Individualizing the Glycemic Goals

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American Board of Clinical Lipidology

Disclosures

- Dr. Michelle Mangual, endocrinologist, declares that she serves as a speaker and/or consultant for the following pharmaceutical companies: ***Eli Lilly and Astra Zeneca.***

Objectives

- Discuss the evidence from the intensive glycemic control trials and observational studies.
- The history of the target of less than 7%.
- Glycemic goals in patients with multiple comorbidities.
- Drug selection in patients with ASCVD or heart failure.
- Glycemic goals in older patients with diabetes.

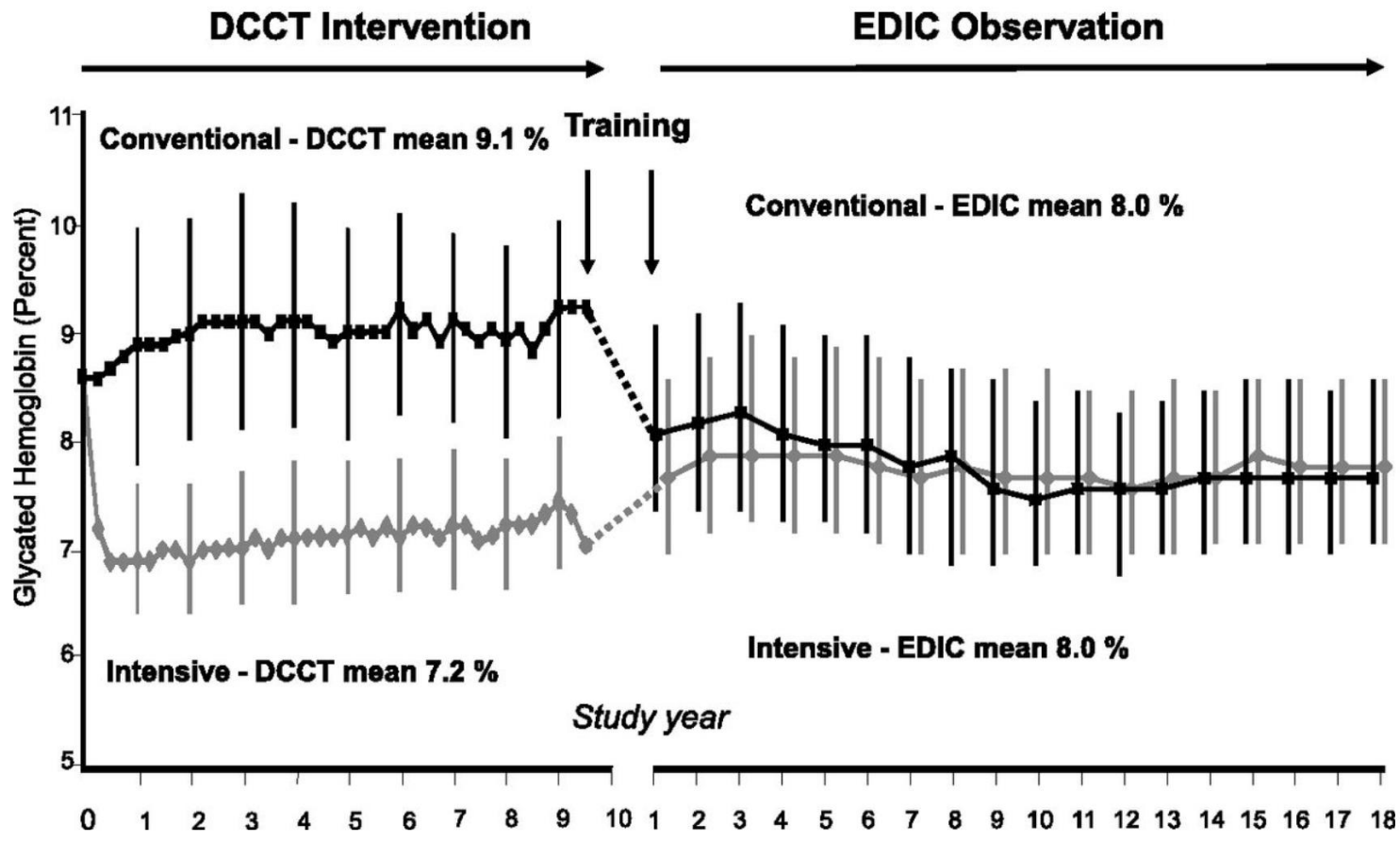
The evidence from trials and observational study

- Diabetes Control and Complications Trial

  (DCCT; 1441 participants with type 1 diabetes duration <15 years)
- The goal was to achieve glycemic control as close to normal without causing adverse events versus asymptomatic glycemic control.
- Contrast achieved: A1c ~7% versus ~9% over ~6.5 years.

A1c during DCCT and EDIC

A1c (%)

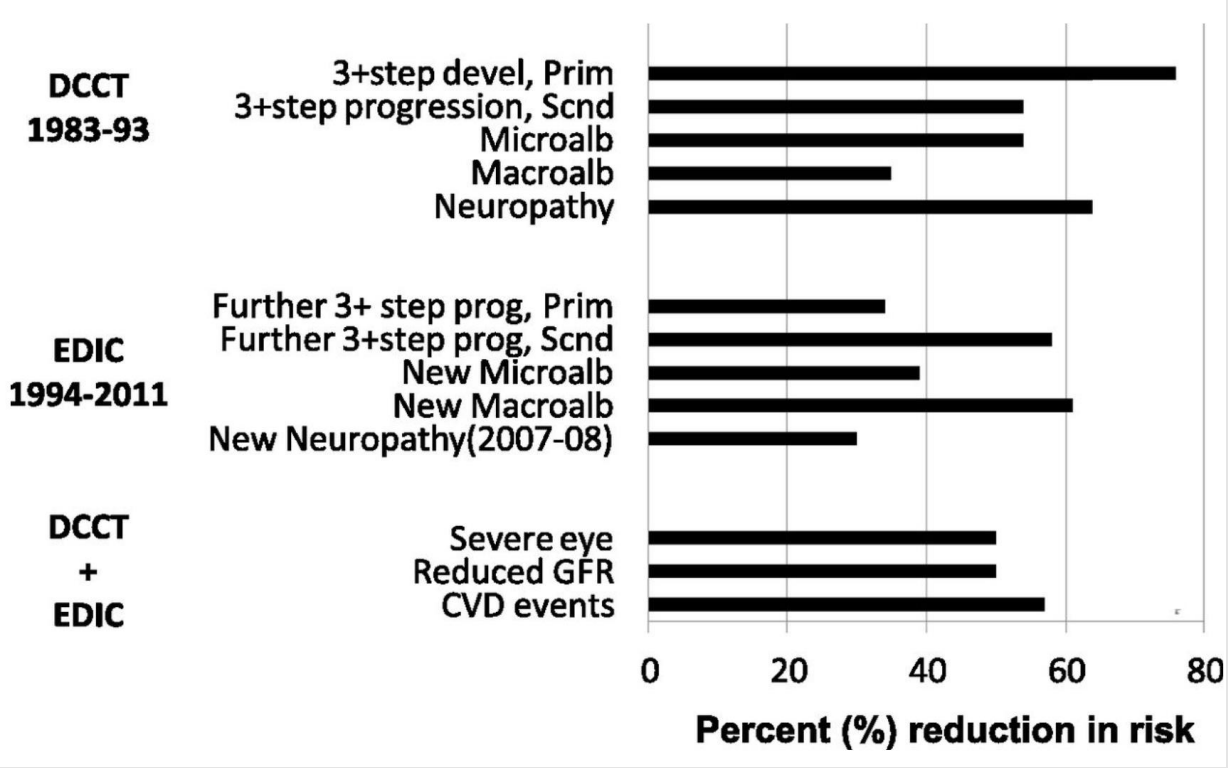


EDIC= Epidemiology of Diabetes Interventions and Complications

After the trial, 96% enrolled in follow-up. A1c converged at 8%.

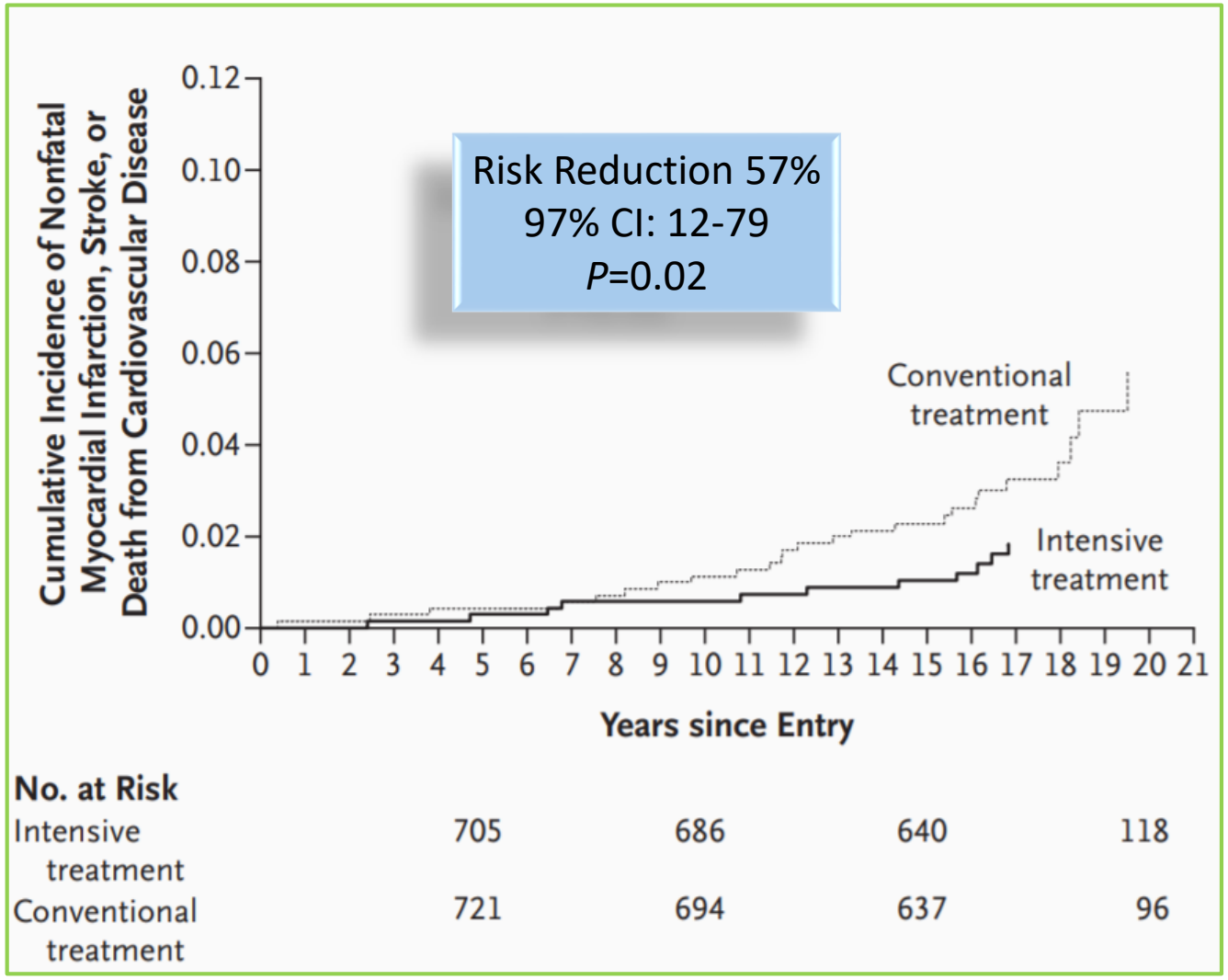
Nathan, D. Diabetes 2013;62:3976–3986.

Reduction in major complications with intensive compared with Conventional during DCCT and EDIC



- At 6 years, 3 step progression of retinopathy was reduced 76%, new or progression of albuminuria was reduced 50%, neuropathy reduced 60%.
- Long term benefits over ~30 years of follow-up included 56% reduction in retinopathy, 50% reduction in nephropathy, 30% reduction in neuropathy.

DCCT/EDIC: Cumulative incidence of the first occurrence of non-fatal MI, stroke, or CV death.



Nathan DM, et al. N Engl J Med. 2005. 353;25

The evidence from trials and observational study

United Kingdom Prospective Diabetes Study

(UKPDS: 4,209 participants with new onset type 2 diabetes and FBG>108 mg/dl after 3-month dietary run in)

- Standard policy (treat for symptoms or glucose >270 mg/dl) vs intensive policy (treat with SU, insulin or metformin)
- Mean A1c contrast achieved ~7% vs ~7.9% over ~10 years.
- Clinically meaningful endpoints improved at end of randomized period.
- Additional ten years of off-trial follow-up, “Legacy Effect”

UKPDS: "Legacy Effect" of insulin or sulfonylurea therapy

After median 8.8 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.009	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

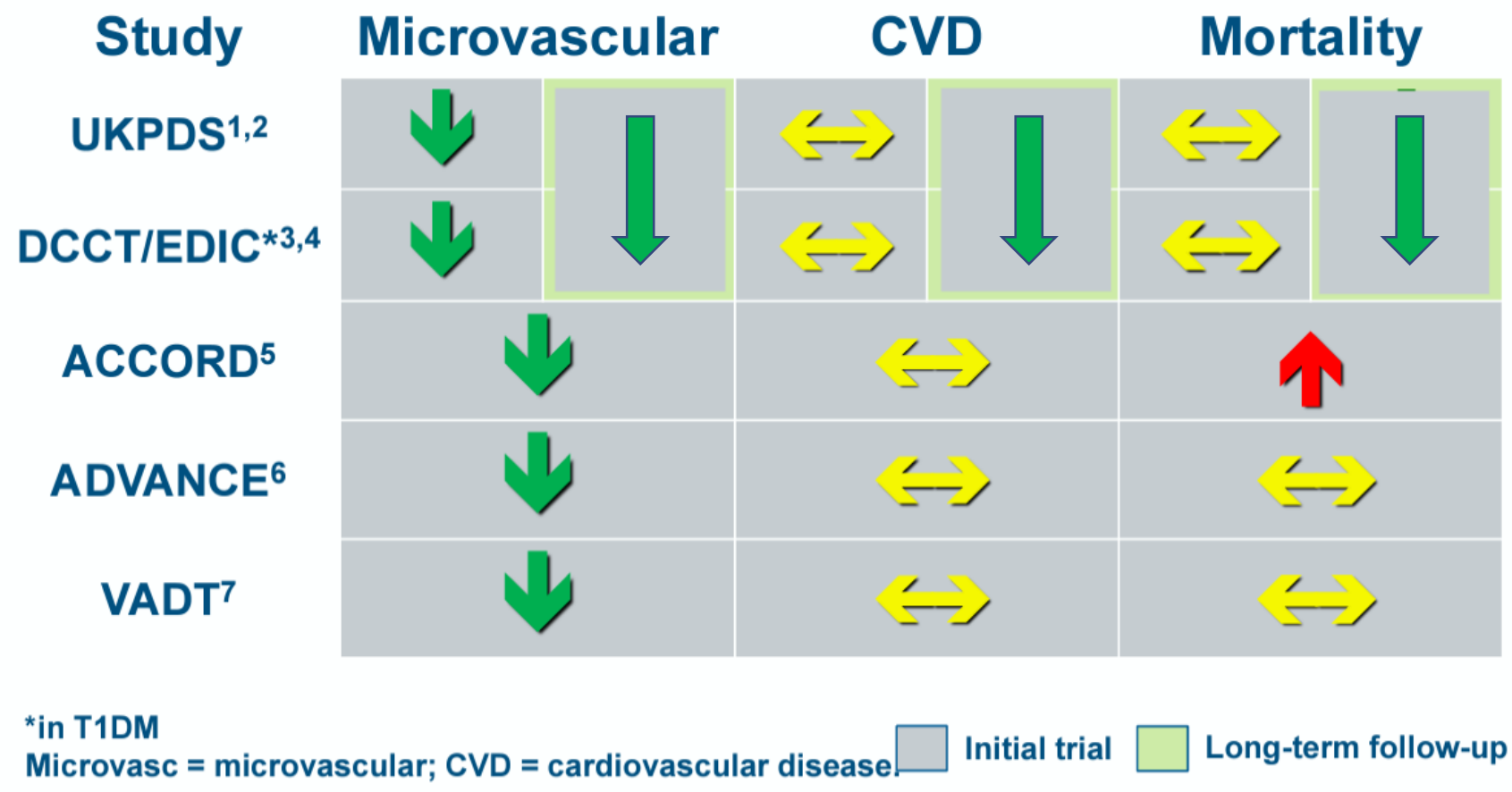
Holman, RR. et al. N Engl J Med 2008; 359:1577-1589

Study, Patient and HbA1c Characteristics of 5 RCTs

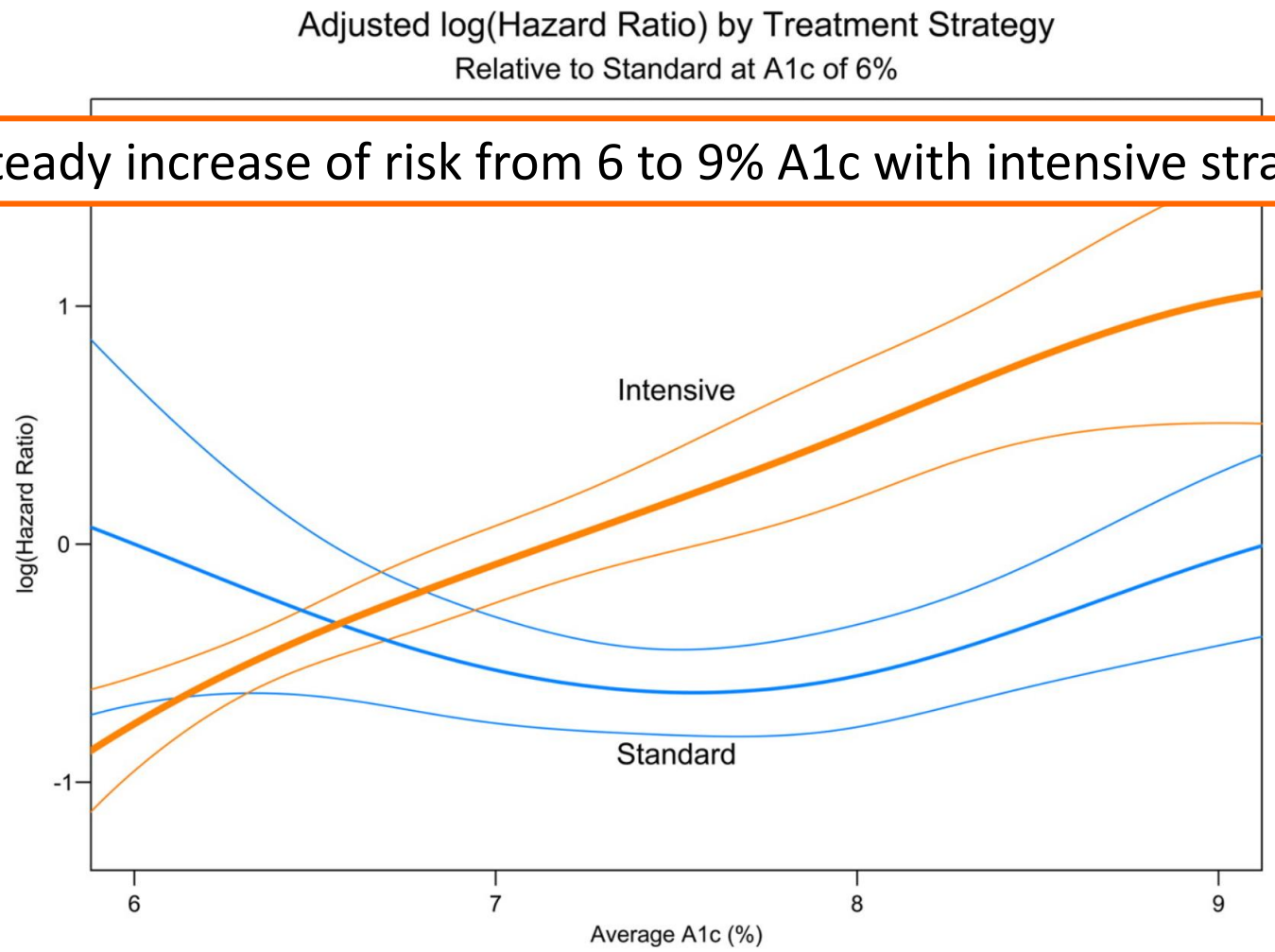
Summary of Major Clinical Trials

Trial Name, Mean or median FU, number enrolled	Age ; Baseline	Diabetes Duration	HbA1c; Baseline (median)	HbA1c Achieved Intensive vs Control
ACCORD 4-5 years; N=10,251	62 years	10 years	8.1%	6.4% vs 7.5%
ADVANCE 5-11 years; N=11,140	66 years	8 years	7.8%	6.4% vs 7.0%
UKPDS 33 (Insulin/SU) 11-17 years; N=3,867	54 years	Newly Dx	7.0%	7.0% vs 7.9%
UKPDS 34 (metformin) 11-18 years; N=753	53 years	Newly Dx	7.2%	7.4% vs 8.4%
VADT 6-12 years; N=1,791	60 years	12 years	9.4%	6.9% vs 8.4%

Impact of Intensive Therapy for Diabetes



ACCORD: Risk of Death over a Range of Mean A1c

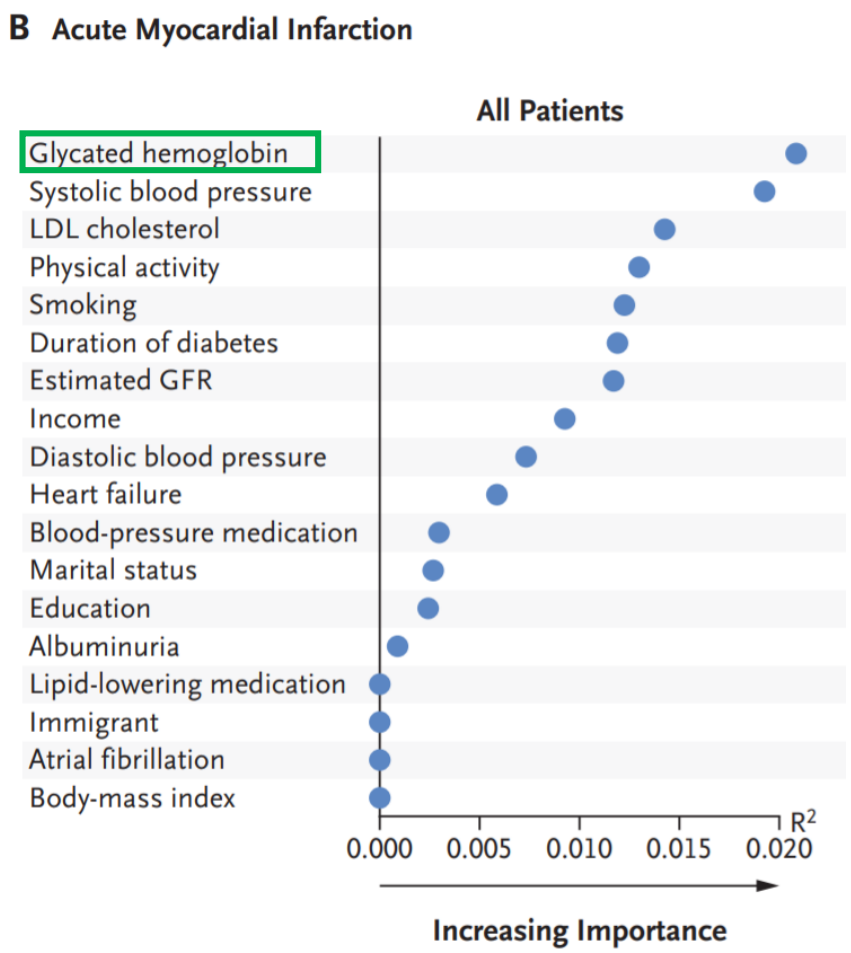


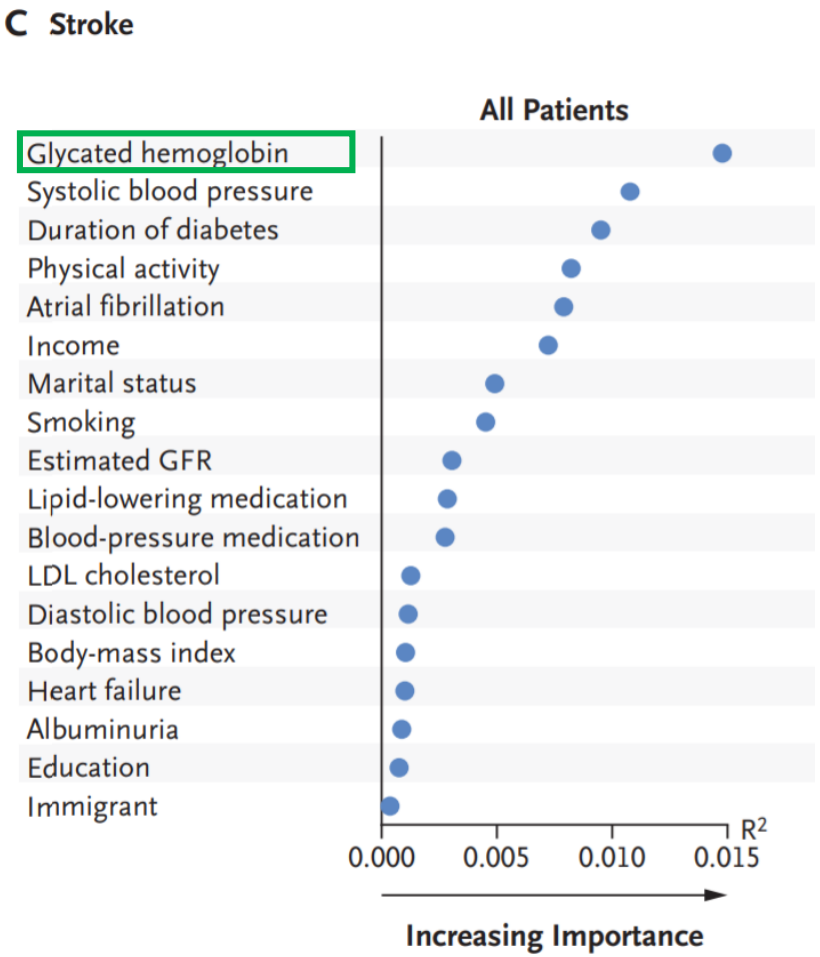
Steady increase of risk from 6 to 9% A1c with intensive strategy

Excess risk of mortality with intensive strategy occurred above an A1c 7%

Riddle et al. Diabetes Care 33:983–990, 2010

Epidemiological analysis: Relative importance of risk factors for acute myocardial infarction and stroke

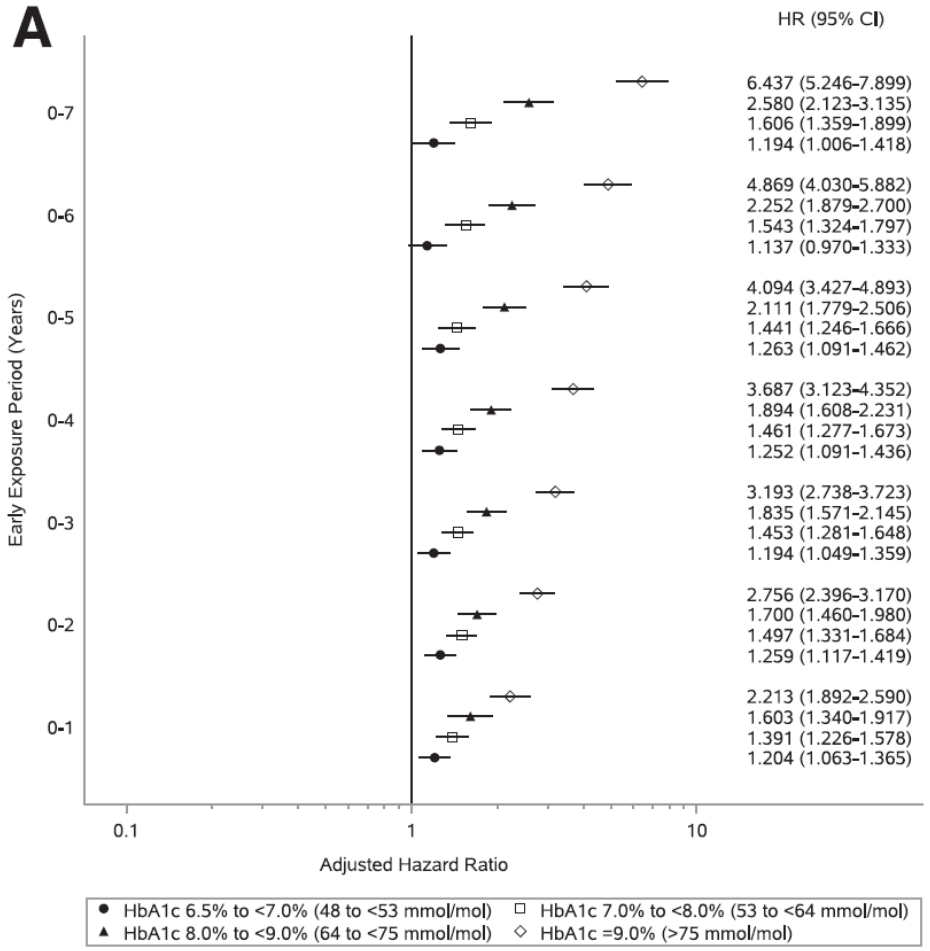




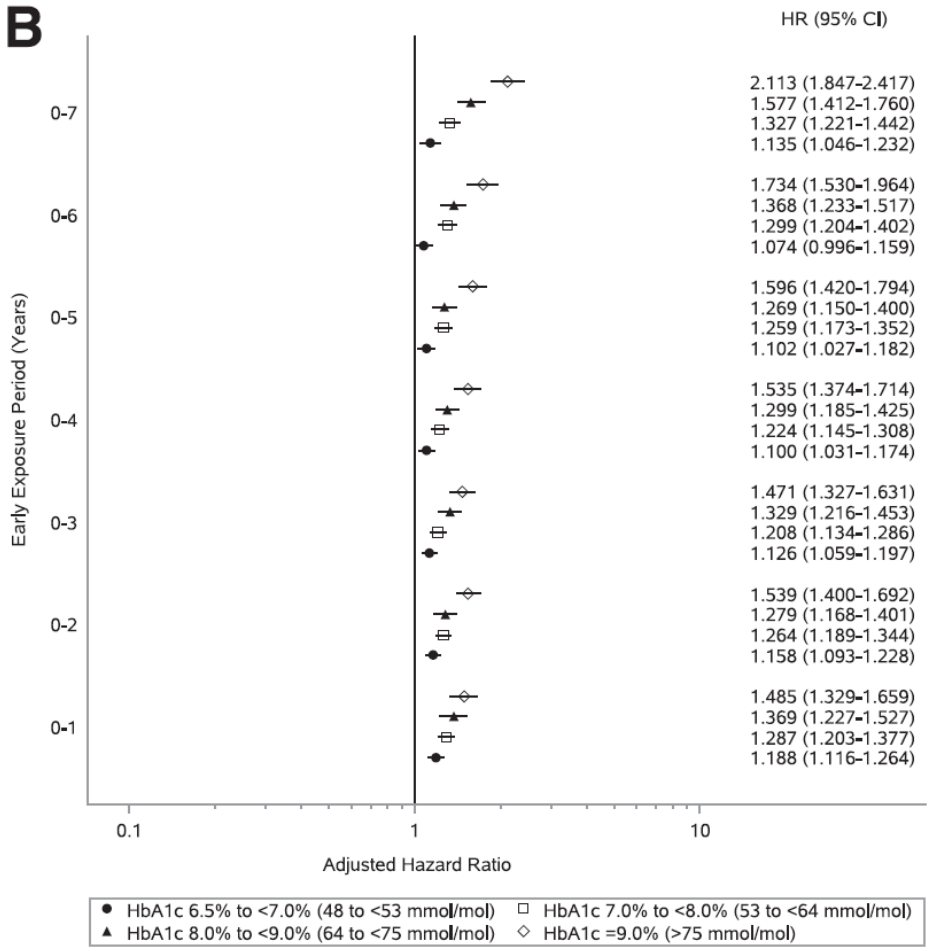
Rawshani, A. et al. N Engl J Med 2018;379:633-44

Epidemiological Analysis: Early glycemic control matters

Microvascular



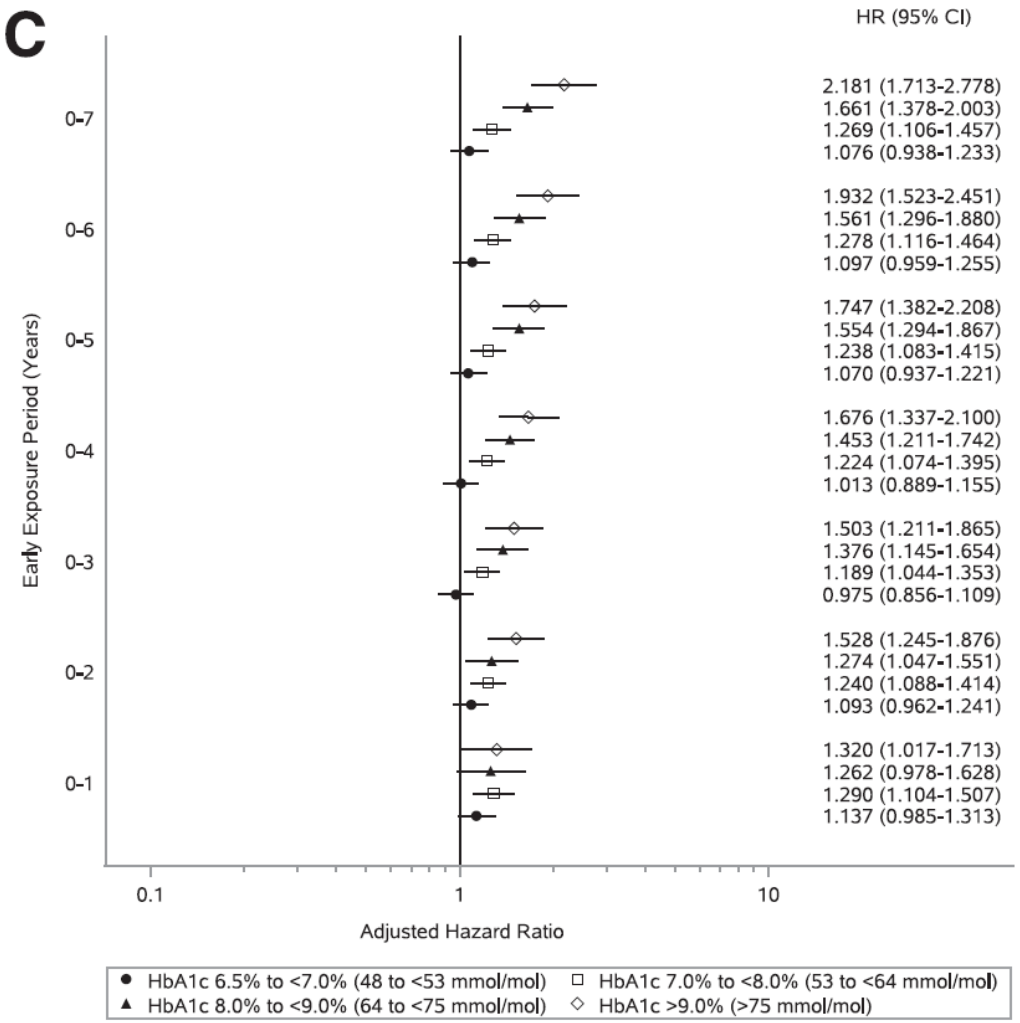
Macrovascular



Laiteerapong, N. et al. Diabetes Care 2019;42:416–426

Epidemiological Analysis: Early glycemic control matters

Mortality



- "Among patients with newly diagnosed diabetes and 10 years of survival, HbA1c levels ≥6.5%for the 1st year after diagnosis were associated with worse outcomes. Immediate, intensive treatment for newly diagnosed patients may be necessary to avoid irremediable long-term risk for diabetic complications and mortality."

Laiteerapong, N. et al. Diabetes Care 2019;42:416–426

Standards of Medical Care in Diabetes
First publication of the A1c goal <7% was in 1994

Table 1—Glycemic control for people with diabetes

Biochemical index	Nondiabetic	Goal	Action suggested
Preprandial glucose	<115	80–120	<80 >140
Bedtime glucose (mg/dl)	<120	100–140	<100 >160
Hemoglobin A_{1c} (%)	<6	<7	>8

These values are for nonpregnant individuals. "Action suggested" depends on individual patient circumstances. Hemoglobin A_{1c} is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, standard deviation 0.5%).

Standards of Medical Care in Diabetes
In 1997, modified to indicate “action suggested >8%”

Table 1—*Glycemic control for people with diabetes*

Biochemical index	Nondiabetic	Goal	Action suggested
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Bedtime glucose (mg/dl)	<120	100–140	<100 >160
Hemoglobin A_{1c} (%)	<6	<7	>8

These values are for nonpregnant individuals. “Action suggested” depends on individual patient circumstances. Such actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation or increased SMBG, or more frequent contact with the patient. HbA_{1c} is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, SD 0.5%).

Standards of Medical Care in Diabetes Since 2003, the A1c goal has been <7%

Table 6—*Summary of recommendations for adults with diabetes mellitus*

Glycemic control	
A1C	<7.0%*
Preprandial plasma glucose	90–130 mg/dl (5.0–7.2 mmol/l)
Peak postprandial plasma glucose	<180 mg/dl (<10.0 mmol/l)
Blood pressure	<130/80 mmHg
Lipids	
LDL	<100 mg/dl (<2.6 mmol/l)
Triglycerides†	<150 mg/dl (<1.7 mmol/l)
HDL	>40 mg/dl (>1.1 mmol/l)‡

Key concepts in setting glycemic goals:

- Goals should be individualized
- Certain populations (children, pregnant women, and elderly) require special considerations
- Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia
- More intensive glycemic goals may further reduce microvascular complications at the cost of increasing hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥200 mg/dl, the "non-HDL cholesterol" (total cholesterol minus HDL) be utilized. The goal is ≤130 mg/dl (53). ‡For women, it has been suggested that the HDL goal be increased by 10 mg/dl.

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CLINICAL GUIDELINE

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Devan Kansagara, MD, MCR; Carrie Horwitch, MD, MPH; Michael J. Barry, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

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Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

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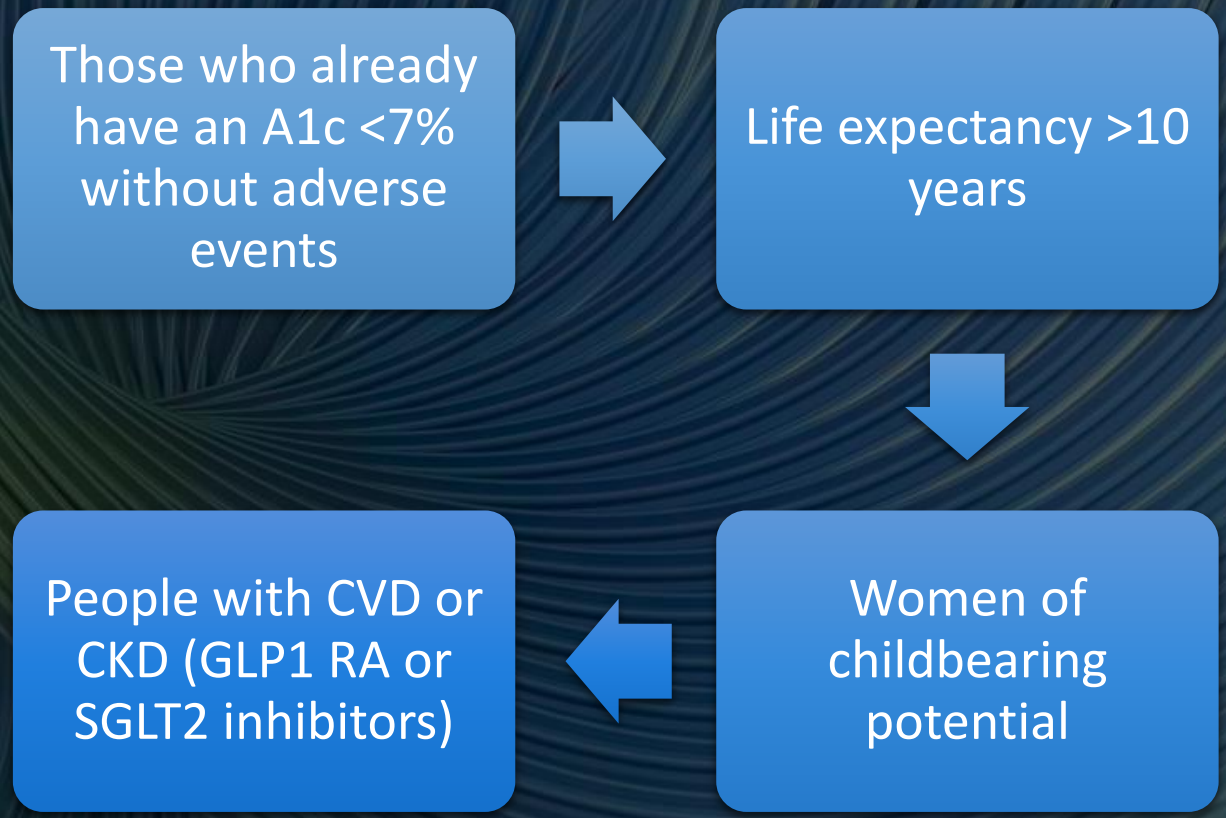
Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Who are “the many” in “a reasonable A1c goal for many nonpregnant adults is <7%”?



A changing paradigm in caring for patients with type 2 diabetes and clinical CVD

Medication	NNT to prevent a Death
Statins (for 5 years)	100
Anti-hypertensives (for 5 years)	125
Empagliflozin (for 3 years)	39
Liraglutide (for 3 years)	98

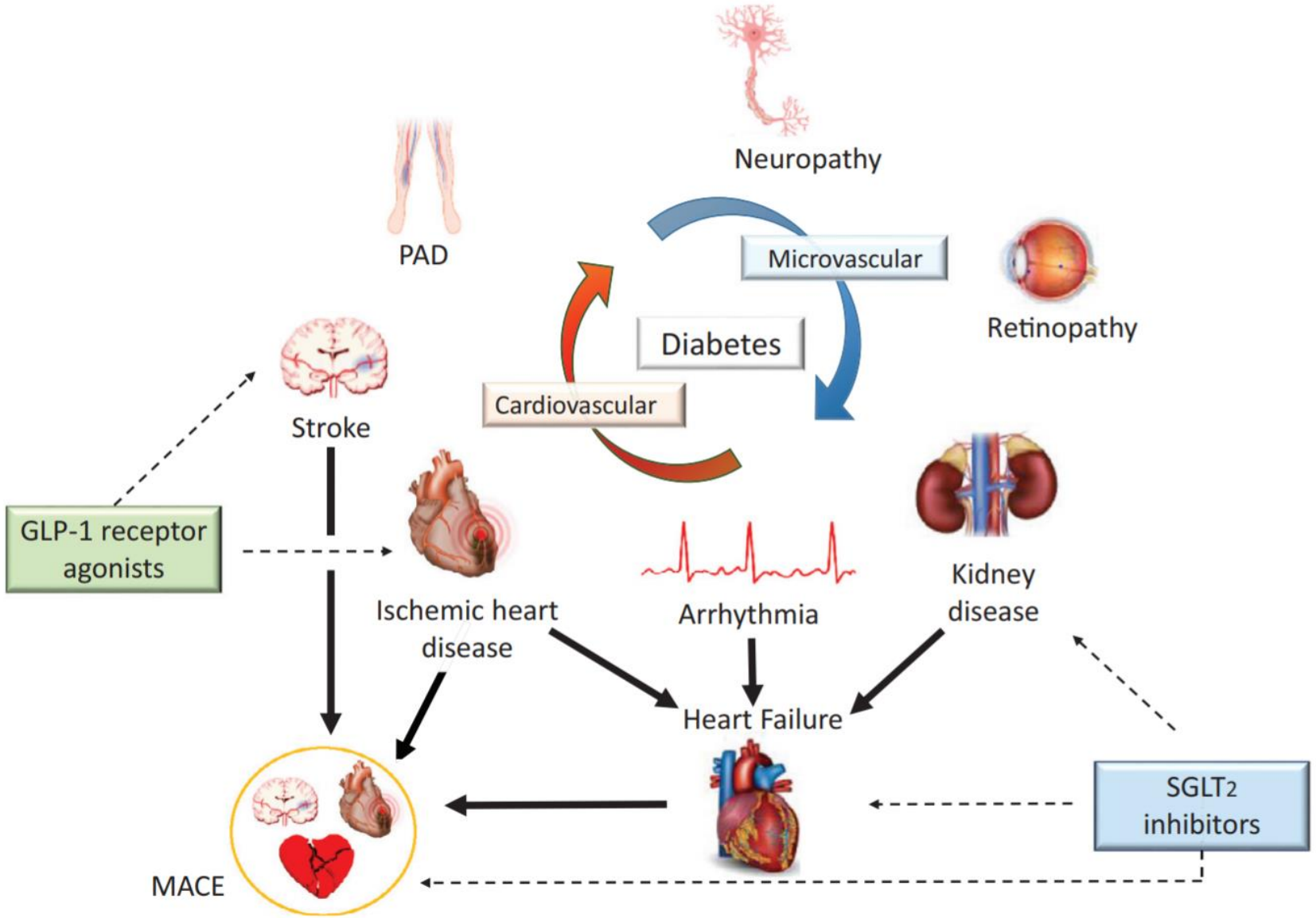
These benefits of GLP-1 receptor agonists and SGLT2 inhibitors emerged in trials were the drugs were added (versus placebo) in patients with CVD and an A1c >7%.

Krumholz, H and Lipska, K. JAMA. 2017 March 14; 317(10): 1017–1018

Drug Selection in people with ASCVD or heart failure

The new era of antidiabetic medications

The major goal of diabetes management is to prevent its complications.



Kato, ET, et al. Trends in Cardiovascular Medicine. January 22, 2020;15:55

FDA-Mandated CV Outcomes Trials in T2DM

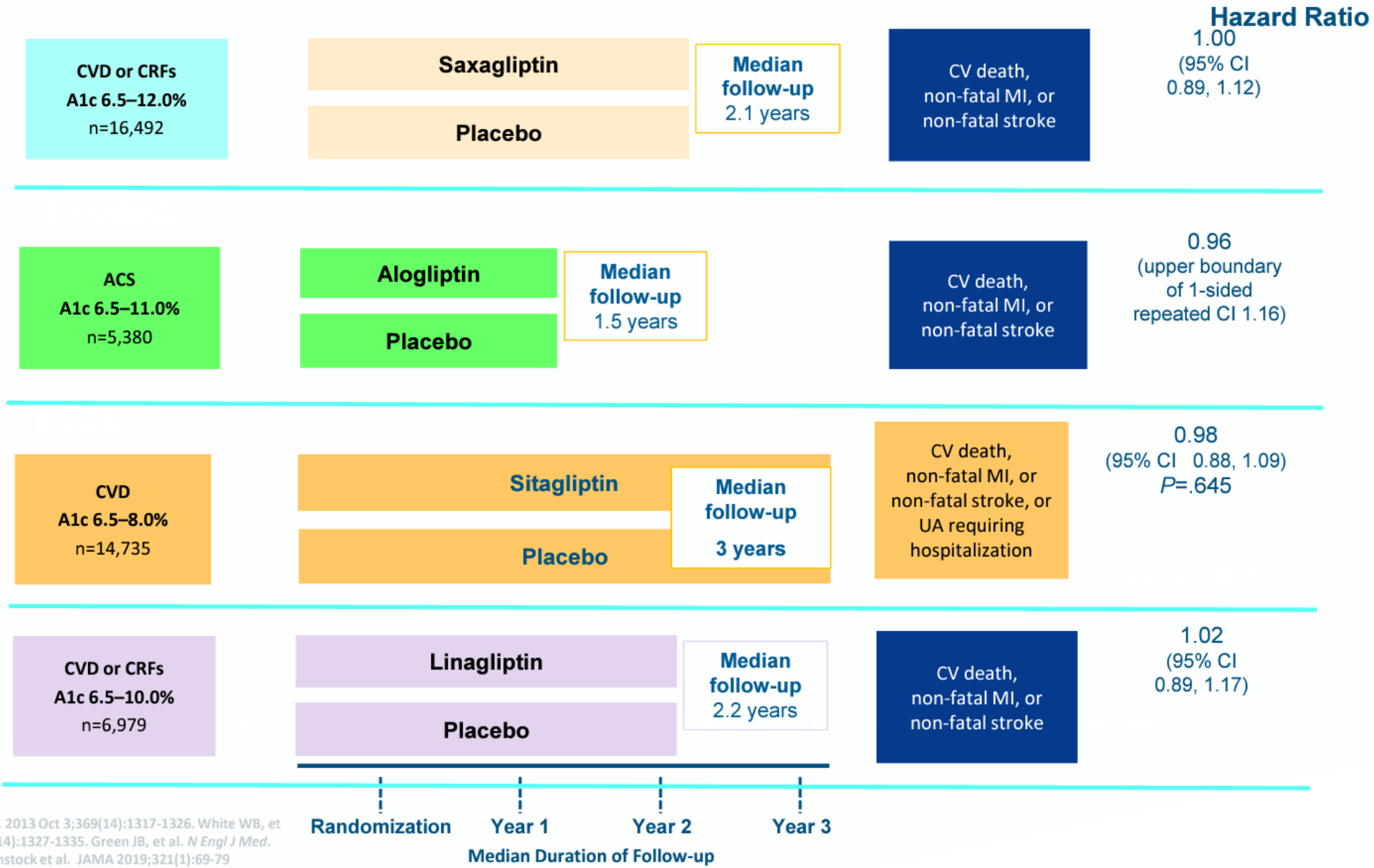
Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	placebo	glimepiride (SU)
N	16,492	5380	14,671	6979	6103
Results	2013	2013	2015	2018	2018

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LR	dulaglutide	albiglutide
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	6068	9340	3297	14,752	9901	9463
Results	2015	2015	2016	2017	2018	2018

Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7020	4330	4401	17,160	8246
Results	2015	2017	2018	2018	2020

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13. NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

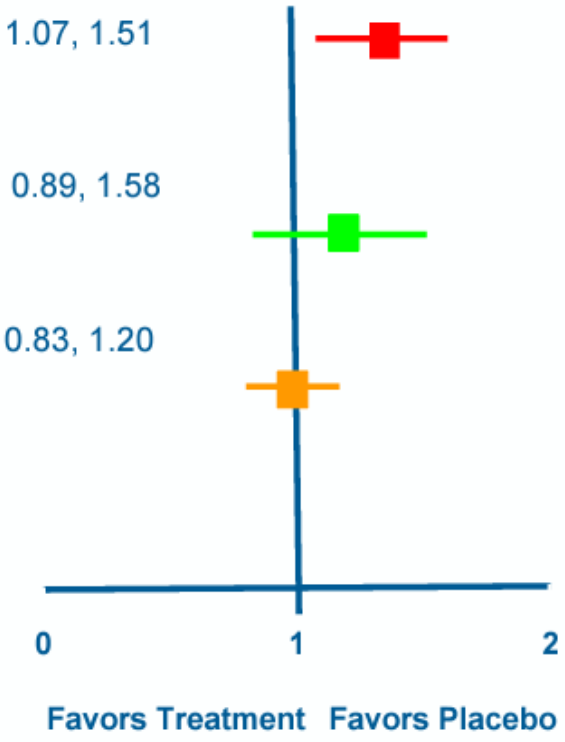
Cardiovascular Outcome Trials for DPP4 Inhibitors



Scirica, BM, et al. *New Eng J Med.* 2013 Oct 3;369(14):1317-1326. White WB, et al. *N Engl J Med.* 2013 Oct 3;369(14):1327-1335. Green JB, et al. *N Engl J Med.* 2015 Jul 16;373(3):232-242. Rosenstock et al. JAMA 2019;321(1):69-79

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

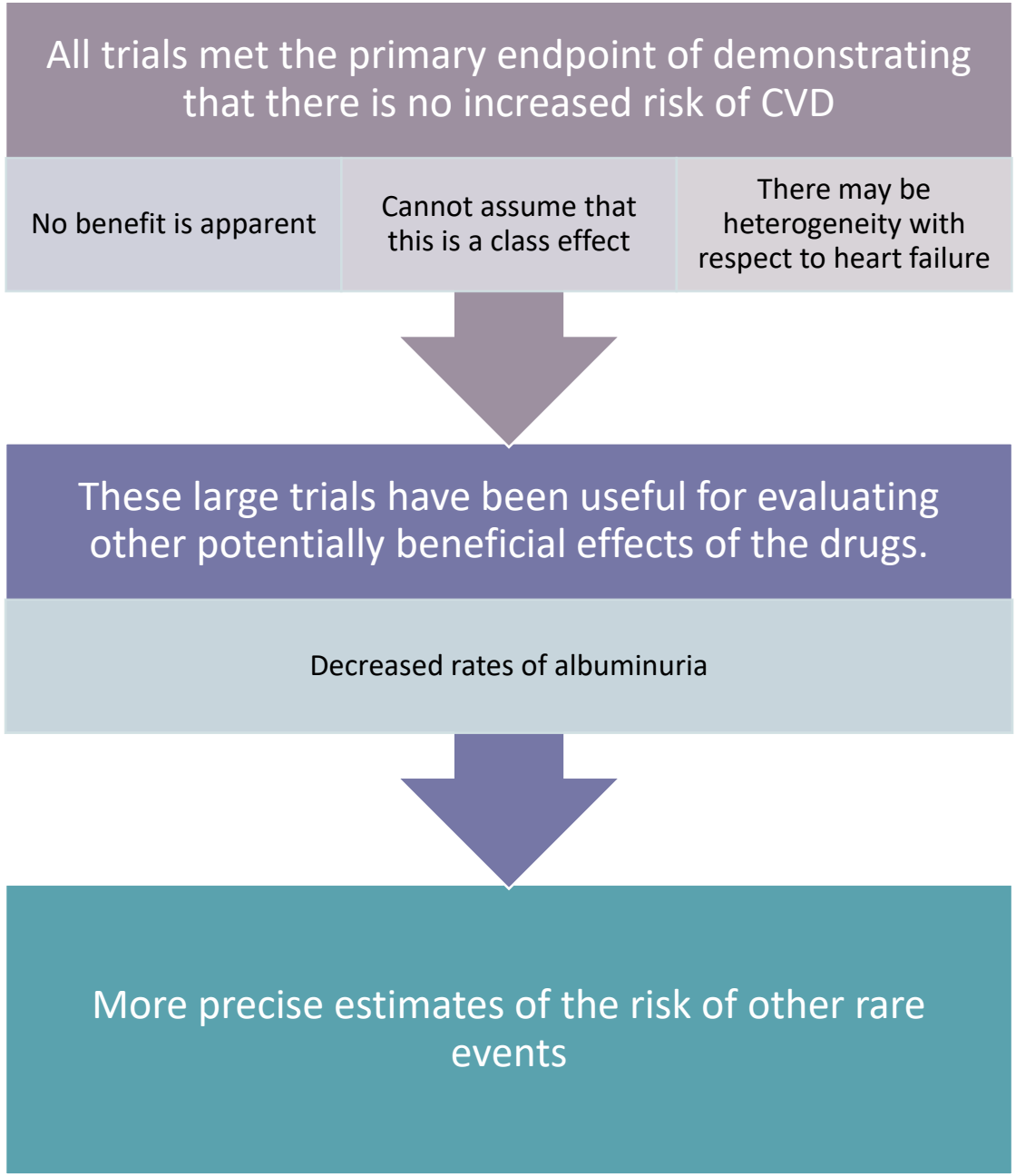
	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P* Value
SAVOR-TIMI (saxagliptin vs placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51	.009*
EXAMINE (alogliptin vs placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58	.238
TECOS (sitagliptin vs placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20	.983



*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.

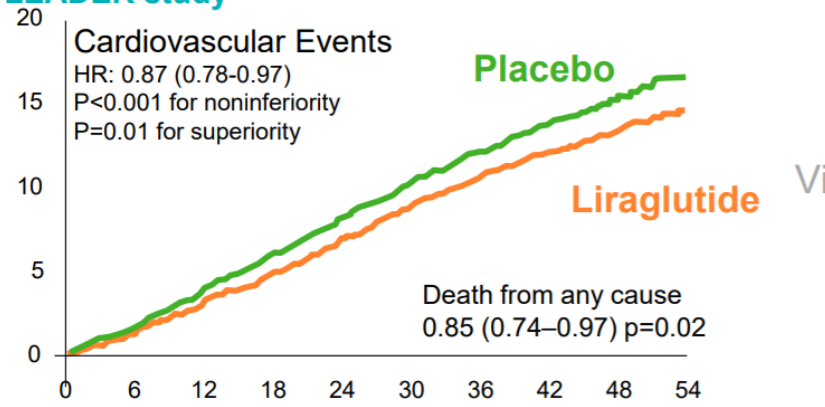
Scirica, BM, et al. *New Engl J Med*. 2013 Oct 3;369(14):1317-1326. White WB, et al. *N Engl J Med*. 2013 Oct 3;369(14):1327-1335. Green JB, et al. *N Engl J Med*. 2015 Jul 16;373(3):232-242.

Summary: DPP4-Inhibitors Cardiovascular Outcome Trials



Cardiovascular benefits of GLP-1 analogs

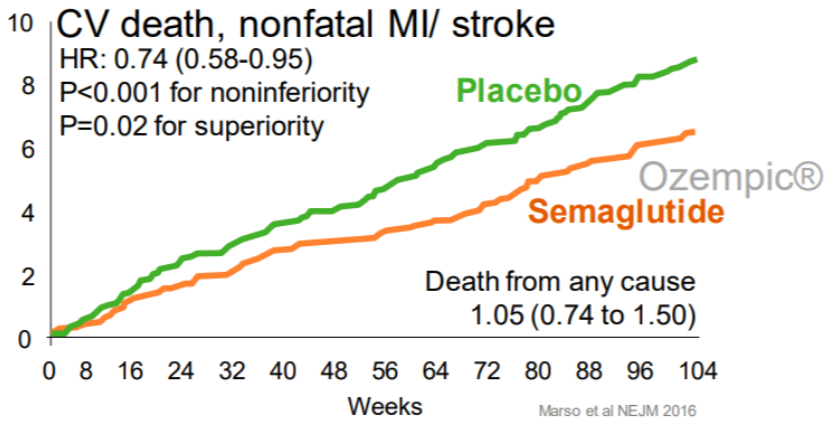
Liraglutide
LEADER study



Victoza®

Marso et al NEJM 2016

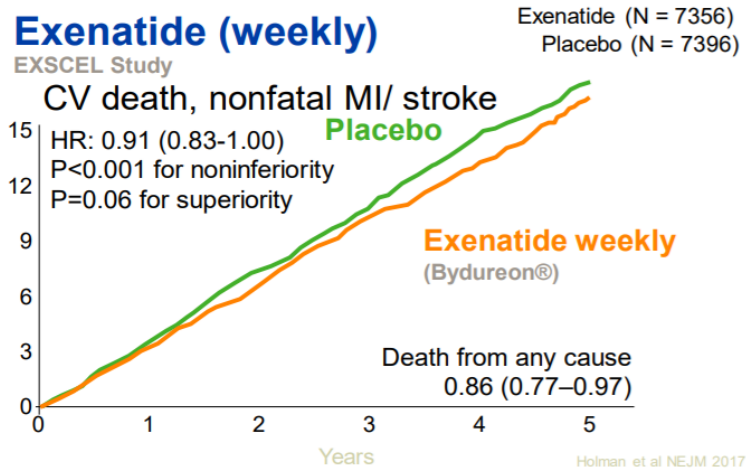
Semaglutide
SUSTAIN-6



Ozempic®

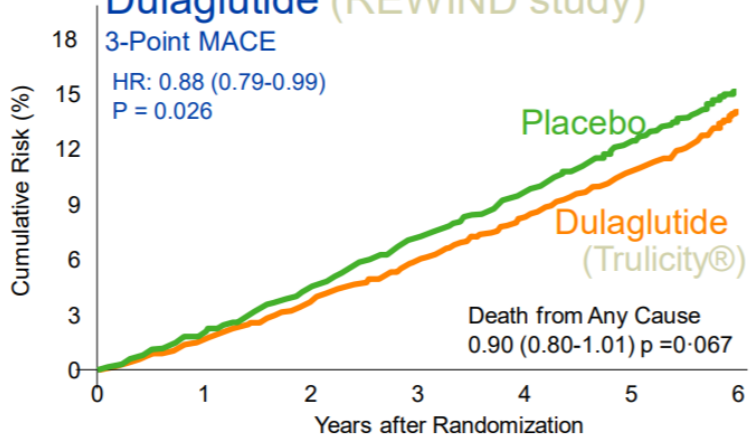
Marso et al NEJM 2016

Exenatide (weekly)
EXSCEL Study



Holman et al NEJM 2017

Dulaglutide (REWIND study)
3-Point MACE

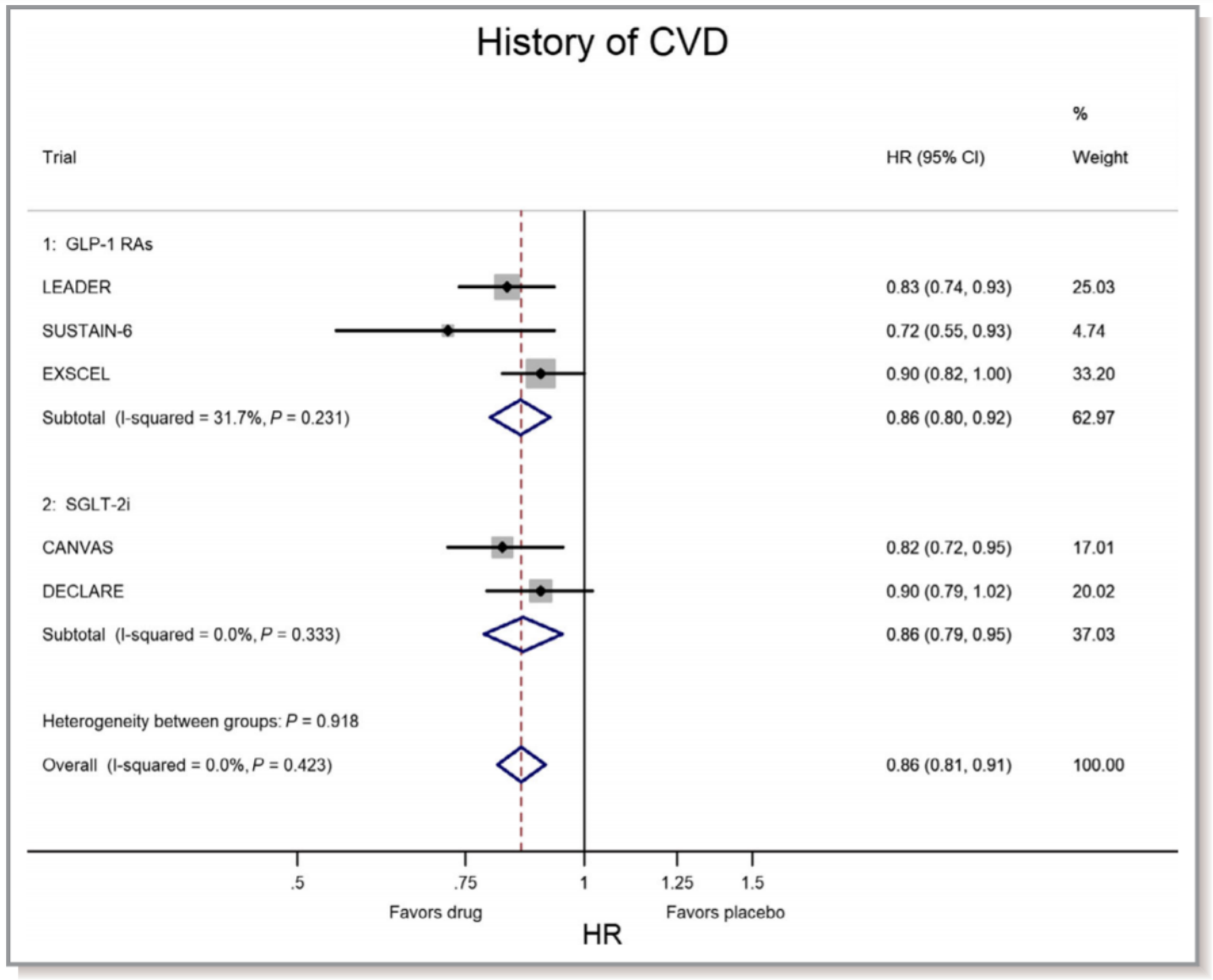


Gerstein et al *Lancet* 2019

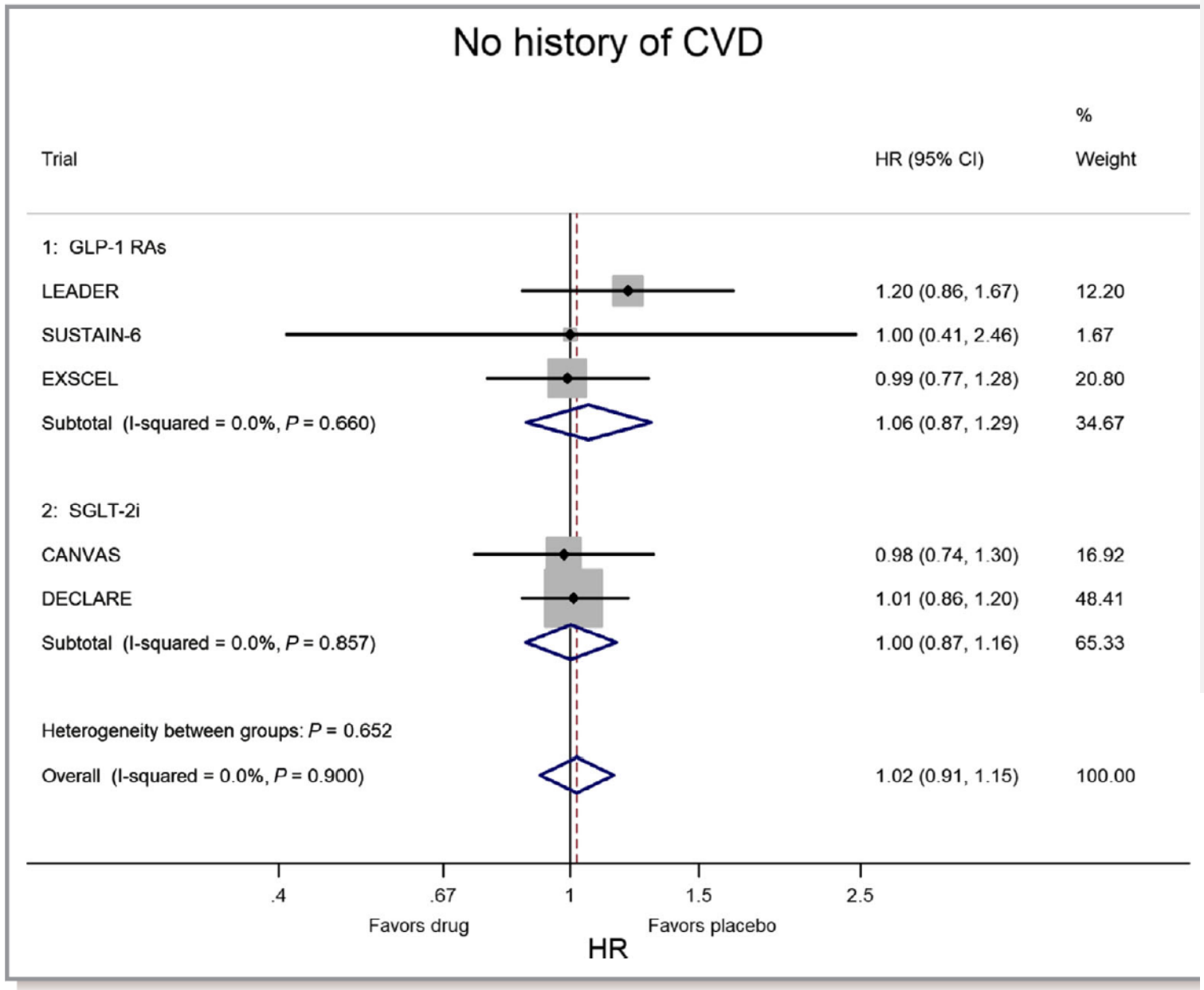
Cardiovascular Benefits of GLP-1 RA

GLP1 receptor agonists

	LEADER	EXSCEL	SUSTAIN-6	ELIXA	Harmony	REWIND
	Liraglutide	Exenatide (MR)	Semaglutide (s.c.)	Lixisenatide	Albiglutide	Dulaglutide
Sample size	9340	14,752	3297	6068	9463	9901
ASCVD%	72.5	73.1	83.0	100	100	31.5
Median fu (yr)	3.8	3.2	2.1	2.1	1.6	5.4
Hx of HF	1305	2389	777	1922	NA	853
eGFR <60 (%)	23.1	21.6	24.0	23.2	23.0	22.2
MACE	0.87 (0.78, 0.97)	0.91 (0.83, 1.00)	0.74 (0.58, 0.95)	1.02 (0.89, 1.17)	0.78 (0.68, 0.90)	0.88 (0.79, 0.99)
CV Death	0.78 (0.66, 0.93)	0.88 (0.76, 1.02)	0.98 (0.65, 1.48)	0.98 (0.78, 1.22)	0.93 (0.73, 1.19)	0.91 (0.78, 1.06)
MI	0.88 (0.75, 1.03)	0.97 (0.85, 1.10)	0.74 (0.51, 1.08)	1.03 (0.87, 1.22)	0.75 (0.61, 0.90)	0.96 (0.79, 1.16)
Stroke	0.89 (0.72, 1.11)	0.85 (0.70, 1.03)	0.61 (0.38, 0.99)	1.12 (0.79, 1.58)	0.86 (0.66, 1.14)	0.76 (0.62, 0.94)
hHF	0.87 (0.73, 1.05)	0.94 (0.78, 1.13)	1.11 (0.77, 1.61)	0.96 (0.75, 1.23)	0.85 (0.70, 1.04)	0.93 (0.77, 1.12)
All Death	0.85 (0.74, 0.97)	0.86 (0.77, 0.97)	1.05 (0.74, 1.50)	0.94 (0.78, 1.13)	0.95 (0.79, 1.16)	0.90 (0.80, 1.01)
Kidney Endpoint		NA	NA	NA	0.88 (0.74, 1.05)	0.85 (0.77, 0.93)

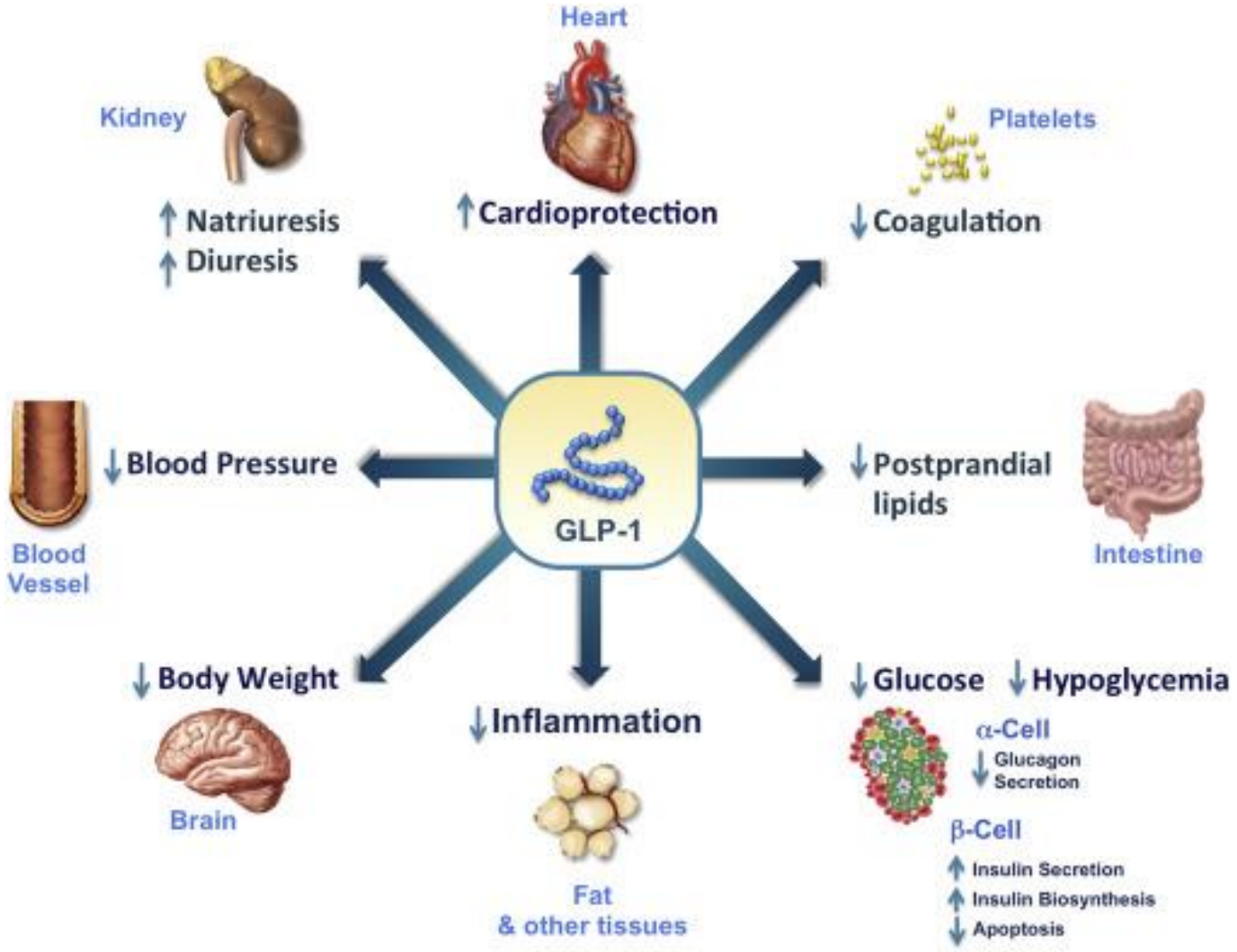


Meta-analysis of 5 CVOTs (3 with GLP-1 RAs and 2 with SGLT-2i) in patients with history of CVD at baseline.



Meta-analysis of the 5 CVOTs in patients without history of CVD at baseline.

Proposed mechanisms of CV benefits of GLP-1 receptor agonists



Drucker, D. Cell Metabolism.2016. Volume 24, Issue 1:15-30

FDA has granted Liraglutide, Semaglutide, and Dulaglutide Additional CV Indications

In adults with T2DM + established CVD…

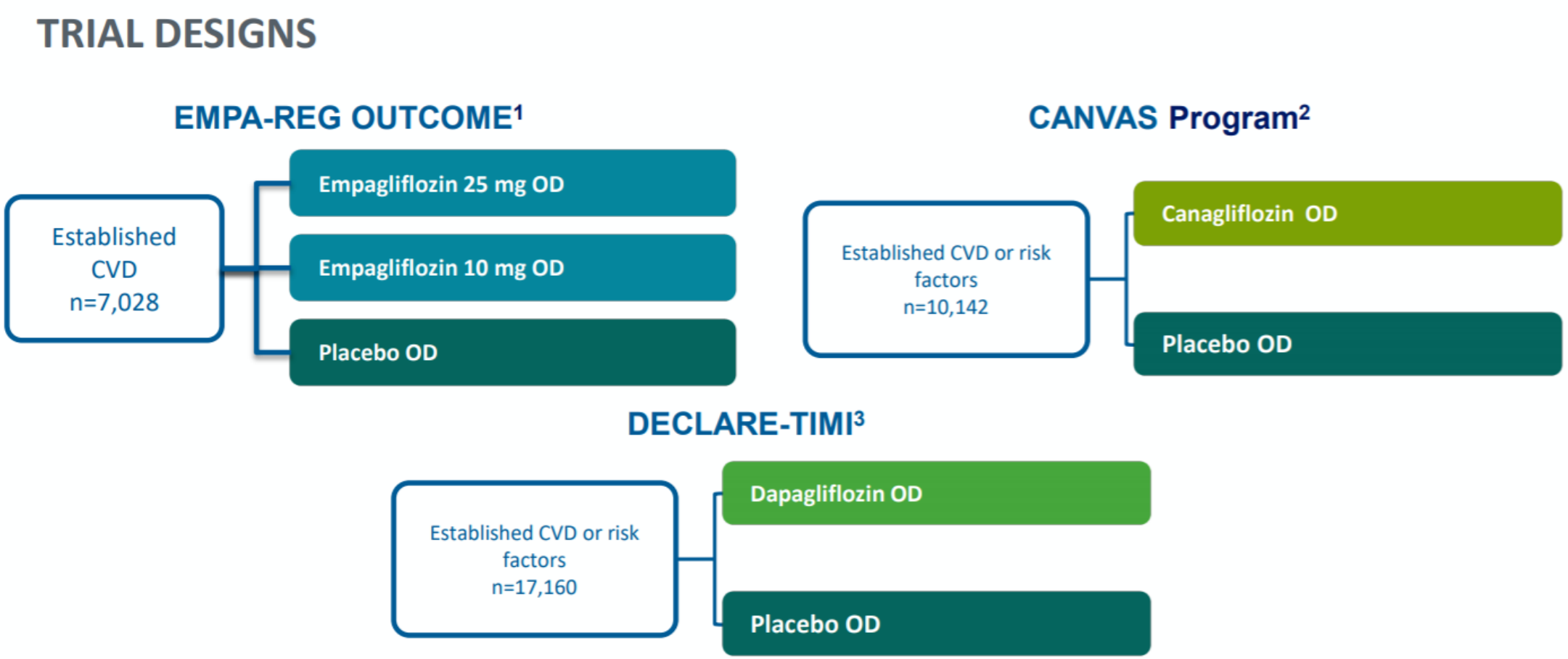
Liraglutide → ↓ MACE

Semaglutide → ↓ MACE

In adults with T2DM + established CVD or high CV risk

Dulaglutide → ↓ MACE

CVOTs with SGLT2 inhibitors



Zinman B et al. N Engl J Med 2015;373:2117–2128; 2. Neal B et al. N Engl J Med 2017;377:644–657.
3. Wiviott SD et al. New Engl JMed 2019380:347–357.

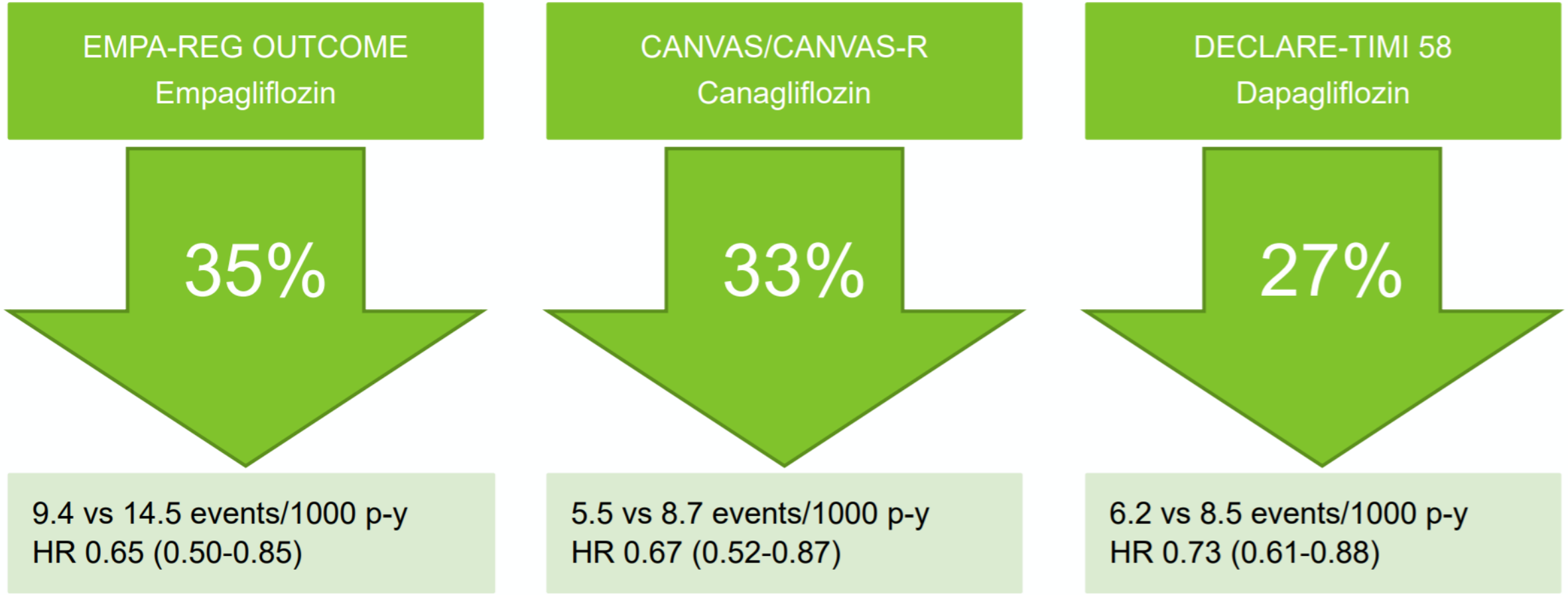
SGLT2 Inhibitors Reduce CV Risk

	Empagliflozin (EMPA-REG)[1]	Canagliflozin (CANVAS)[2]	Dapagliflozin (DECLARE-TIMI 58)[3]	Ertugliflozin (VERTIS CV)[4]
MACE*	↓14%	↓14%	↓7% *Not statistically significant*	
CV Death	↓38%	↓13%	↓16%	*Trial ongoing*
HF hospitalization	↓35%	↓33%	Composite CV death /HF Hospitalization	

*MACE = Death From CV Causes, Nonfatal MI, or Nonfatal Stroke (+/- hospitalization for unstable angina)

(1) Zinman B, et al. N Engl J Med. 2015 Nov 26;373(22):2117-28. (2) Neal B, et al. N Engl J Med. 2017 Aug 17;377(7):644-657. (3) Wiviott SD, et al. N Engl J Med.2019 Jan 24;380(4):347-357. (4) Cannon CP, et al. Am Heart J. 2018 Dec;206:11-23 (5) Cefalu W, et al. Diabetes Care. 2018;41(1):14-31.

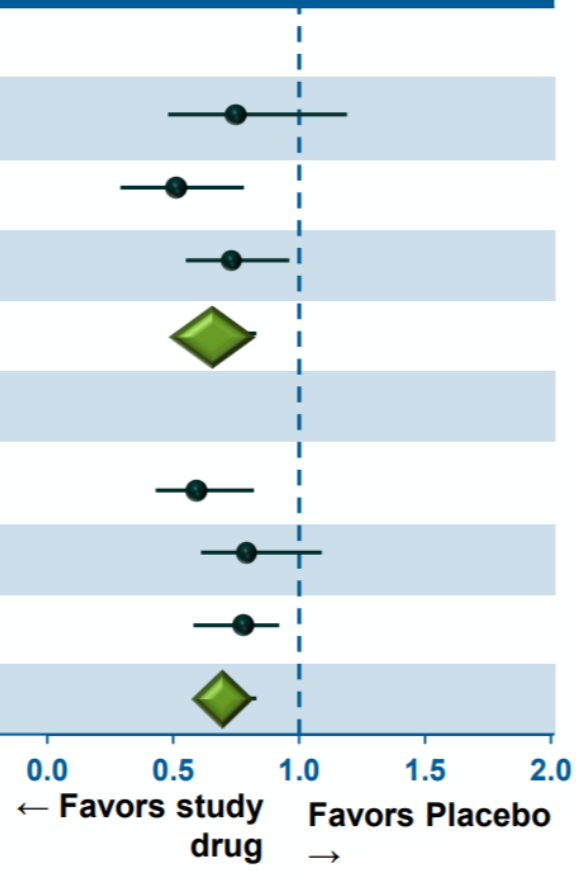
Hospitalization for Heart Failure: Effects of SGLT2 Inhibitors



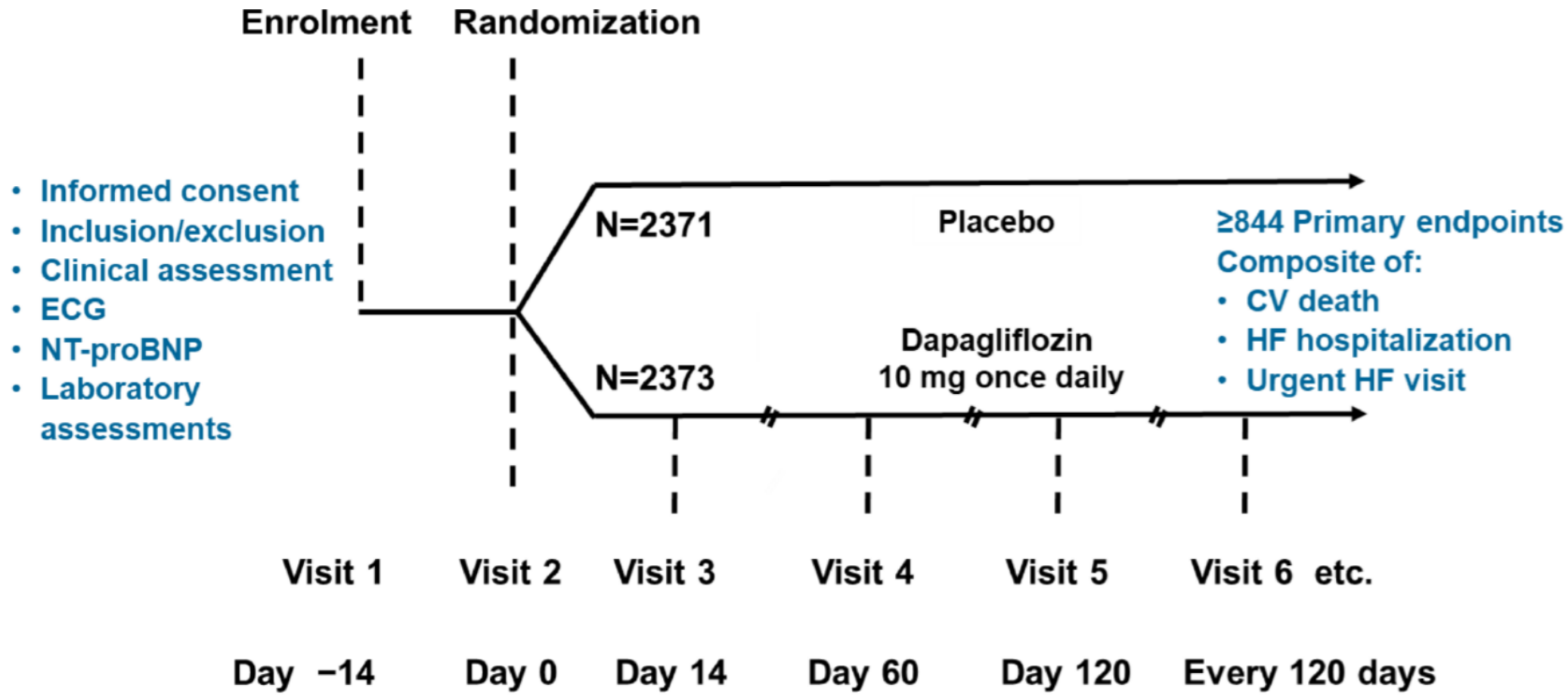
Zinman B, et al. N Engl J Med. 2015;373(22):2117-2128
Neal B, et al. N Engl J Med. 2017;377(7):644-657
Wiviott SD, N Engl J Med. 2019;380(4):347-357

Heart Failure Hospitalization By Prior Heart Failure

	Events per 1000 Patient-Years		Hazard Ratio (95% C.I.)
	SGLT2i	Placebo	
History of HF			
EMPA-REG Outcomes	40.7	52.4	0.75 (0.48, 1.19)
CANVAS Program	14.1	28.1	0.51 (0.33, 0.78)
DECLARE-TIMI 58	27.7	37.2	0.73 (0.55, 0.96)
Fixed effects model for history of HF (p=0.0002)			0.68 (0.55, 0.83)
No history of HF	**Heterogeneity Q=1.73, p=0.42, I^2=0.0%**		
EMPA-REG Outcomes	6.4	10.8	0.59 (0.43, 0.82)
CANVAS Program	4.3	5.7	0.79 (0.57, 1.09)
DECLARE-TIMI 58	4.0	5.6	0.78 (0.58, 0.92)
Fixed effects model for MRF (p<0.0001)			0.71 (0.60, 0.83)

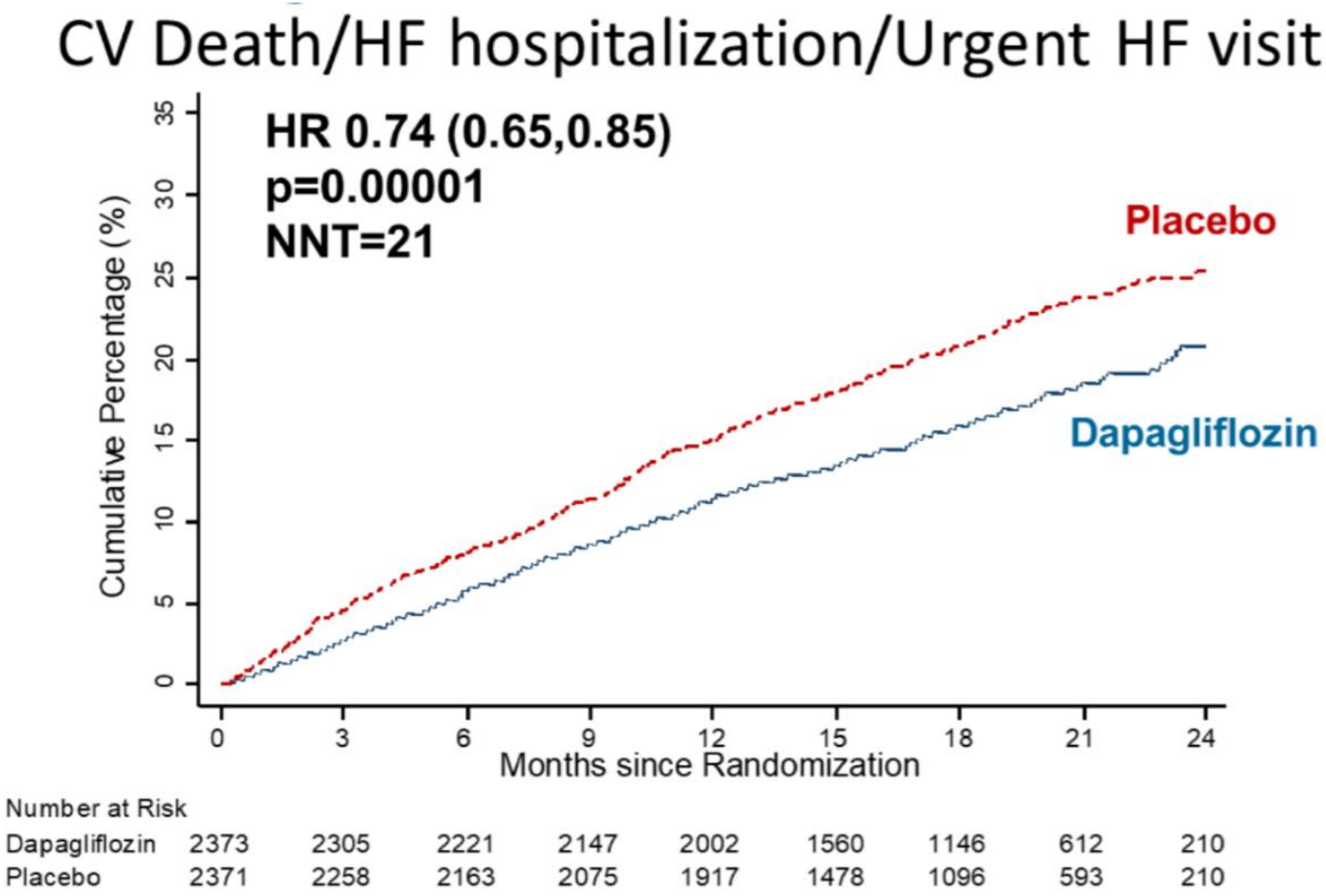


DAPA-HF Design



McMurray et al. ESC 2019

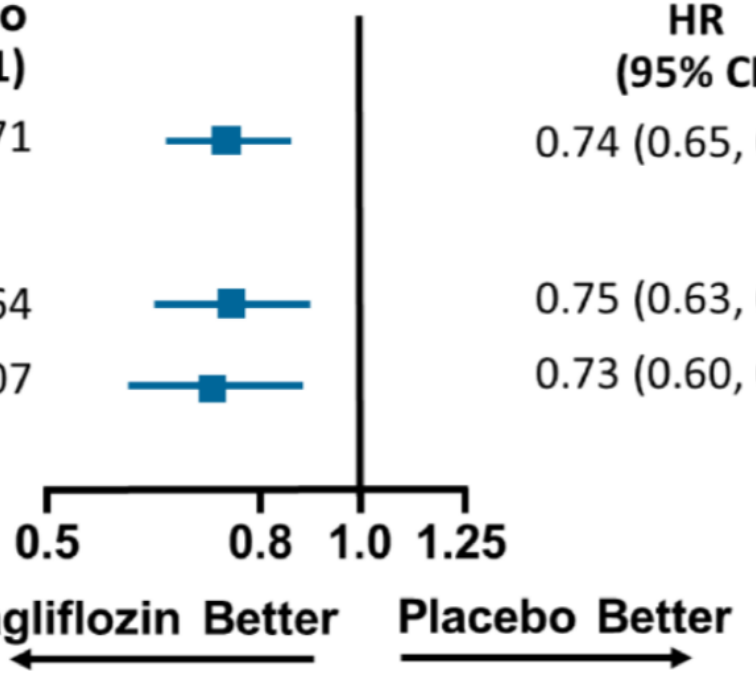
DAPA-HF: Primary Outcome



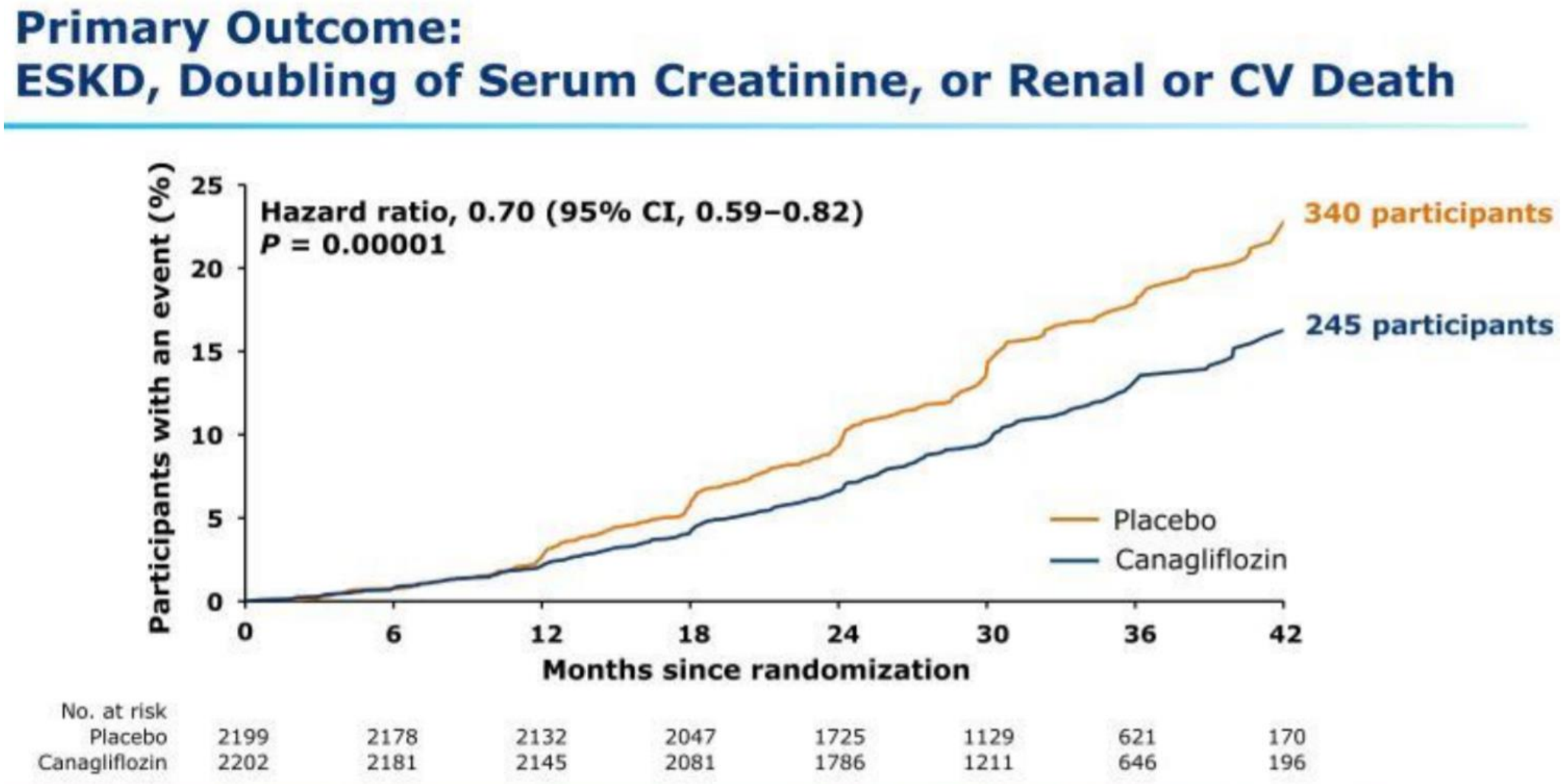
DAPA-HF: Results in T2DM and Non-DM Patients

Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)

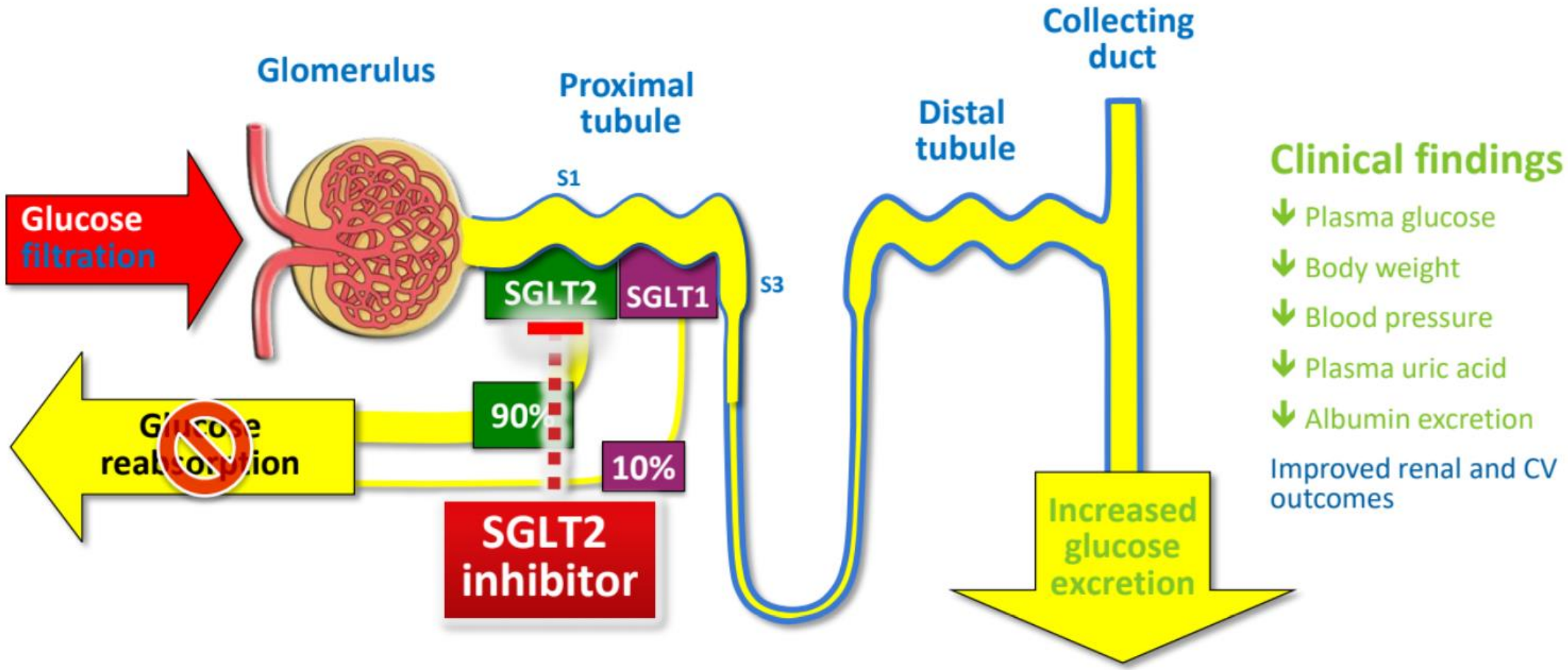


CREDENCE Trial: Renal outcomes in type 2 diabetes and nephropathy.

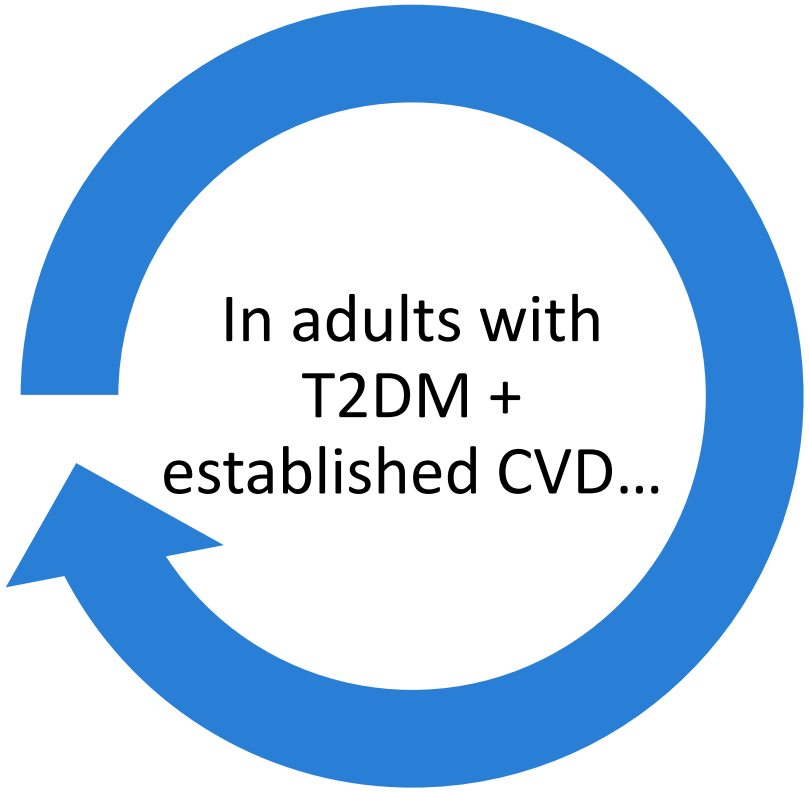


Perkovic, V., et al. N Engl J Med 2019; 380:2295-2306

Proposed mechanisms of CV benefits of SGLT-2 inhibitors



FDA Granted Select SGLT2i's Additional CV Indications



- Empagliflozin ↓ risk of CV death
- Canagliflozin ↓ risk of MACE
- Canagliflozin ↓ risk of ESKD
- Dapagliflozin ↓ risk of HHF

FDA-Mandated CV Outcomes Trials in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pla	pla	pla	placebo	glimepiride
N	16,492	5,380	14,671	6,979	6,033
Results	2013	2013	2015	2018	2018
	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide LAR	dulaglutide	~~albiglutide~~
Comparator	placebo	placebo	placebo	placebo	placebo	placebo
N	6,068	9340	3,297	14,752	9,901	9463
Results	2015	2015	2016	2017	2018	2018
	NEUTRAL	+	+	NEUTRAL	+	+

Study	EMPA-REG[12]	CANVAS[13]	(CREDENCE[14])	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo	placebo
N	7020	4330	4401	17160	8246
Results	2015	2017	2018	2018	2020
	+	+	+	+	

1. NCT01107886 (SAVOR). 2. NCT00968708 (EXAMINE). 3. NCT00790205 (TECOS). 4. NCT01897532 (CARMELINA). 5. NCT01243424 (CAROLINA). 6. NCT01147250 (ELIXA). 7. NCT01179048 (LEADER). 8. NCT01720446 (SUSTAIN 6). 9. NCT01144338 (EXSCEL). 10. NCT01394952 (REWIND). 11. NCT02465515 (HARMONY). 12. NCT01131676 (EMPA-REG). 13.NCT01032629 (CANVAS). 14. NCT02065791 (CREDENCE). 15. NCT01730534 (DECLARE). 16. NCT01986881 (VERTIS CV).

SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association.

Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

Dario Giugliano, MD; Maria Ida Maiorino, MD, PhD; Giuseppe Bellastella, MD; Paolo Chiodini, MSc; Katherine Esposito, MD, PhD

Giugliano, D., et al. JAHA. Volume 8, Issue 12, 18 June 2019

IGCTs, CVOTs, and Risk of MACE in Patients With T2DM

Trials	ΔA1C (%)	Hazard Ratio for MACE
IGCTs	−0.90 (−1.30 to −0.50)	0.91 (0.84 to 0.99)
N=27 049		
CVOTs	−0.42 (−0.53 to −0.30)	0.92 (0.87 to 0.96)
N=120 765		
CVOTs	−0.90	0.67 (0.49 to 0.93)
meta-regression		

CVOTs indicates cardiovascular outcome trials; ΔA1C, change in glycated hemoglobin; IGCTs, intensive glucose control trials; MACE, major cardiovascular events; T2DM, type 2 diabetes mellitus.

Reduction in MACE associated with reduction in A1c in CVOTs

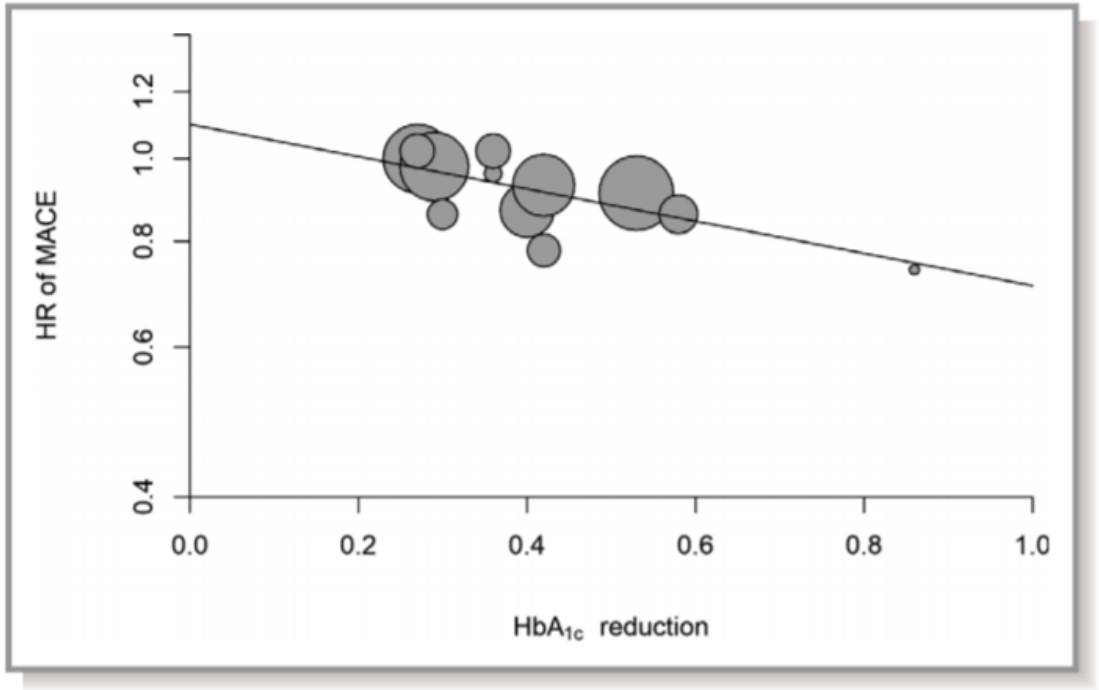


Figure 1. Meta-regression analysis between reduction of HbA_{1c} and MACE risk in the 12 CVOTs. CVOT indicates cardiovascular outcome trial; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; MACE, major cardiovascular events.

Giugliano, D., et al. JAHA. Volume 8, Issue 12, 18 June 2019

Treatment of Diabetes in Older Adults

ENDOCRINE SOCIETY

An Endocrine Society Clinical Practice Guideline

Diabetes in the older population

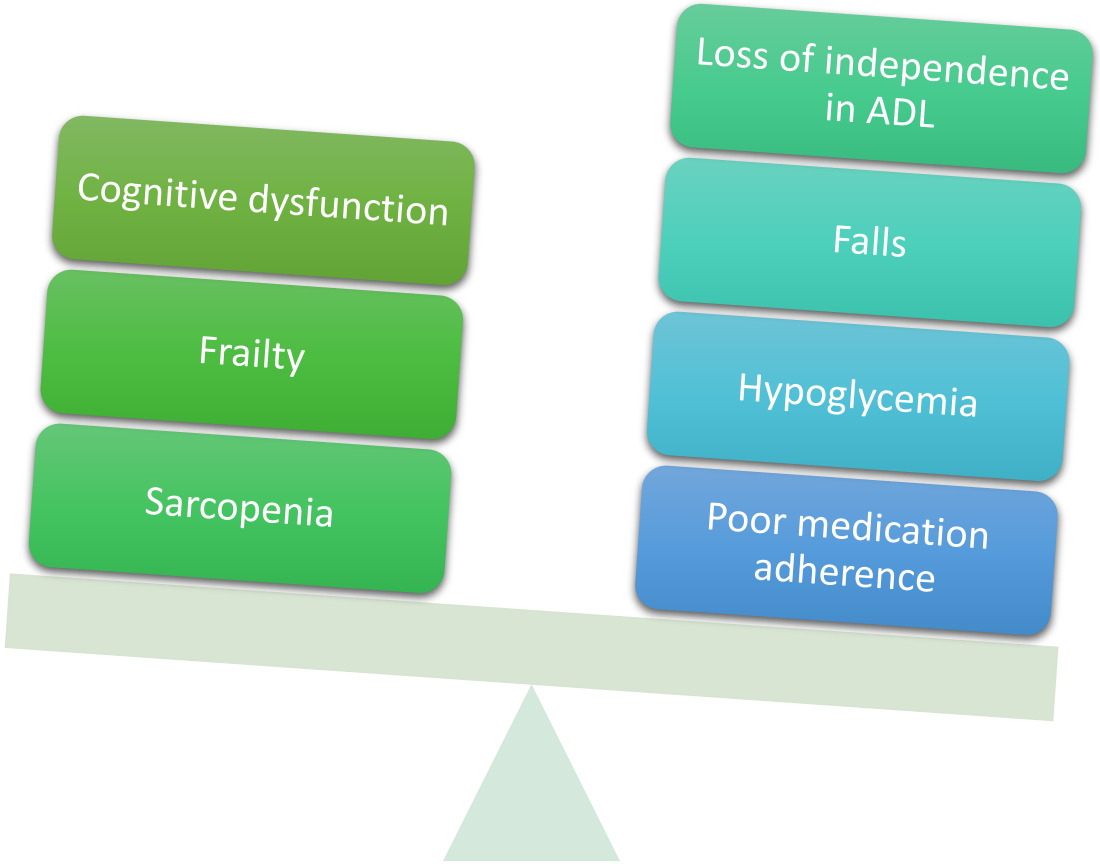
- Prediabetes is highly prevalent in older people, however interventions to delay progression from prediabetes to diabetes are especially effective in this age group.
- The prevalence of type 2 diabetes increases as individuals age and exaggerates the incidence of both microvascular and macrovascular complications.
- Clinicians should perform regular screening for prediabetes and diabetes in the older population and implement interventions as indicated in this guideline.
- Given the heterogeneity of the health status of older people with diabetes the guideline emphasizes shared decision-making and provides a framework to assist healthcare providers to individualize treatment goals.

LeRoith, D., et al. J Clin Endocrinol Metab 104: 1520–1574, 2019

Diabetes in the older population

Older individuals with diabetes

Increased risk



Key Recommendation for Overall Health Assessment

- In patients aged 65 and older with diabetes, we advise assessing the patient's overall health and personal values prior to the determination of treatment goals and strategies. (Ungraded Good Practice Statement)

Step 1: Assessing overall health

Overall Health Category	**Group 1: Good Health**	**Group 2: Intermediate Health**	**Group 3: Poor Health**
Patient characteristics	No comorbidities **or** 1-2 non-diabetes chronic illnesses* **and** No ADL€ impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses* **and/or** Any one of the following: mild cognitive impairment or early dementia ≥2 IADL impairments	Any **one** of the following: End-stage medical condition(s)** Moderate to severe dementia ≥2 ADL impairments Residence in a long-term nursing facility
	Reasonable glucose target ranges and HbA1c by group		
	Shared decision-making: individualized goal may be lower or higher		

*Does not include diabetes ** e.g. metastatic cancer, oxygen requiring COPD, ESKD on HD, advanced HF.
ADL: Activities of daily living (e.g. eating, bathing, dressing)
IADL: Instrumental activities of daily living (e.g. managing money, doing housework)

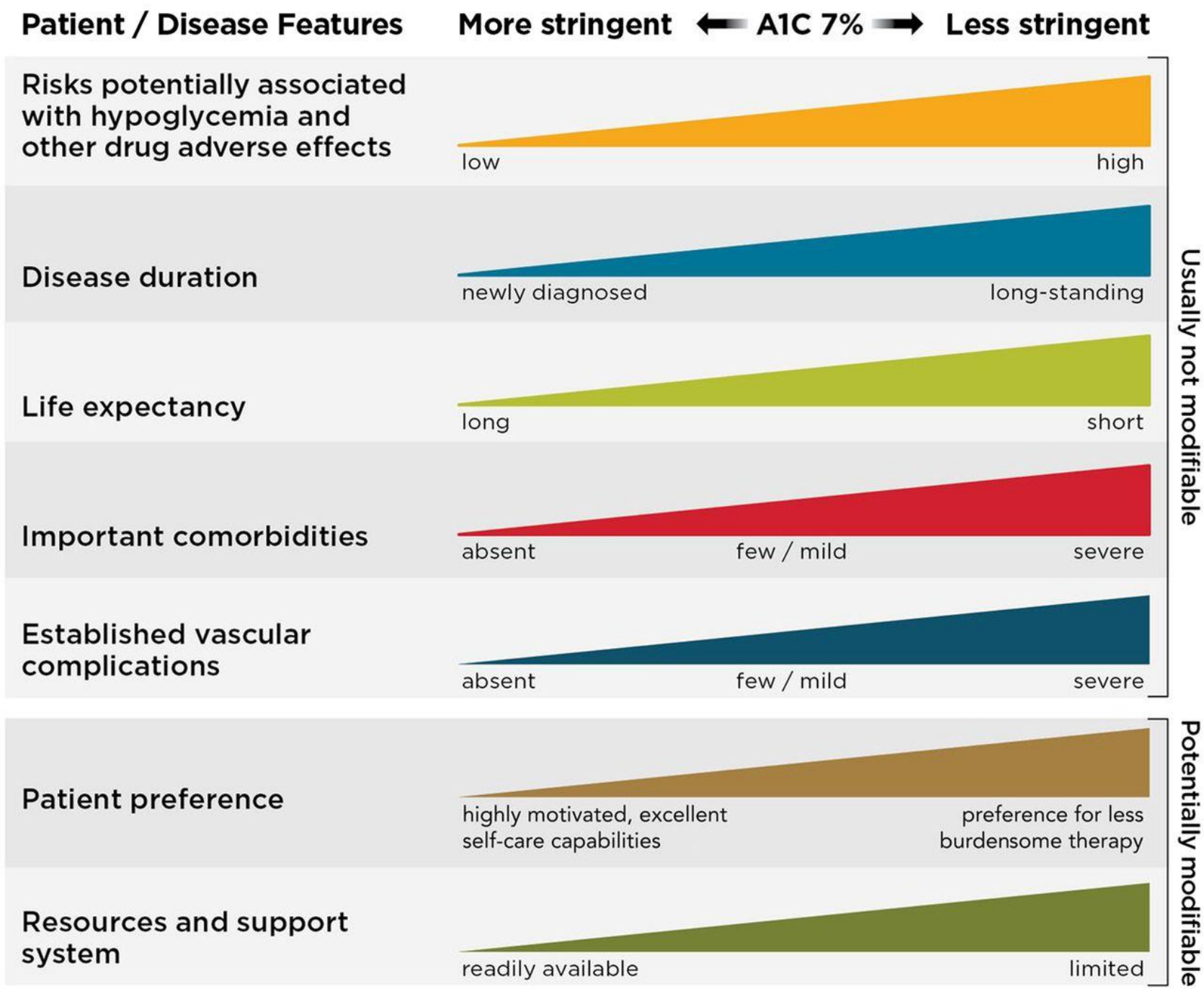
LeRoith, D., et al. J Clin Endocrinol Metab 104: 1520–1574, 2019

Step 2: Identify HbA1c and glucose targets

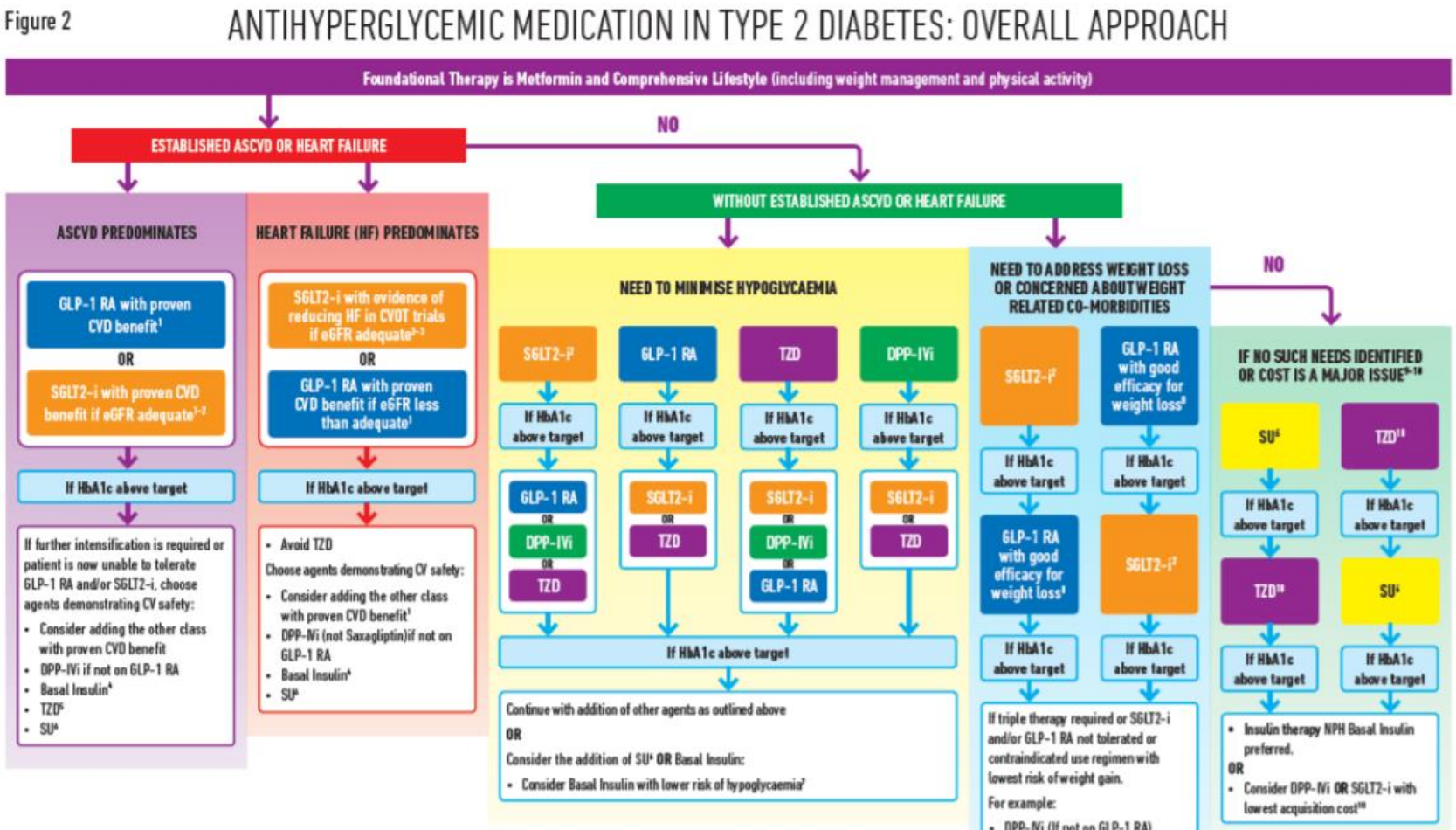
Overall Health Category		Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)	No	Fasting: 90-130 mg/dL Bedtime: 90-150 mg/dL <7.5%	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL <8%	Fasting: 100-180 mg/dL Bedtime: 110-200 mg/dL <8.5%¥
	Yes£	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL ≥7.0 and <7.5%	Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL ≥7.5 and <8.0%	Fasting: 100-180 mg/dL Bedtime: 150-250 mg/dL ≥8.0 and <8.5%¥

LeRoith, D., et al. J Clin Endocrinol Metab 104: 1520–1574, 2019

Approach to Individualization of Glycemic Targets

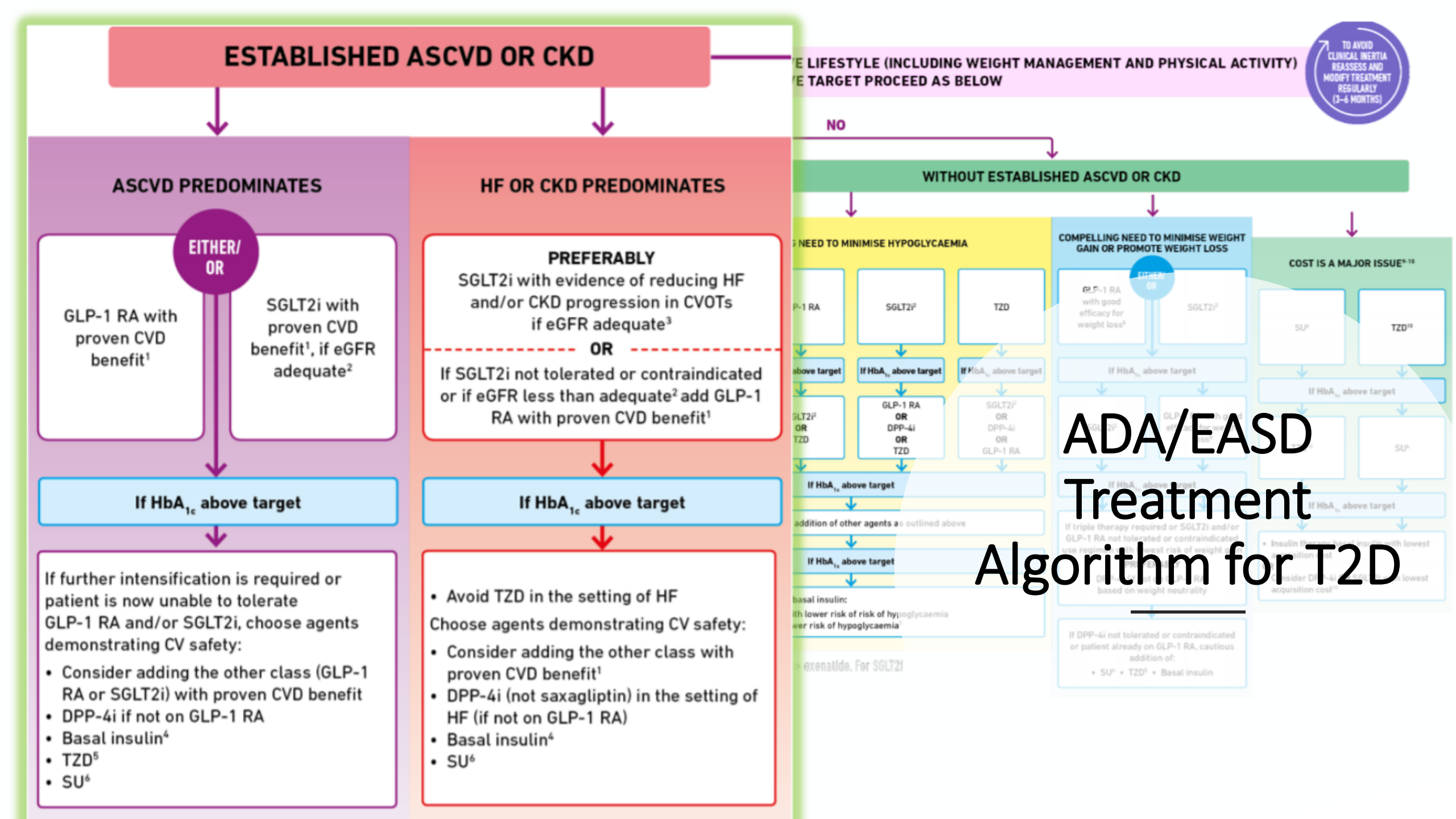


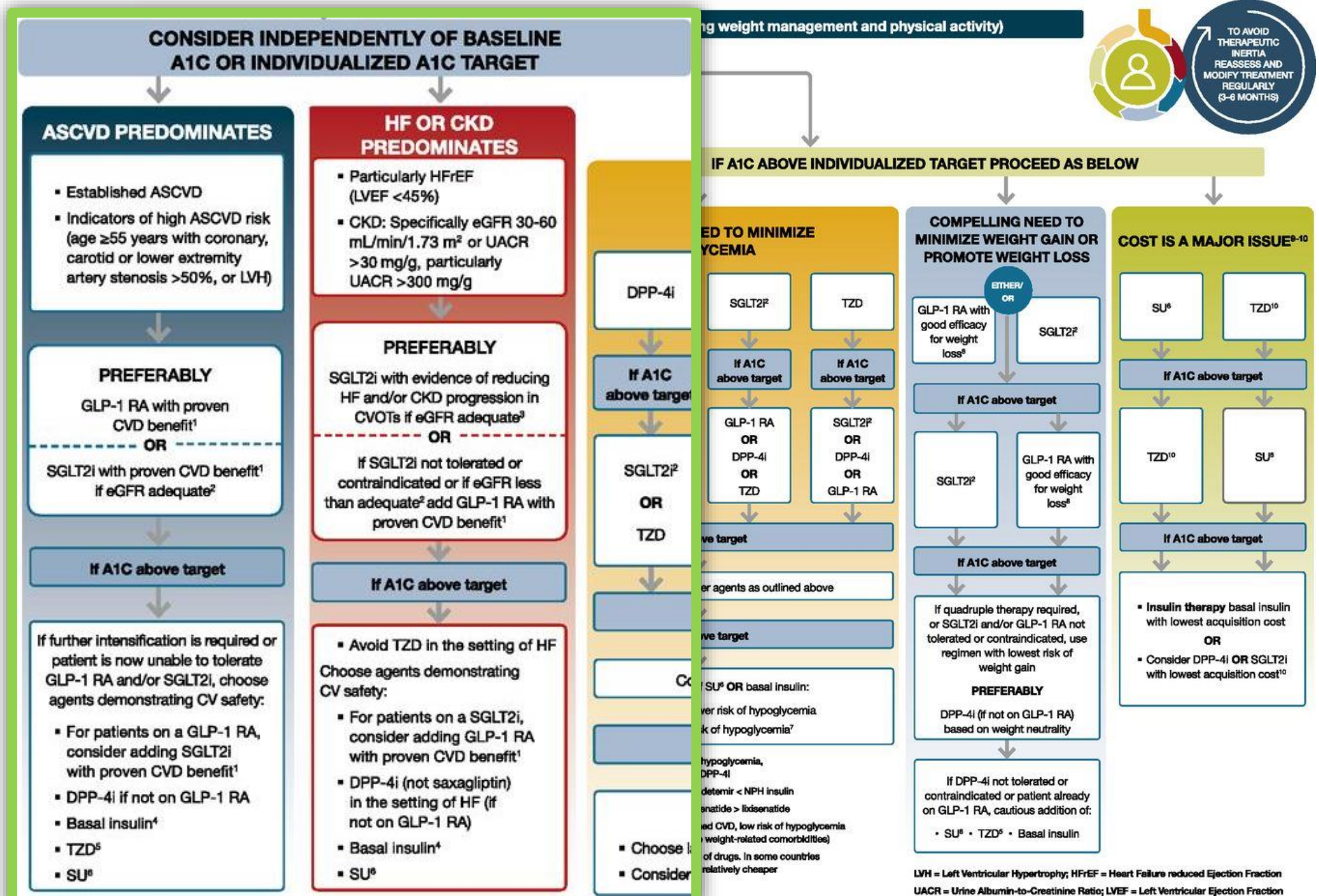
ADA/EASD Treatment Algorithm for T2D

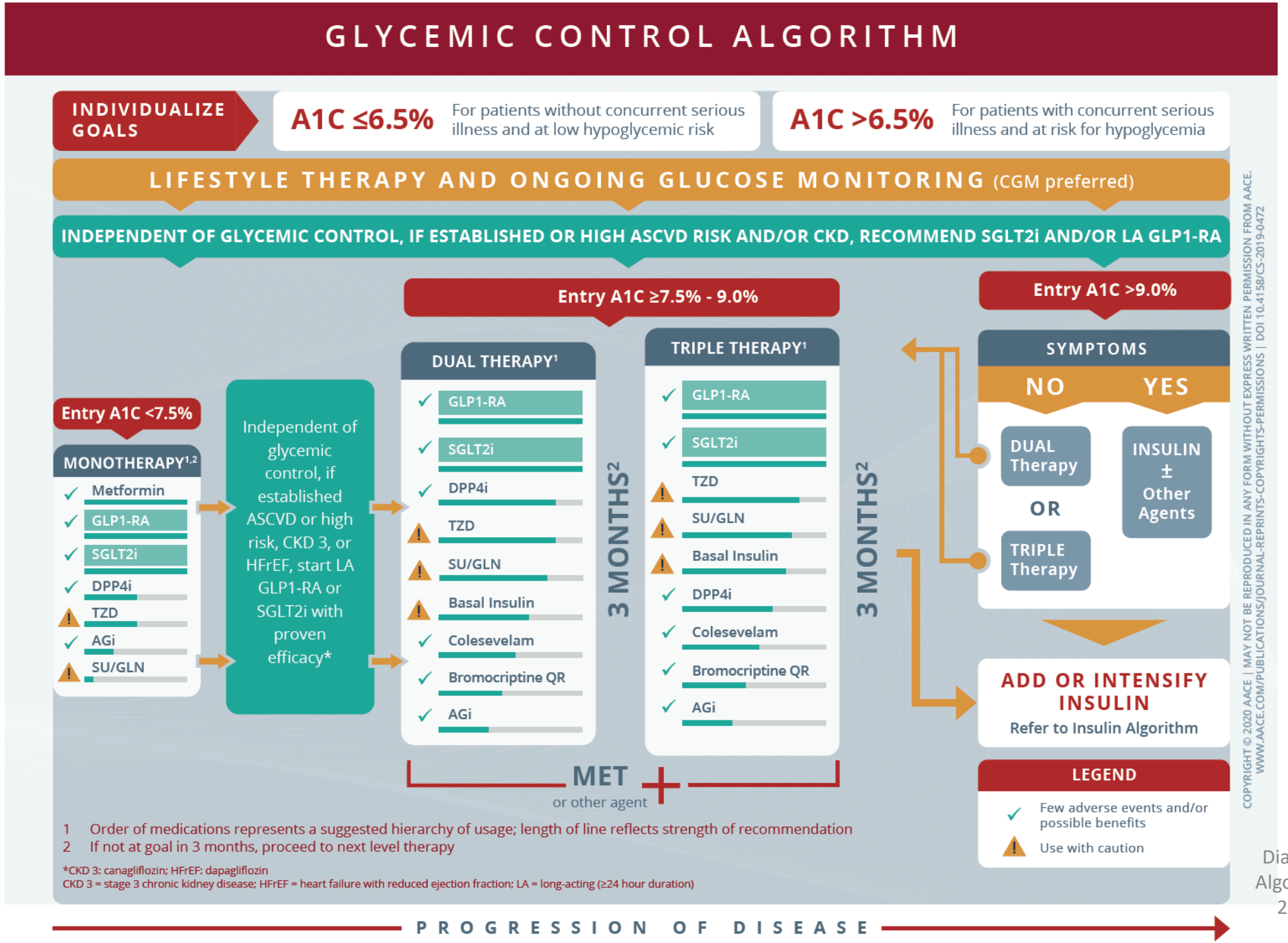


1. SGLT2-i= Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class
2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both Empagliflozin and Canagliflozin have shown reduction in HF in CVOT trials
4. Degludec or U100 Glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of risk of hypoglycaemia
7. Degludec / Glargine U300 < Glagine U100 / Detemir < NPH insulin
8. GLP-1 RA with best efficacy for weight loss Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide
9. If no specific co-morbidities (i.e. established CVD), low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related co-morbidities: using the algorithm to minimise medication costs
10. Consider country and region specific cost of drugs. In some countries TZD relatively more expensive and DPP-IVi relatively cheaper

Davies MJ et al. Diabetes Care. 2018;41:2669-2701.


ESTABLISHED ASCVD OR CKD
ASCVD PREDOMINATES
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
If HbA1c above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin[4]
• TZD[5]
• SU[6]
HF OR CKD PREDOMINATES
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If HbA1c above target
• Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
• Consider adding the other class with proven CVD benefit[1]
• DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
• Basal insulin[4]
• SU[6]
E LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
E TARGET PROCEED AS BELOW
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
NO
WITHOUT ESTABLISHED ASCVD OR CKD
NEED TO MINIMISE HYPOGLYCAEMIA
COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
COST IS A MAJOR ISSUE
GLP-1 RA OR DPP-4i OR TZD
ADA/EASD Treatment Algorithm for T2D


g weight management and physical activity)
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
DPP-4i if not on GLP-1 RA
Basal insulin[4]
TZD[5]
SU[6]
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If A1C above target
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[4]
SU[6]
DPP-4i
If A1C above target
SGLT2i[2]
OR
TZD
Choose
Consider
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
ED TO MINIMIZE
YCEMIA
SGLT2i[2]
TZD
If A1C above target
GLP-1 RA
OR
DPP-4i
OR
TZD
SGLT2i[2]
OR
DPP-4i
OR
GLP-1 RA
ve target
er agents as outlined above
ve target
SU[6] OR basal insulin:
er risk of hypoglycemia
k of hypoglycemia[7]
hypoglycemia,
DPP-4i
detemir < NPH insulin
natide > lixisenatide
ed CVD, low risk of hypoglycemia
weight-related comorbidities)
of drugs. In some countries
relatively cheaper
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If A1C above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
• SU[6] • TZD[5] • Basal insulin
COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If A1C above target
TZD[10]
SU[6]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]
LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction



Diabetes Management Algorithm, Endocr Pract. 2020;26(No. 1) 137

Conclusions

- There are many individuals for whom an A1c <7% is clearly reasonable.
- Our best evidence suggests that the A1c level attained and how it is approached is probably the key to achieve optimal outcomes.
- The goal of an A1c less than 7% is fundamentally a tactic to achieve a strategy to minimize the risk of complications while maintaining quality of life.
- Recent CVOTs have shown benefits for patients beyond glycemic control and should be considered in certain population.
- New guidance for glycemic control in the older population is available.