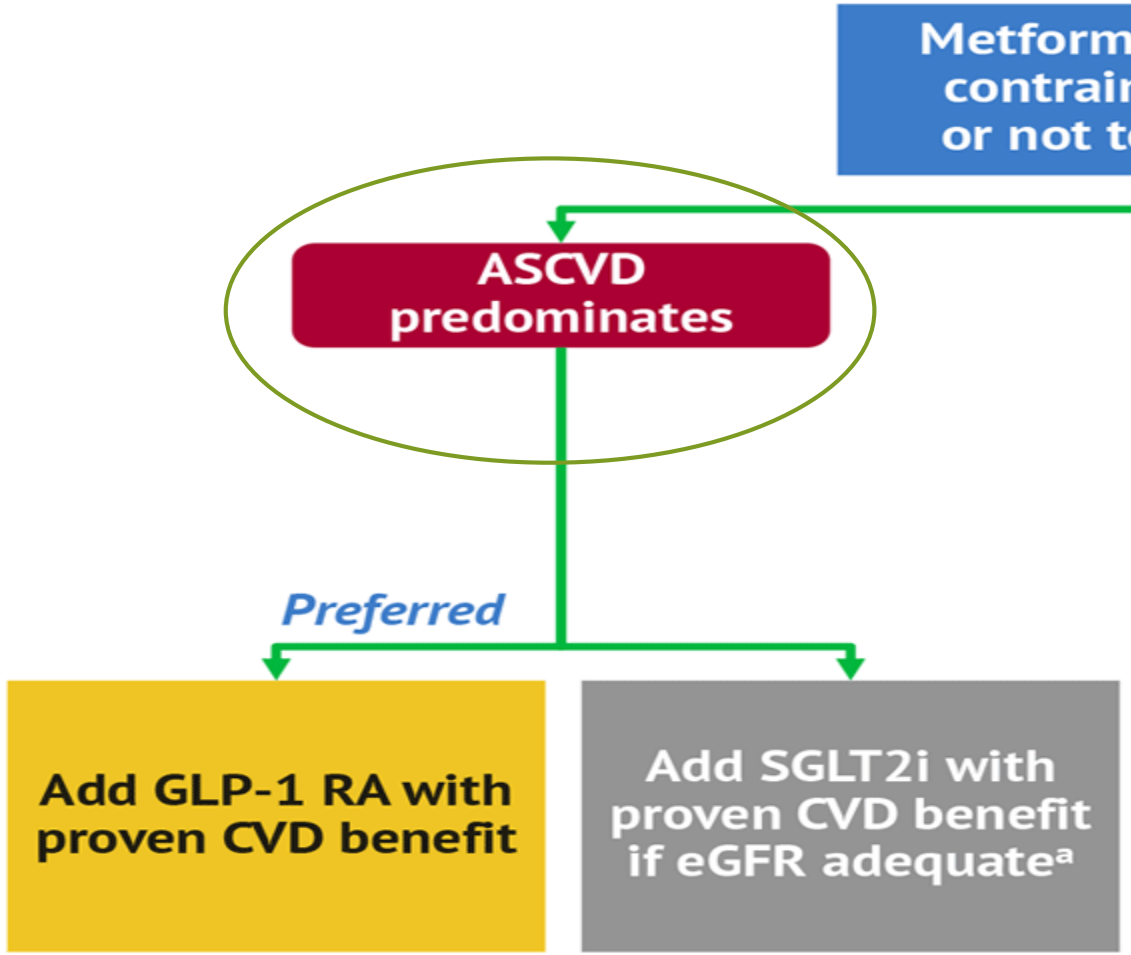
- For patients with established ASCVD or indicators of high ASCVD risk (such as patients>55 years of age with coronary, carotid, or lower-extremity artery stenosis > 50% or left ventricular hypertrophy), heart failure, or CKD

An SGLT2-I or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose lowering regimen independent of A1C, independent of metformin use, and in consideration of patient-specific factors

ADA Guidelines: Glucose-Lowering Medications in Patients at High Risk[4]

Second senario

MR A.M



64 year old male

DM2 since 2015

HAD ACS , PTCA in 2020

TX for glucose

Metformin 1000 BD

HbA1c 6,9

Add a GLP1RA

[a] SGLT1i labeling varies by region and individual agent with regard to indicated level of eGFR.

Conclusions -1

- Metformin possesses many of the features expected of an ideal OAD; it is safe, effective, cheap, pairs well with most other agents with little to no adverse interaction and is available globally.

- It is unlikely that dedicated prospective trials looking at MACE outcomes to fully elucidate the cardiovascular benefits realized in experimental models and observational data will ever happen and metformin's current role as a "foundation therapy" for newly diagnosed individuals with T2D may continue to be both justified and equally challenged.

Florez, J.C. The pharmacogenetics of metformin. Diabetologia **2017**, 60, 1648–1655.

Conclusions-2

- There is an increasing emphasis to transition existing algorithms from an approach based solely on HbA1c to a more comprehensive strategy targeting additional patient factors especially CVD prevention.

- Until further safety data becomes available for SGLT2i and GLP-1RA use in treatment-naïve individuals, we recommend that not only the efficacy but also the cost and the long-term safety profile should guide decisions in clinical practice and metformin should continue to be used as a first-line therapy for newly diagnosed individuals with T2D

Conclusions-3

- The key message is to avoid therapeutic inertia, as the uptake of these "newer" OADs with proven cardiovascular benefits remains generally low and to consider early addition of these agents to baseline metformin therapy where indicated.