Approach to Cardiovascular Risk Factor Control Among Patients with Diabetes

(Hypertension and Diabetic Kidney Disease)

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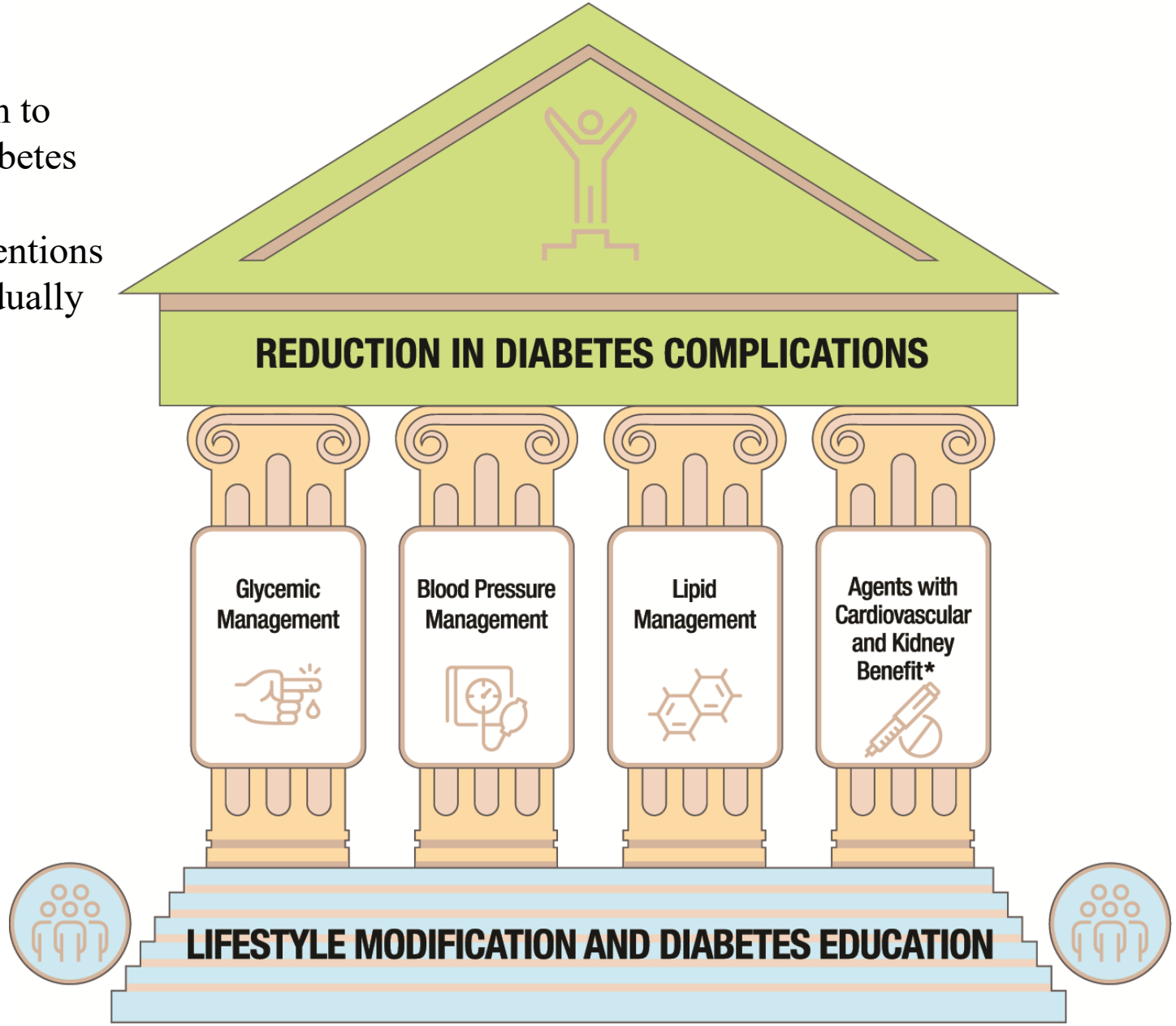
Agenda

1. Overview Hypertension Control among Diabetic Population in Tehran
2. Definition of Hypertension Using Different Guidelines
3. Blood Pressure Targets
4. Choice of Anti Hypertensive Agents
5. Management of the Patient with Hypertension
6. Oral Antihypertensive Medication
7. Diabetic Kidney Disease
8. Effects on the kidney that are Direct, i.e., not Mediated Through Glycemia, Role of SGL2-I and GLP1- Analogue
9. Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

Figure 10.1
Multifactorial approach to reduction in risk of diabetes complications.
*Risk reduction interventions to be applied as individually appropriate.



Clinical Case Scenario

40 y/o man, type 2 diabetes patient, CAD:+ve, Smoker: 25 Pack/year

✓ PMHx:
- Angioplasty: Minimal CAD 5 months ago, otherwise unremarkable

✓ FHx:
- CVD:+ve in both parents

✓ P/E:
- Office BP: 130/100
- BMI:33 kg/ m^2
- Echo report: Mild LVH, NL EF

✓ Daily medications:
- Atorvastatin 40 mg
- ASA 80 mg
- Clopidogrel 75 mg

Lab Data
FBS:132, HbA1c: 7.5%
Cr: 1 , eGFR: 94
TG: 150 TC: 144, LDL: 68, HDL:46
U/A: Protein +1

Clinical Case Scenario

What's your decision on his BP value?

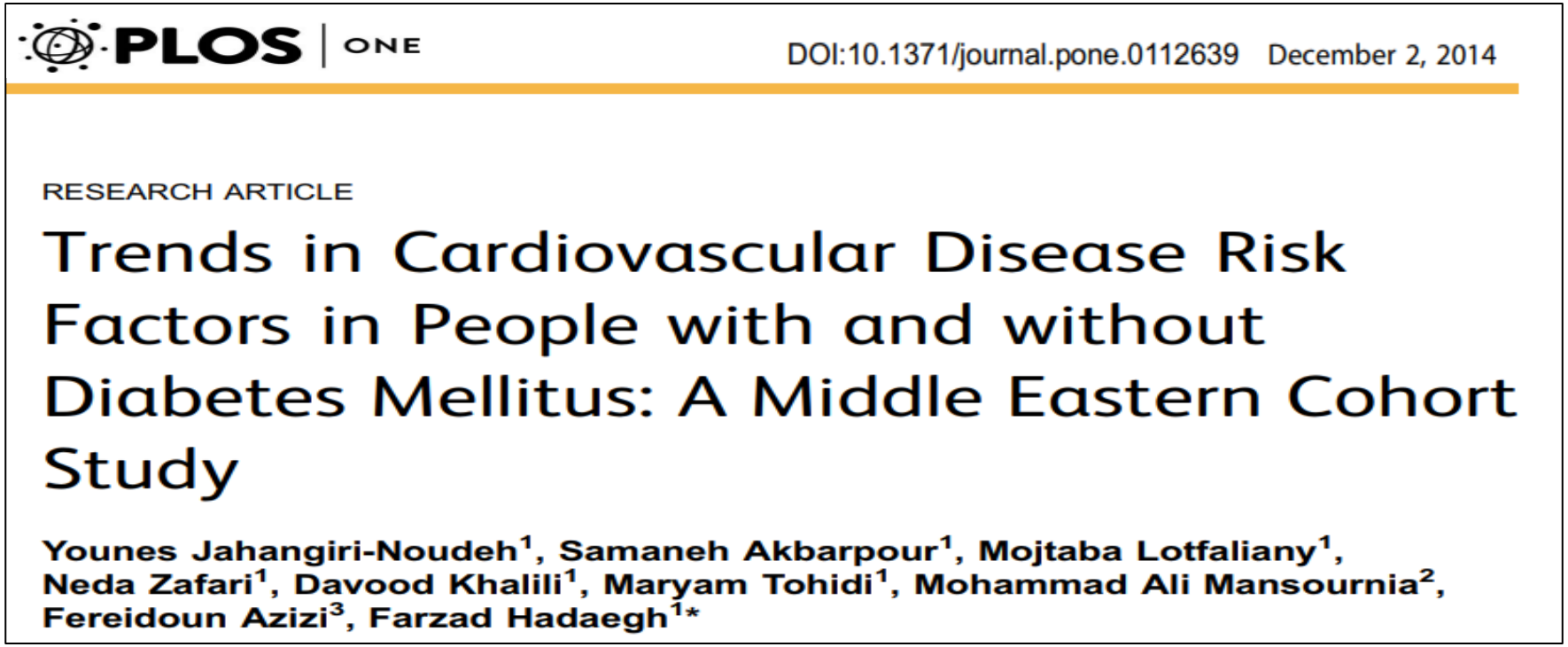
A Prehypertension

B Confirmation with Second OBPM

C Confirmation with HBPM/ABPM

D Stage 1 hypertension

Overview Hypertension Control among Diabetic Population in Tehran



PLOS ONE | DOI:10.1371/journal.pone.0112639 December 2, 2014

RESEARCH ARTICLE

Trends in Cardiovascular Disease Risk Factors in People with and without Diabetes Mellitus: A Middle Eastern Cohort Study

Younes Jahangiri-Noudeh[1], Samaneh Akbarpour[1], Mojtaba Lotfaliany[1], Neda Zafari[1], Davood Khalili[1], Maryam Tohidi[1], Mohammad Ali Mansournia[2], Fereidoun Azizi[3], Farzad Hadaegh[1]*

Aims/Hypothesis: To investigate secular trends in cardiovascular disease (CVD) risk factors during a decade of follow-up in a Middle Eastern cohort, and to compare observed trends between diabetic and non-diabetic populations.

Methods: In a population of 6181 participants (2622 males and 3559 females), diabetes status and CVD risk factors were evaluated in 4 study phases from 1999– 2011. 1045 subjects had type 2 diabetes mellitus at baseline and 5136 participants were diabetes-free.

Table 2. Age-adjusted percentage of subjects in diabetic and non-diabetic groups who reached goal levels of lipid measures and blood pressure and trends of obesity and medications consumption; Teheran Lipid and Glucose Study (March 1999- December 2011).

Males		Phase1 (1999–2002)	Phase2 (2002–2005)	Phase3 (2005–2008)	Phase4 (2008–2011)	P_{trend}	$P_{interaction}$
Reached blood pressure control goal (%)	DM	38.85	47.39	47.49	37.36	0.942	0.036
	Non-DM	81.23	85.38	84.86	80.25	0.274	
Antihypertensive medication use (%)	DM	19.17	20.45	10.58	30.18	0.012	0.266
	Non-DM	4.59	4.91	3.21	7.21	0.002	
Females							
Reached blood pressure control goal (%)	DM	27.67	43.59	51.03	40.43	P<0.001	P<0.001
	Non-DM	82.94	88.92	90.97	87.58	P<0.001	
Antihypertensive medication use (%)	DM	31.66	32.55	19.05	41.91	0.038	0.203
	Non-DM	8.01	8.22	4.26	8.60	0.77	

Definition of Hypertension Using Different Guidelines

Key updates to the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines

- New categorization of blood pressure, including lower threshold for hypertension.
- Emphasis on accurate technique for blood pressure measurement in the clinic.
- Incorporation of out-of-office (home or ambulatory) blood pressure monitoring to confirm diagnosis of hypertension, rule out white coat hypertension or masked hypertension in selected patients, and guide treatment decisions.
- Enhanced emphasis on lifestyle/nonpharmacologic therapy for high blood pressure.
- Calculation of 10-y atherosclerotic cardiovascular disease risk score to guide initiation and intensity of medication treatment.
- The diagnosis should be confirmed with out-of-office BP monitoring if possible.
- Diagnosis of hypertension requires careful measurement of BP, with a finding of an average systolic BP of 130 mmHg or higher or an average diastolic BP of 80 mmHg or higher based on 2 or more readings obtained on 2 or more occasions.

Hypertension. Ann Intern Med. 2019 May 7;170(9):ITC65-ITC80.
ADA 2023

Key updates to the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines

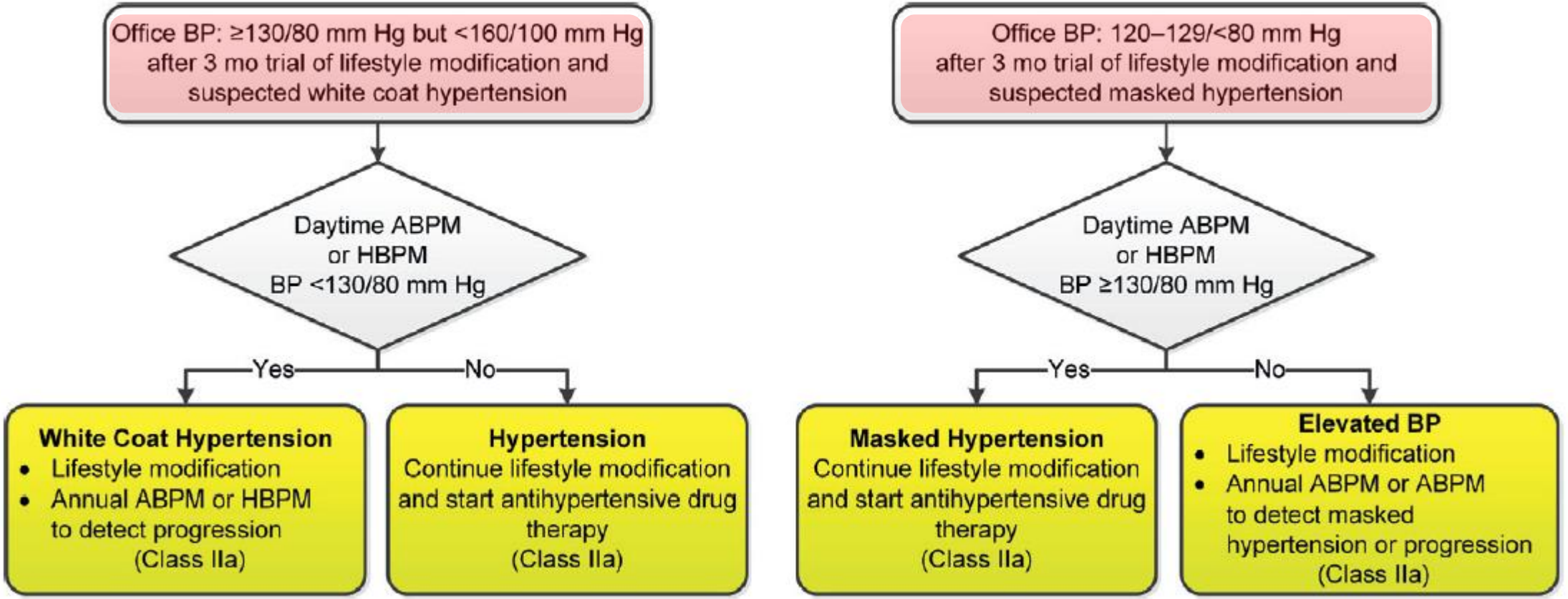
- Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. E
- Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.
- All people with hypertension and diabetes should monitor their blood pressure at home.
- The goals of the initial evaluation are to search for a secondary cause, detect other CVD risk factors, and detect damage to target organs.
- The history should focus on past treatment, current medications, and modifiable lifestyle factors.
- The physical examination should focus on the eye grounds, the cardiovascular system, and the nervous system.
- The clinician should measure hemoglobin, serum creatinine, glucose, lipid, and electrolyte levels and arrange for urinalysis and an electrocardiogram.

Hypertension. Ann Intern Med. 2019 May 7;170(9):ITC65-ITC80.
ADA 2023

Supplemental Table 2. Classification of blood pressure according to the 2017 ACC/AHA guideline and the JNC7 guideline.

Blood pressure levels			Guideline classification	
SBP, mm Hg		DBP, mm Hg	2017 ACC/AHA	JNC7
<120	And	<80	Normal blood pressure	Normal blood pressure
120–129	And	<80	Elevated blood pressure	**Prehypertension**
130–139	Or	80–89	Stage 1 Hypertension	**Prehypertension**
140-159	Or	90 - 99	Stage 2 Hypertension	Stage 1 Hypertension
≥ 160	Or	≥ 100	Stage 2 Hypertension	Stage 2 Hypertension

FIGURE 1 Detection of white coat hypertension or masked hypertension in patients not on drug therapy. Colors correspond to Class of Recommendation in Table 1. ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; and HBPM, home blood pressure monitoring.



ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; and HBPM, home blood pressure monitoring.

BP Levels Used to Define Hypertension, Recommend Antihypertensive Medication, and Treatment Goal According to the 2017 ACC/AHA Guideline, the JNC7 Guideline, and the JNC8 Panel Member Report

	2017 ACC/AHA	JNC7	JNC8 Panel Member Report
Guideline *definition of hypertension*			
SBP, mm Hg			
General population	≥130	≥140	≥140
DBP, mm Hg			
General population	≥80	≥90	≥90
Guideline–recommended *antihypertensive medication*			
SBP, mm Hg			
General population	≥140	≥140	≥140
Diabetes or CKD	≥130	≥130	≥140
High CVD risk†	≥130	—	—
Age ≥65 yrs	≥130	—	—
DBP, mm Hg			
General population	≥90	≥90	≥90
Diabetes or CKD	≥80	≥80	—
High CVD risk†	≥80	—	—
Guideline *treatment goal* among those taking antihypertensive medication			
SBP, mm Hg			
General population	<130	<140	<140
Age ≥65 yrs	<130	—	—
Diabetes or CKD	<130	<130	<140
DBP, mm Hg			
General population	<80	<90	<90
Diabetes or CKD	<80	<80	—

Systolic and diastolic blood pressure levels should be based on **multiple measurements taken at two or more visits**

†High cardiovascular risk is defined as a history of CVD or 10-year predicted CVD risk ≥10% using the Pooled Cohort risk equations.

Corresponding Values of SBP/DBP for Clinic, HBPM, Daytime, Nighttime, and 24-Hour ABPM Measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65 (NOCTUNAL DIPPNIG)	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	**145/90**	145/90	140/85	145/90

Compared with dippers, those with non-dipping or reverse-dipping BP patterns are reported to have an increased risk of cardiovascular target-organ damage (increased LVH and carotid IMT) and CVD outcomes

Procedures for Use of HBPM

Patient training should occur under medical supervision, including:

- Information about hypertension
- Selection of equipment
- Acknowledgment that individual BP readings may vary substantially
- Interpretation of results

Devices:

- Verify use of automated validated devices. Use of auscultatory devices (mercury, aneroid, or other) is not generally useful for HBPM because patients rarely master the technique required for measurement of BP with auscultatory devices.
- Monitors with provision for storage of readings in memory are preferred.
- Verify use of appropriate cuff size to fit the arm.
- Verify that left/right inter-arm differences are insignificant. If differences are significant, instruct patient to measure BPs in the arm with higher readings.

Procedures for Use of HBPM

Instructions on HBPM procedures:

- Remain still:
  - Avoid smoking, caffeinated beverages, or exercise within 30 min before BP measurements.
  - Ensure ≥5 min of quiet rest before BP measurements.
- Sit correctly:
  - Sit with back straight and supported (on a straight-backed dining chair, for example, rather than a sofa).
  - Sit with feet flat on the floor and legs uncrossed.
  - Keep arm supported on a flat surface (such as a table), with the upper arm at heart level.
- Bottom of the cuff should be placed directly above the antecubital fossa (bend of the elbow).

- **Take multiple readings**:
  - Take at least 2 readings 1 min apart in MORNING before taking MEDICATIONS and in EVENING before SUPPER. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit.

- **Record all readings accurately:**
  - Monitors with built-in memory should be brought to all clinic appointments.
  - BP should be based on an average of readings on **≥2 occasions for clinical decision making.**

Discussion

- What is your interpretation?
- What would be your Tx approach and your target?

HBPM Diary

Date	Time	Event	Systolic	Diastolic	Heart Rate
1/23/2021	6:00 AM	Wake	129	79	72
1/23/2021	9:00 PM	Before Meal	135	**92**	74
1/24/2021	6:00 AM	Wake	133	80	75
1/24/2021	9:00 PM	Before Meal	**143**	**91**	80
1/25/2021	6:00 AM	Wake	**141**	84	70
1/25/2021	9:00 PM	Before Meal	132	80	68
1/26/2021	6:00 AM	Wake	138	79	77
1/26/2021	9:00 PM	Before Meal	**144**	**92**	82
1/27/2021	6:00 AM	Wake	132	89	75
1/27/2021	9:00 PM	Before Meal	**146**	**92**	70
1/28/2021	6:00 AM	Wake	**150**	**107**	79
1/28/2021	9:00 PM	Before Meal	136	82	84
Averages			**138**	**87**	**76**

ADA 2023 (Primary Prevention)

- **10.1** Blood pressure should be measured at every routine clinical visit. When possible, patients found to have elevated blood pressure (≥ 130/80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension.
- **10.2** All hypertensive patients with diabetes should monitor their blood pressure at home. A

Blood Pressure Targets

Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Systolic blood pressure target: <120 mmHg Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg	Systolic blood pressure target: 130–140 mmHg Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg	• No benefit in primary end point: **composite of nonfatal MI, nonfatal stroke, and CVD death** • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of **perindopril and indapamide** Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	• **Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)** • **6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant**

Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
HOT	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	Systolic blood pressure target: 130–140 mmHg DBP target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150mmHg Achieved (mean): 135.3 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

Primary & Secondary Outcomes (ACCORD)

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.88 (0.73-1.06)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.96)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585

Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Symptoms affecting quality of life — no./total no. (%)‡			
Hives or swelling	44/501 (8.8)	41/468 (8.8)	1.00
Dizziness when standing	217/501 (44.3)	188/467 (40.3)	0.36
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m^2	99 (4.2)	52 (2.2)	<0.001

Conclusions

- The ACCORD BP trial evaluated the effect of targeting a SBP goal of 120 mm Hg, compared to a goal of 140 mm Hg, in patients with type 2 diabetes at increased cardiovascular risk.

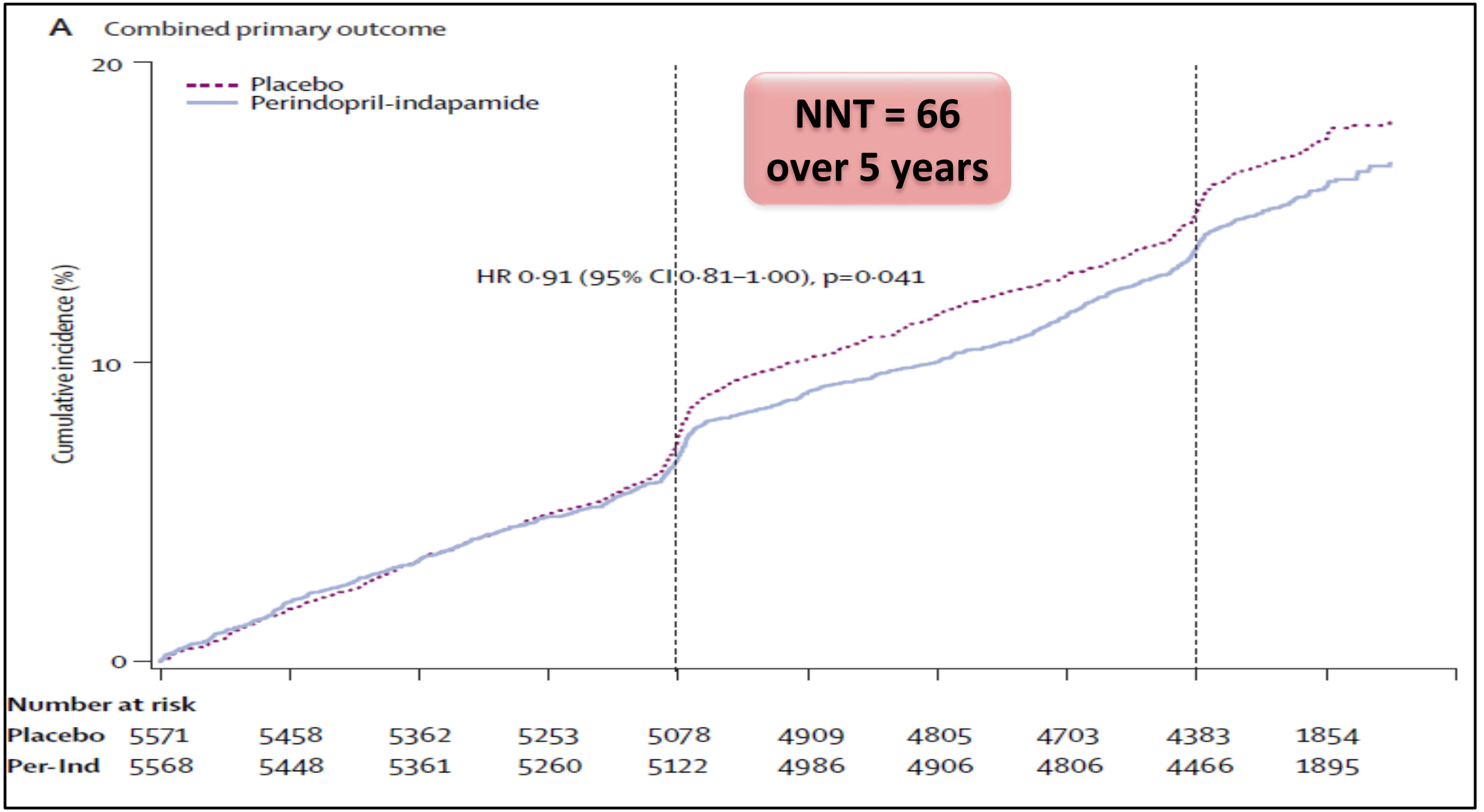
- The results provide no conclusive evidence that the intensive BP control strategy reduces the rate of a composite of major CVD events in such patients.

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

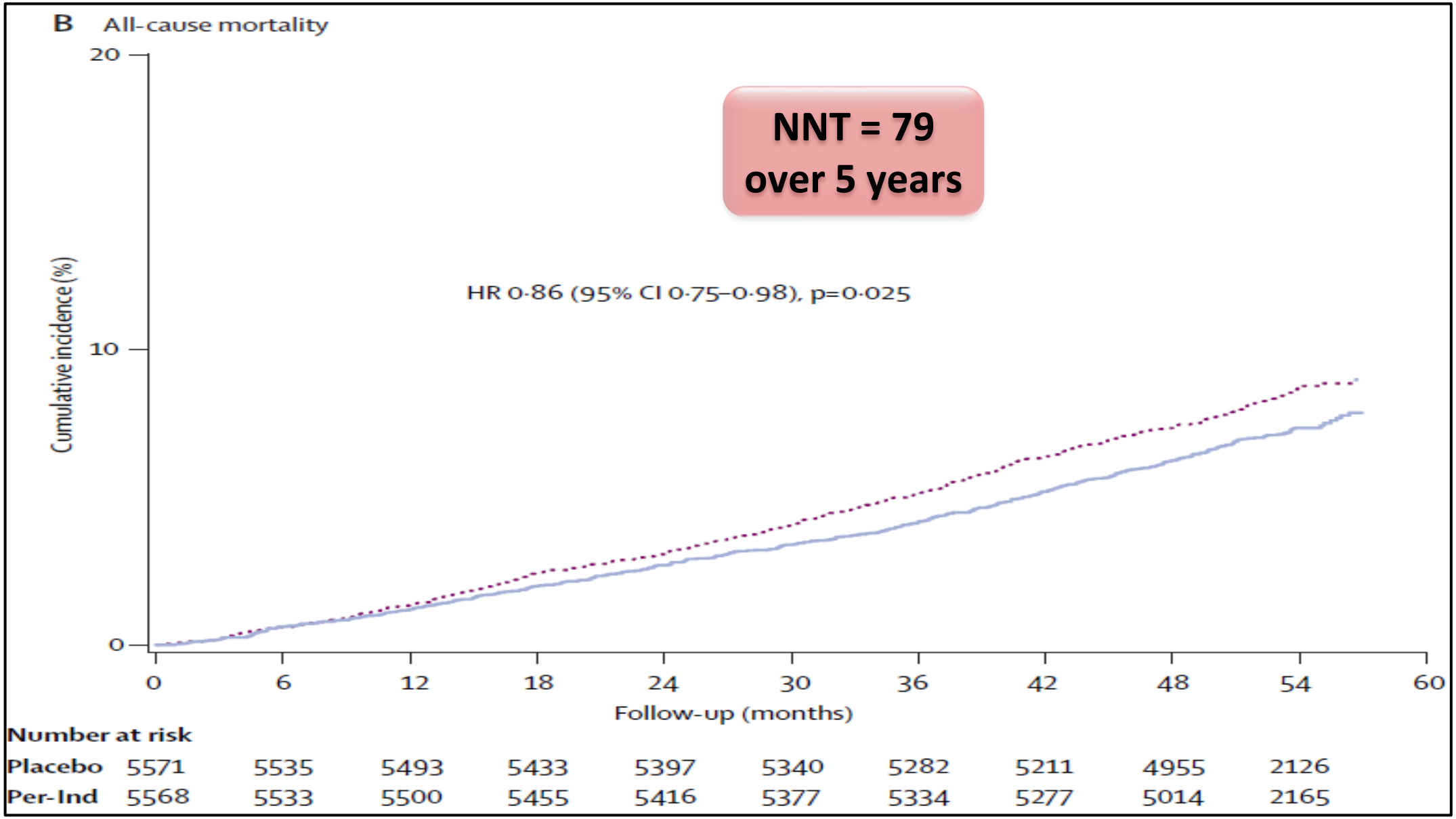
ADVANCE Collaborative Group*

We assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

The primary endpoints were composites of major macrovascular and microvascular events, defined as death from CVD ,non-fatal stroke or non-fatal MI, and new or worsening renal or diabetic eye disease, and was by intention-to-treat.



Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007



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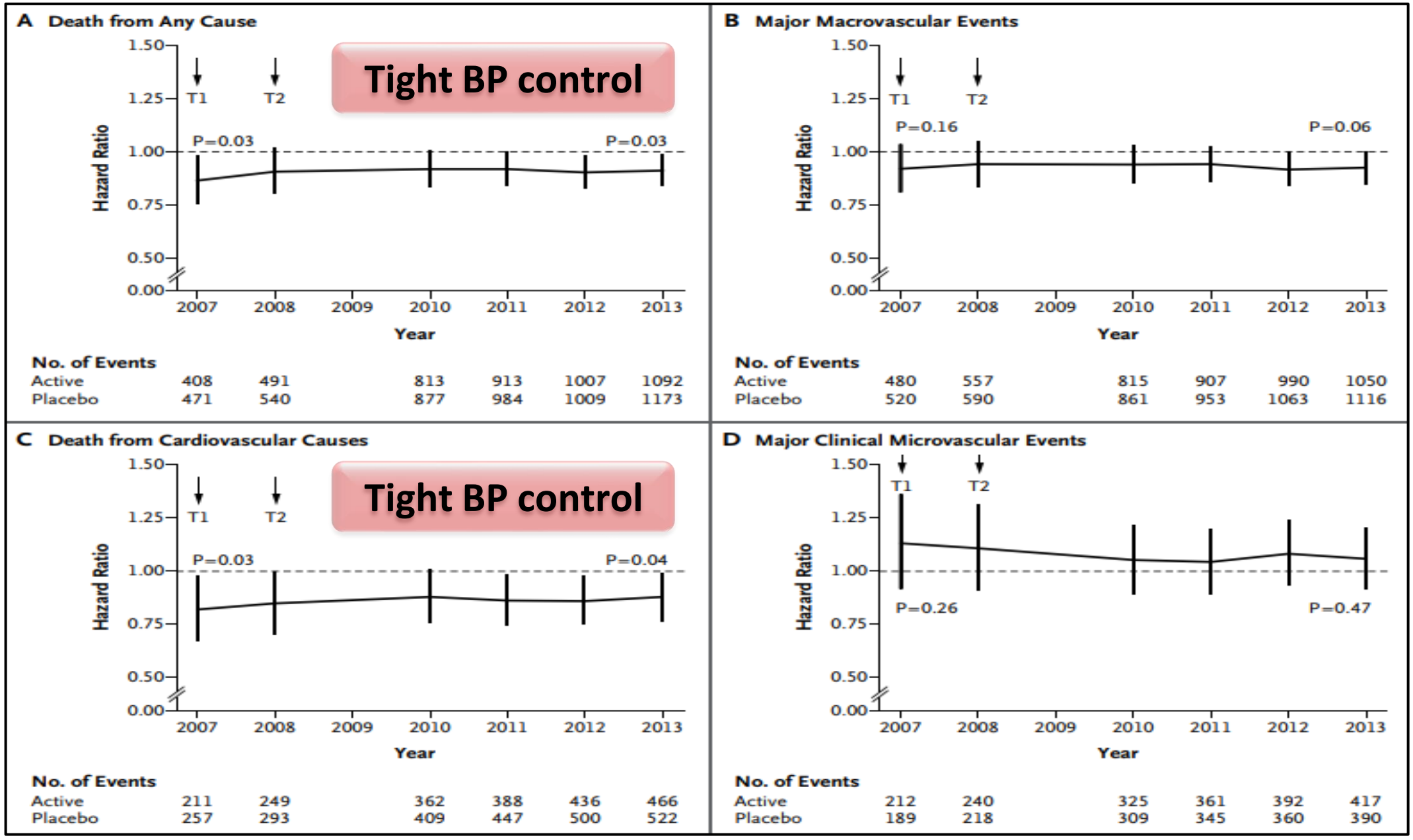

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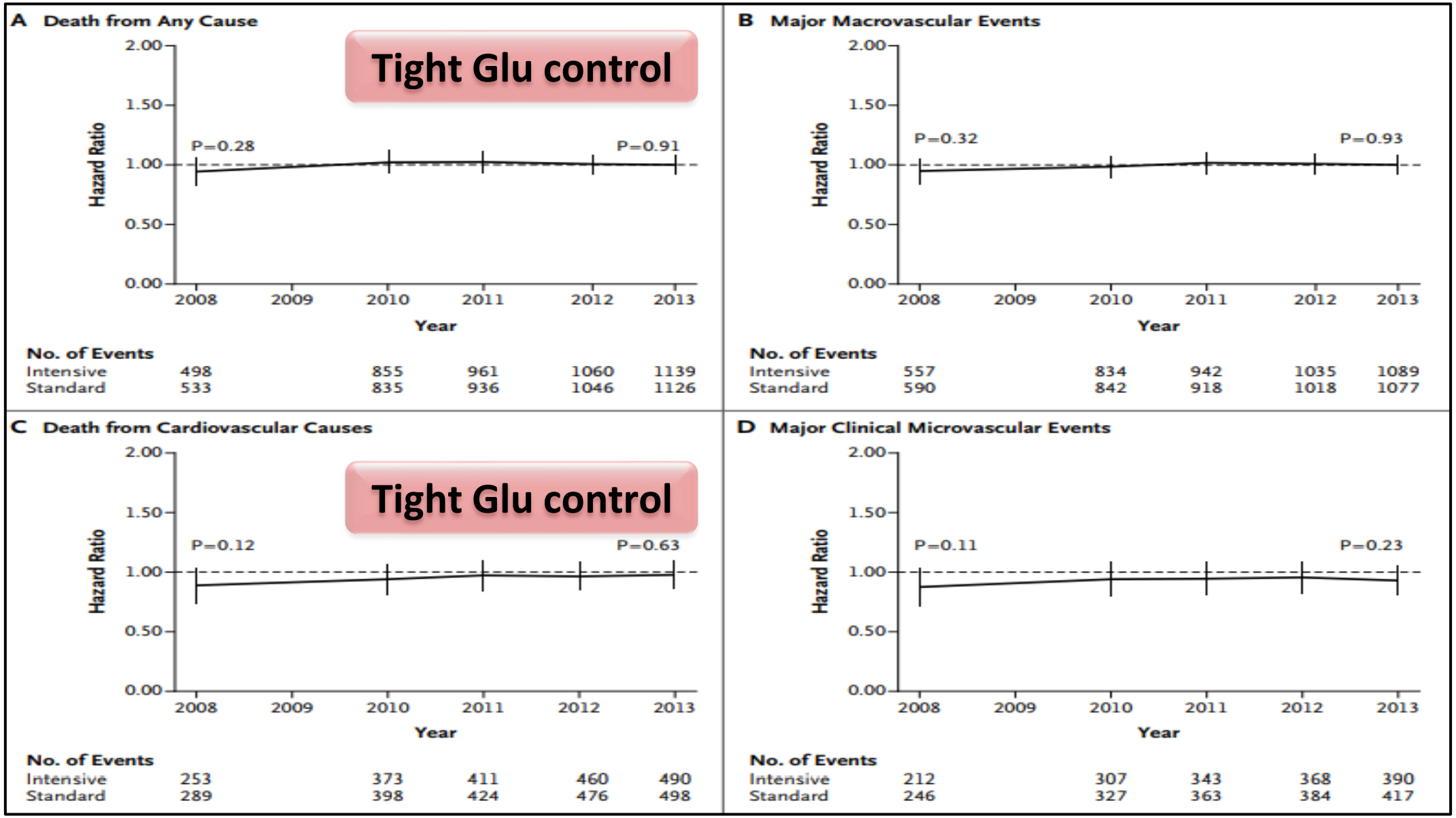

A Death from Any Cause
Tight Glu control
Hazard Ratio
2.00
1.50
1.00
0.50
0.00
P=0.28
P=0.91
2008
2009
2010
2011
2012
2013
Year
No. of Events
Intensive 498 855 961 1060 1139
Standard 533 835 936 1046 1126
B Major Macrovascular Events
Hazard Ratio
P=0.32
P=0.93
Year
No. of Events
Intensive 557 834 942 1035 1089
Standard 590 842 918 1018 1077
C Death from Cardiovascular Causes
Tight Glu control
Hazard Ratio
P=0.12
P=0.63
Year
No. of Events
Intensive 253 373 411 460 490
Standard 289 398 424 476 498
D Major Clinical Microvascular Events
Hazard Ratio
P=0.11
P=0.23
Year
No. of Events
Intensive 212 307 343 368 390
Standard 246 327 363 384 417

Original Investigation

JAMA. 2015;313(6):603-615.

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD

- OBJECTIVE: To determine the associations between BP-lowering treatment and vascular disease in type 2 diabetes.
- DATA SOURCES AND STUDY SELECTION: We searched MEDLINE for large-scale randomized controlled trials of BP-lowering treatment including patients with diabetes, published between January 1966 and October 2014.
- MAIN OUTCOMES AND MEASURES: All-cause mortality, cardiovascular events, coronary heart disease events, stroke, heart failure, retinopathy, new or worsening albuminuria, and renal failure.
- RESULTS: 100,354 participants were included.

- **RESULTS:** 100,354 participants were included.

Each 10-mm Hg lower systolic BP was associated with a significantly lower risk of :

- Mortality (relative risk [RR], 0.87; 95% CI, 0.78-0.96); 13% ↓
- CVD(RR, 0.89 [95% CI, 0.83-0.95]; 11% ↓
- CHD(RR, 0.88 [95% CI, 0.80-0.98]; 12% ↓
- Stroke (RR, 0.73 [95% CI, 0.64-0.83]; 27% ↓
- Albuminuria (RR, 0.83 [95% CI, 0.79-0.87]; 17% ↓
- Retinopathy (RR, 0.87 [95% CI, 0.76-0.99]; 13% ↓
- **When trials were stratified by mean baseline , lower RRs observed among those with baseline BP of ≥ 140 mm Hg**

Figure 4. Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes, Stratified by Mean Achieved Systolic BP in the Active Group of Each Trial

Outcome	No. of Studies	Achieved SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	*P* for Interaction
Mortality, mm Hg								
≥130[16, 18, 19, 27-31, 35-41, 51, 55, 56, 58, 64, 65, 77-80]	16	138	2090	22 367	2079	20 545	0.75 (0.65-0.86)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	244	5326	240	5319	1.06 (0.90-1.25)	*P* = .001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 51-53, 58]	13	138	2551	20 529	2558	19 668	0.74 (0.64-0.85)	
<130[17, 59, 60, 80, 81]	3	123	597	4831	631	4829	0.96 (0.88-1.05)	*P* = .002
Overall							0.89 (0.83-0.96)	
Coronary heart disease, mm Hg								
≥130[16, 18, 27, 29, 30, 32, 35-41, 51, 58, 64, 65]	12	138	1055	20 428	1126	19 077	0.70 (0.58-0.83)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	305	5326	302	5319	0.97 (0.85-1.10)	*P* = .004
Overall							0.87 (0.78-0.96)	
Stroke, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 45, 51, 55, 56, 58, 64, 65]	15	138	1196	24 066	1261	22 915	0.76 (0.64-0.90)	
<130[59, 60, 63, 80, 81]	3	121	106	3152	149	3167	0.72 (0.57-0.90)	*P* = .69
Overall							0.74 (0.65-0.85)	
Heart failure, mm Hg								
≥130[16, 18, 29, 30, 32, 35, 38-41, 58, 64, 65]	9	138	1043	18 194	1106	17 322	0.75 (0.59-0.95)	
<130[42, 43, 59, 60, 80, 81]	3	121	167	3094	209	3104	1.00 (0.81-1.23)	*P* = .07
Overall							0.88 (0.75-1.03)	
Retinopathy, mm Hg								
≥130[16, 29, 30, 36-38, 64, 65, 77-80]	5	137	694	8897	736	8707	0.84 (0.70-1.01)	
<130[59, 60, 80, 81]	2	120	150	884	169	859	0.90 (0.75-1.08)	*P* = .59
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥130[16, 28-30, 36-38, 64, 65]	5	137	1822	9398	2049	8601	0.71 (0.64-0.79)	
<130[17, 59, 60]	2	122	977	4406	1114	4220	0.86 (0.81-0.90)	*P* = .002
Overall							0.83 (0.79-0.87)	

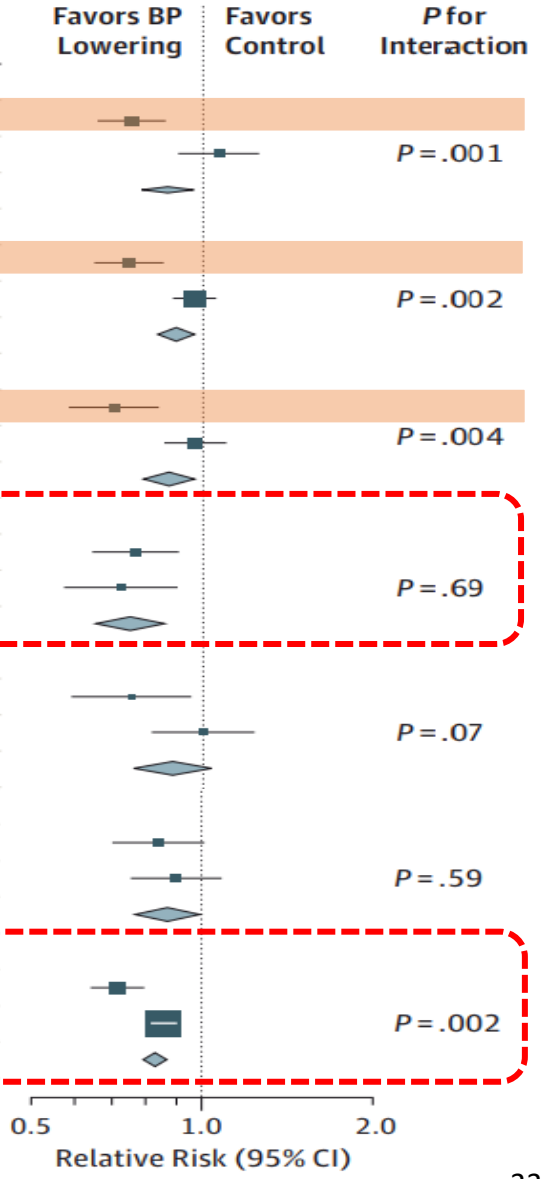
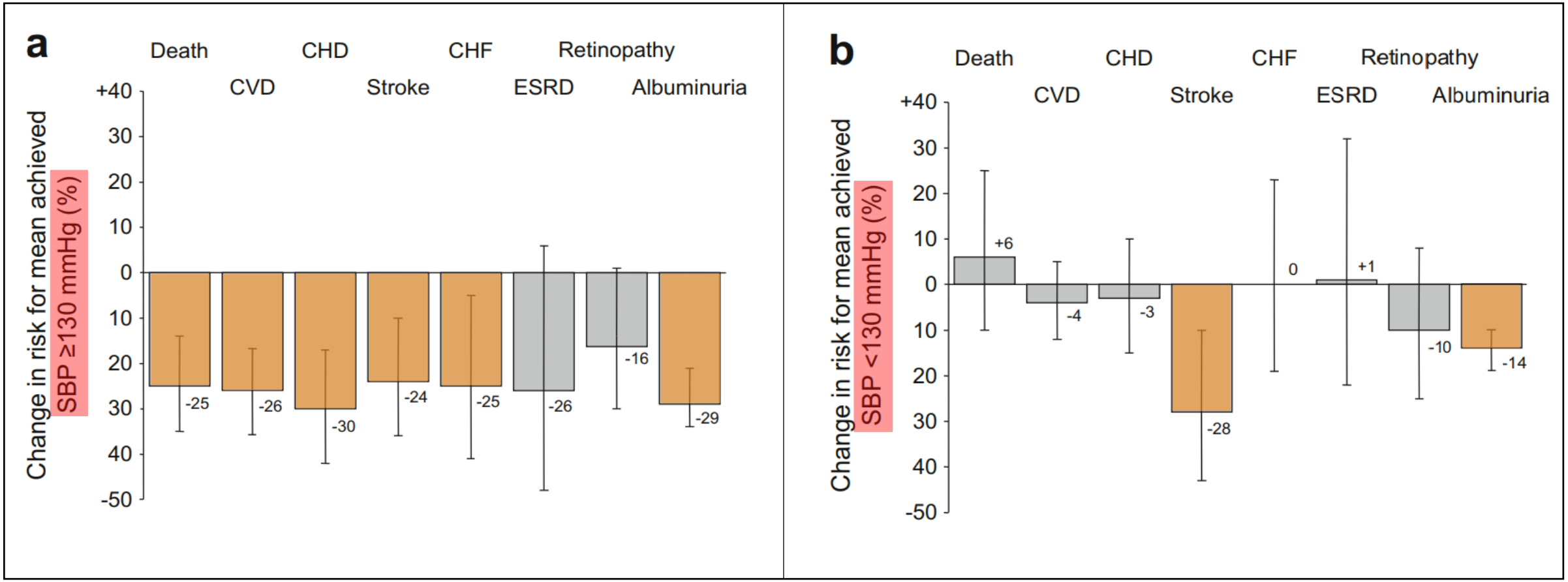
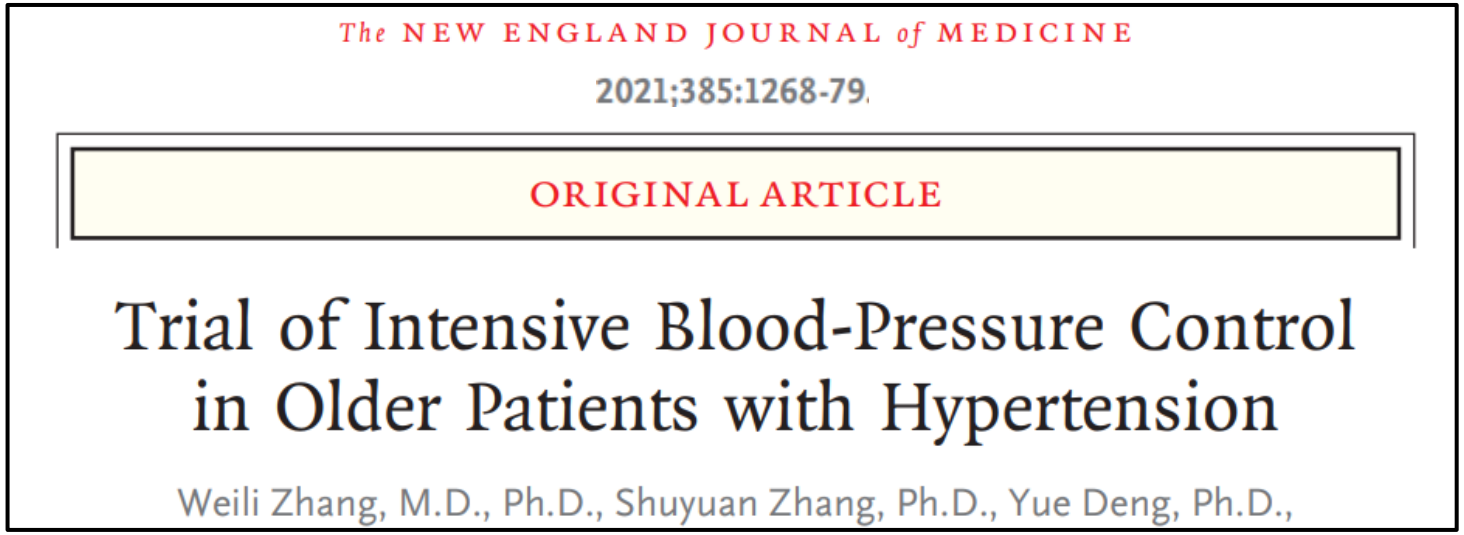


Fig. 2 Effect of 10 mmHg reduction of SBP on outcomes in 40 trials on 100,354 diabetic individuals



STEP

(Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients)



BACKGROUND

The appropriate target for systolic blood pressure to reduce cardiovascular risk in older patients with hypertension remains unclear.

METHODS

In this multicenter, randomized, controlled trial, we assigned Chinese patients 60 to 80 years of age with hypertension to a systolic blood-pressure target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). The primary outcome was a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

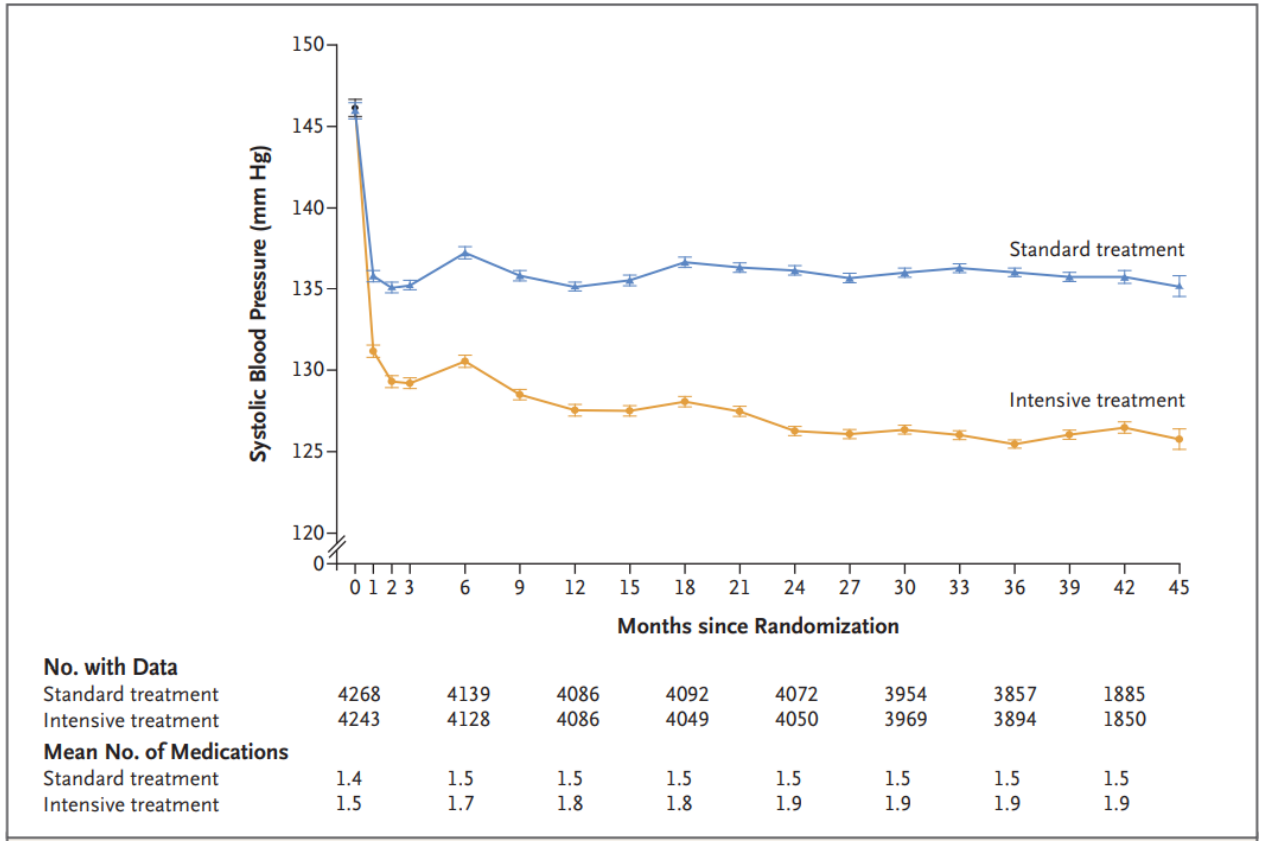


Figure 2. Office Systolic Blood-Pressure Measurements.
The systolic blood-pressure target was 110 to less than 130 mm Hg in the intensive-treatment group and 130 to less than 150 mm Hg in the standard-treatment group.

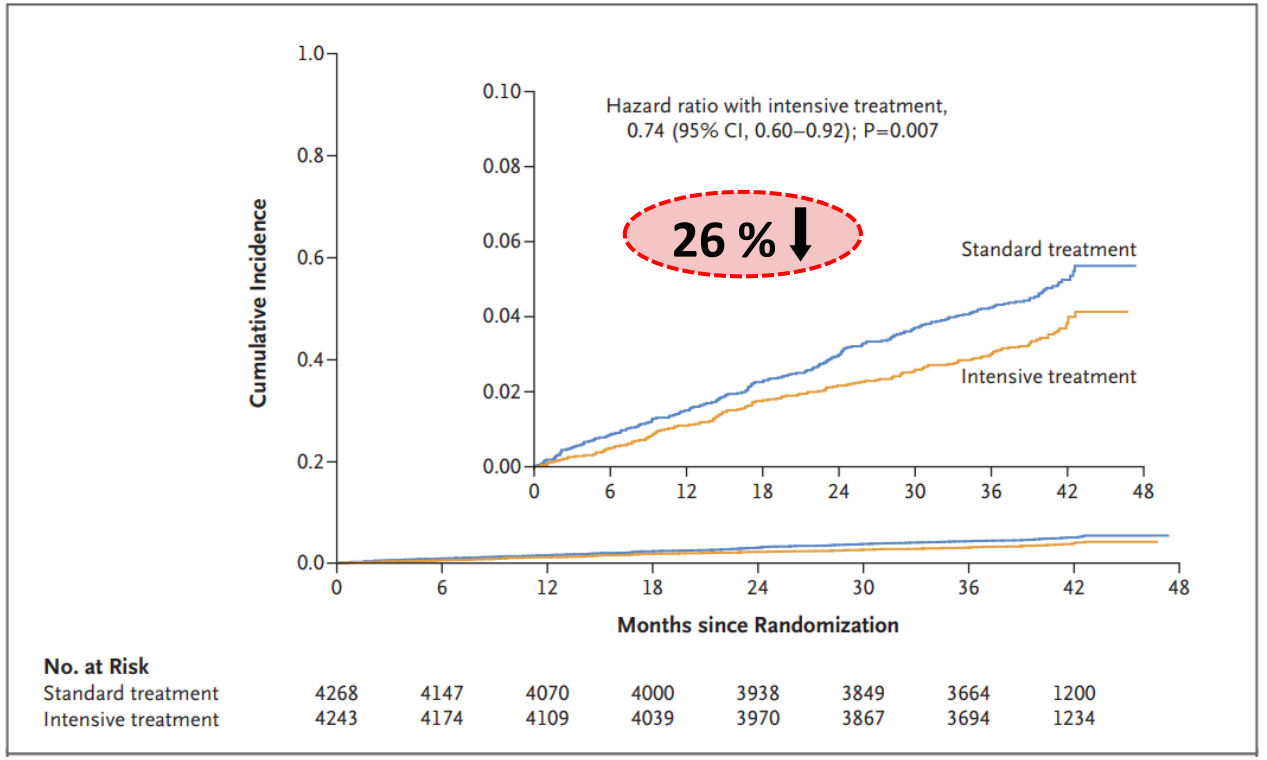


Figure 3. Cumulative Incidence for the Primary Outcome.
The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

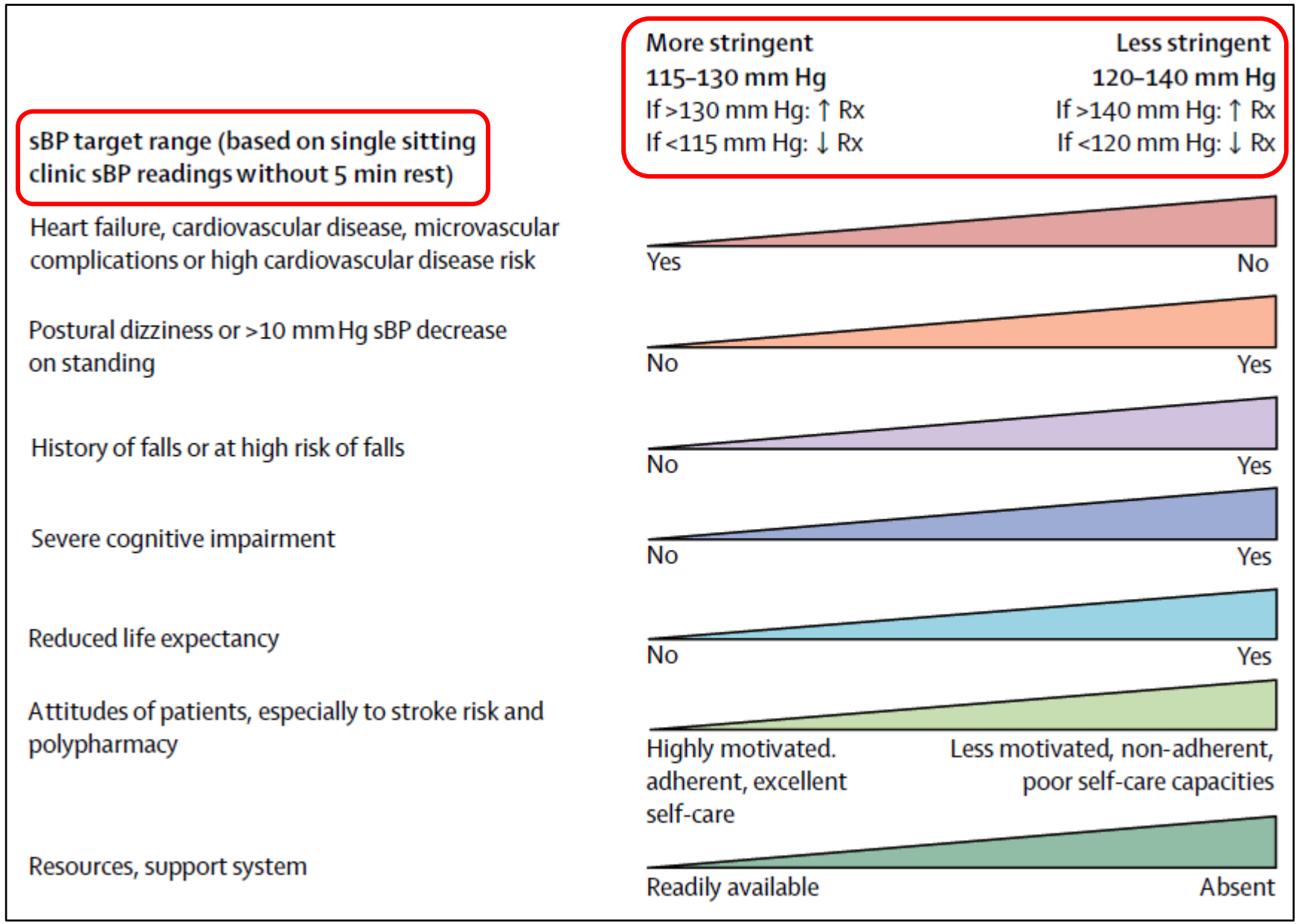


Figure: Personalised sBP target range
Rx=treatment. sBP=systolic blood pressure. Using this approach, physicians can decide on the most appropriate sBP target range depending on the presence or absence of relevant risk factors.

Choice of Anti Hypertensive Agents

Clinical Case Scenario

65 y/o man, T2DM 9 yrs, HTN 7 yrs

✓ PMHx:

- CABG: 2 years ago
- DKD

✓ P/E:

- Lower extremity: 2+ edema, foot deformity
- Average Repeated Office BP:160/110 mmHg
- HBPM logbook:

  -Morning AVG: 167/128

  -Evening AVG: 148/90

Lab Data
FBS:140 , HbA1c:7.4%
Cr:1.1 , eGFR:70
Urine Cr/Alb Ratio: 250
Urea: 15
Na: 142, K: 4

✓ Daily medications:

- Metformin/sitagliptin 2 gr/ 100 mg, Empagliflozin 10 mg, Gliclazide MR 60 mg, Rosuvastatin 20 mg, ASA 80 mg, Amlodipine/Valsartan 10/160

Clinical Case Scenario

What would be the GOAL for his BP Value?

65 y/o ♂

FBS:140
A1c: 7.4%

Cr: 1.1
eGFR: 70

24-hr Urine
microalb: 250

NA: 142
K: 4

A ≤150/90

B ≤140/90

C ≤130/80

D ≤125/75

Metf/sita 2 gr/ 100 mg, GlCZ MR 60 mg, Empa 10mg, Rosu 20 mg, ASA 80 mg, AML+LOSAR 10/160 mg

Clinical Case Scenario

What do you recommend for his optimal HTN management?

65 y/o ♂

FBS:140
A1c: 7.4%

Cr: 1.1
eGFR: 70

24-hr Urine
microalb: 250

NA: 142
K: 4

A Increase AML+VALS dose to 10/320

B Switch AML+VALS to LosarH

C Add Indapamide 1.5 mg

D Add sprinolactone

Metf/sita 2 gr/ 100 mg, GlCZ MR 60 mg, Empa 10mg, Rosu 20 mg, ASA 80 mg, AML+LOSAR 10/160 mg

- ✓ An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urine albumin-to creatinine ratio ≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B)

In order to reduce risk of progressive kidney disease

- ✓ ACE/ARB reduce the risk of both incident and recurrent atherosclerotic ischemic events.
- ✓ In patients with CAD after MI and with low EF, the role of ACE/ARB is more prominent

- In patients receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease.

- β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions.

- For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually.

Cardiovascular Events During Differing Hypertension Therapies in Patients With Diabetes

J Am Coll Cardiol. 2010 Jun 29;56(1):77-85

Michael A. Weber, MD,* George L. Bakris, MD,† Kenneth Jamerson, MD,‡ Matthew Weir, MD,§ Sverre E. Kjeldsen, MD,‖ Richard B. Devereux, MD,¶ Eric J. Velazquez, MD,# Björn Dahlöf, MD,** Roxzana Y. Kelly, MS,†† Tsushung A. Hua, PHD,†† Allen Hester, PHD,†† Bertram Pitt, MD,‡ for the ACCOMPLISH Investigators

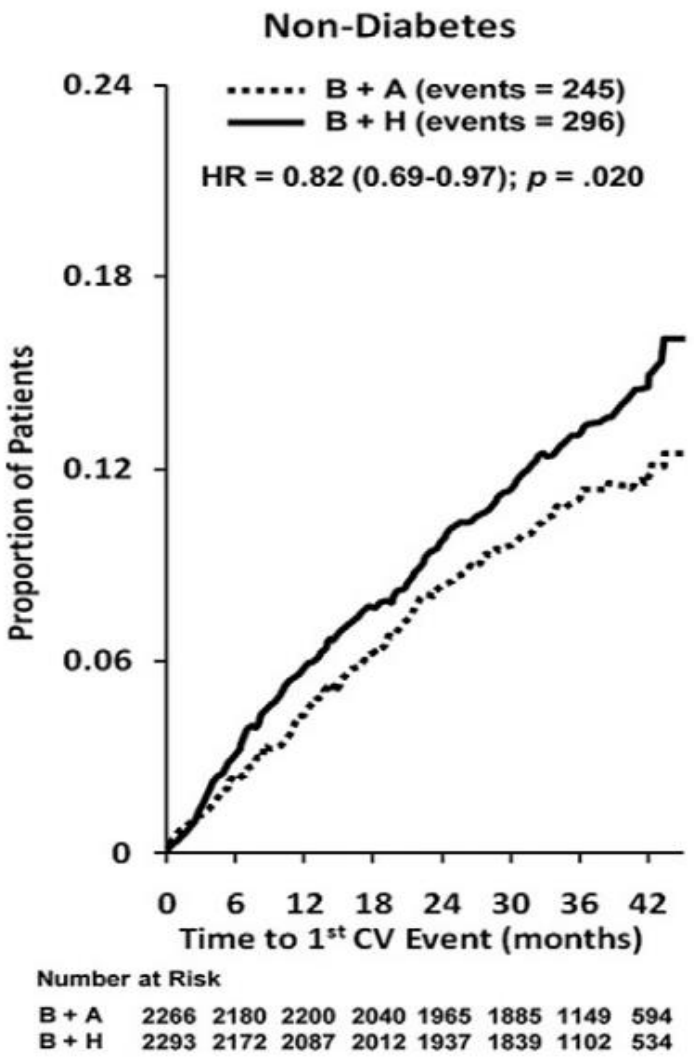
Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension

Aim: To determine which combination therapy in patients with hypertension and diabetes most effectively decreases CVD

Trial compared the outcomes effects of a renin-angiotensin system blocker, benazepril, combined with amlodipine (BA) or hydrochlorothiazide (BH).

A total of 6,946 patients with diabetes were randomized to treatment with BA or BH. A subgroup of 2,842 diabetic patients at very high risk (previous CVD or stroke events) was also analyzed, as were 4,559 patients without diabetes.

NNT= 48



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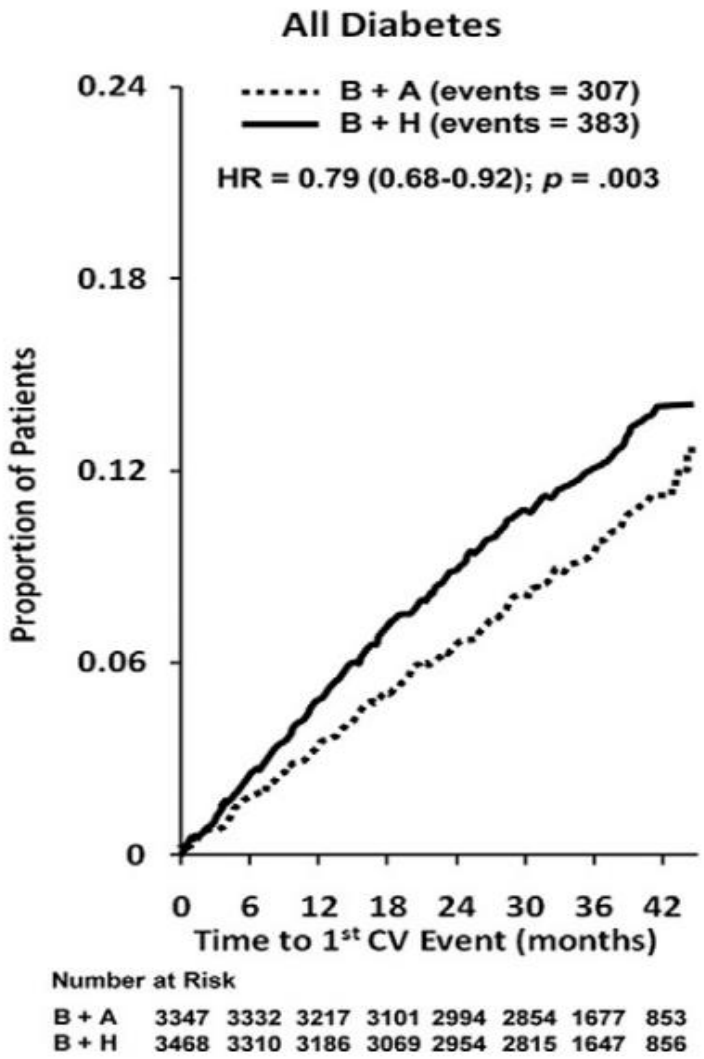

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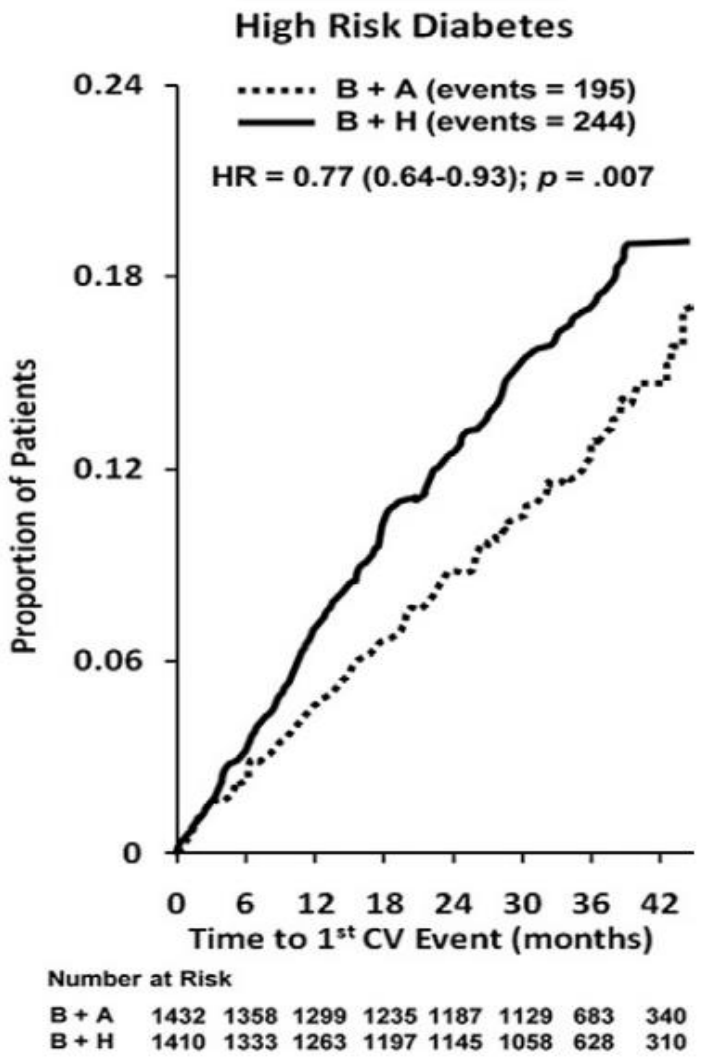


Key messages

- In patients with diabetes and hypertension, combining a renin-angiotensin system blocker with amlodipine, compared with HCT, was superior in reducing CVD and could influence future management of hypertension in patients with diabetes.
- Other such trials are needed to confirm these outcomes and assess other antihypertensive medication combinations.

Hypertension 2019 Nov 4

Original Article

OPEN

Thiazide Use and Cardiovascular Events in Type 2 Diabetic Patients With Well-Controlled Blood Pressure

Tetsuro Tsujimoto, Hiroshi Kajio

Evidence regarding the efficacy and safety of thiazides in patients with well-controlled and relatively low blood pressure (BP) is lacking. This study aimed to assess whether thiazide use is effective and safe in type 2 diabetic patients well-controlled BP and whether intensive BP control leads to decreased risk of cardiovascular events depending on thiazide use. We performed an observational cohort study using data from the ACCORD study (Action to Control Cardiovascular Risk in Diabetes). The primary outcome was major adverse cardiovascular events (MACE), which was a composite end point including cardiovascular death, myocardial infarction, and stroke. Hazard ratios for primary and secondary outcomes with 95% CIs were calculated using Cox proportional hazards models. We included 10 011 type 2 diabetic patients. The overall mean follow-up period was 7.7 years Mean systolic BP at baseline in patients taking and not taking thiazides was 137.2 and 135.7 mm Hg, respectively.

Table 2. Cardiovascular Events and Death in Type 2 Diabetic Patients Taking and Not Taking Thiazides

	All			Standard BP Control			Intensive BP Control		
	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value
Event	n=7242	n=2769		n=1643	n=672		n=1659	n=652	
MACE*									
No. of events	1262	514		279	114		238	124	
Event rate (per 1000 person-years)	22.5	24.2		21.8	21.8		18.6	24.7	
Unadjusted HR (95% CI)	1.00 (ref)	1.08 (0.97–1.20)	0.14	1.00 (ref)	1.01 (0.81–1.25)	0.96	1.00 (ref)	1.34 (1.07–1.66)	0.009
Adjusted HR (95% CI)	1.00 (ref)	1.12 (1.01–1.25)	0.03	1.00 (ref)	1.09 (0.86–1.37)	0.47	1.00 (ref)	1.49 (1.18–1.88)	<0.001
All-cause death									
No. of events	1375	521		295	103		296	106	
Event rate (per 1000 person-years)	20.8	20.7		19.3	16.5		19.5	17.6	
Unadjusted HR (95% CI)	1.00 (ref)	1.01 (0.91–1.11)	0.91	1.00 (ref)	0.86 (0.69–1.08)	0.18	1.00 (ref)	0.90 (0.72–1.12)	0.35
Adjusted HR (95% CI)	1.00 (ref)	1.03 (0.93–1.15)	0.58	1.00 (ref)	0.91 (0.72–1.15)	0.42	1.00 (ref)	0.99 (0.78–1.26)	0.95
Cardiovascular death									
No. of events	470	174		93	29		85	33	
Event rate (per 1000 person-years)	7.1	6.9		6.1	4.6		5.6	5.5	
Unadjusted HR (95% CI)	1.00 (ref)	0.98 (0.82–1.17)	0.83	1.00 (ref)	0.77 (0.51–1.17)	0.22	1.00 (ref)	0.98 (0.66–1.47)	0.93
Adjusted HR (95% CI)	1.00 (ref)	1.07 (0.89–1.29)	0.45	1.00 (ref)	0.93 (0.60–1.46)	0.76	1.00 (ref)	1.11 (0.73–1.71)	0.61

Table 2. Cardiovascular Events and Death in Type 2 Diabetic Patients Taking and Not Taking Thiazides

	All			Standard BP Control			Intensive BP Control		
	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value	Thiazide (–)	Thiazide (+)	*P* Value
Event	n=7242	n=2769		n=1643	n=672		n=1659	n=652	
Major coronary events‡									
No. of events	1333	477		295	105		276	98	
Event rate (per 1000 person-years)	24.0	22.6		23.3	20.1		22.0	19.5	
Unadjusted HR (95% CI)	1.00 (ref)	0.94 (0.84–1.04)	0.22	1.00 (ref)	0.87 (0.69–1.08)	0.20	1.00 (ref)	0.89 (0.71–1.12)	0.31
Adjusted HR (95% CI)	1.00 (ref)	0.97 (0.87–1.09)	0.64	1.00 (ref)	0.94 (0.74–1.19)	0.61	1.00 (ref)	0.98 (0.77–1.25)	0.89
Stroke									
No. of events	334	170		82	44		58	49	
Event rate (per 1000 person-years)	5.7	7.7		6.1	8.1		4.4	9.3	
Unadjusted HR (95% CI)	1.00 (ref)	1.35 (1.13–1.63)	0.001	1.00 (ref)	1.33 (0.92–1.91)	0.13	1.00 (ref)	2.15 (1.47–3.15)	<0.001
Adjusted HR (95% CI)	1.00 (ref)	1.34 (1.10–1.63)	0.004	1.00 (ref)	1.36 (0.91–2.02)	0.13	1.00 (ref)	2.21 (1.47–3.32)	<0.001

Data are presented as n or HR (95% CI). BP indicates blood pressure; HR, hazard ratio; and MACE, major adverse cardiovascular events.
*MACE were defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
‡Major coronary events were defined as fatal coronary events, nonfatal myocardial infarction, or unstable angina.

Thiazide use may be harmful in type 2 diabetic patients with relatively low BP.

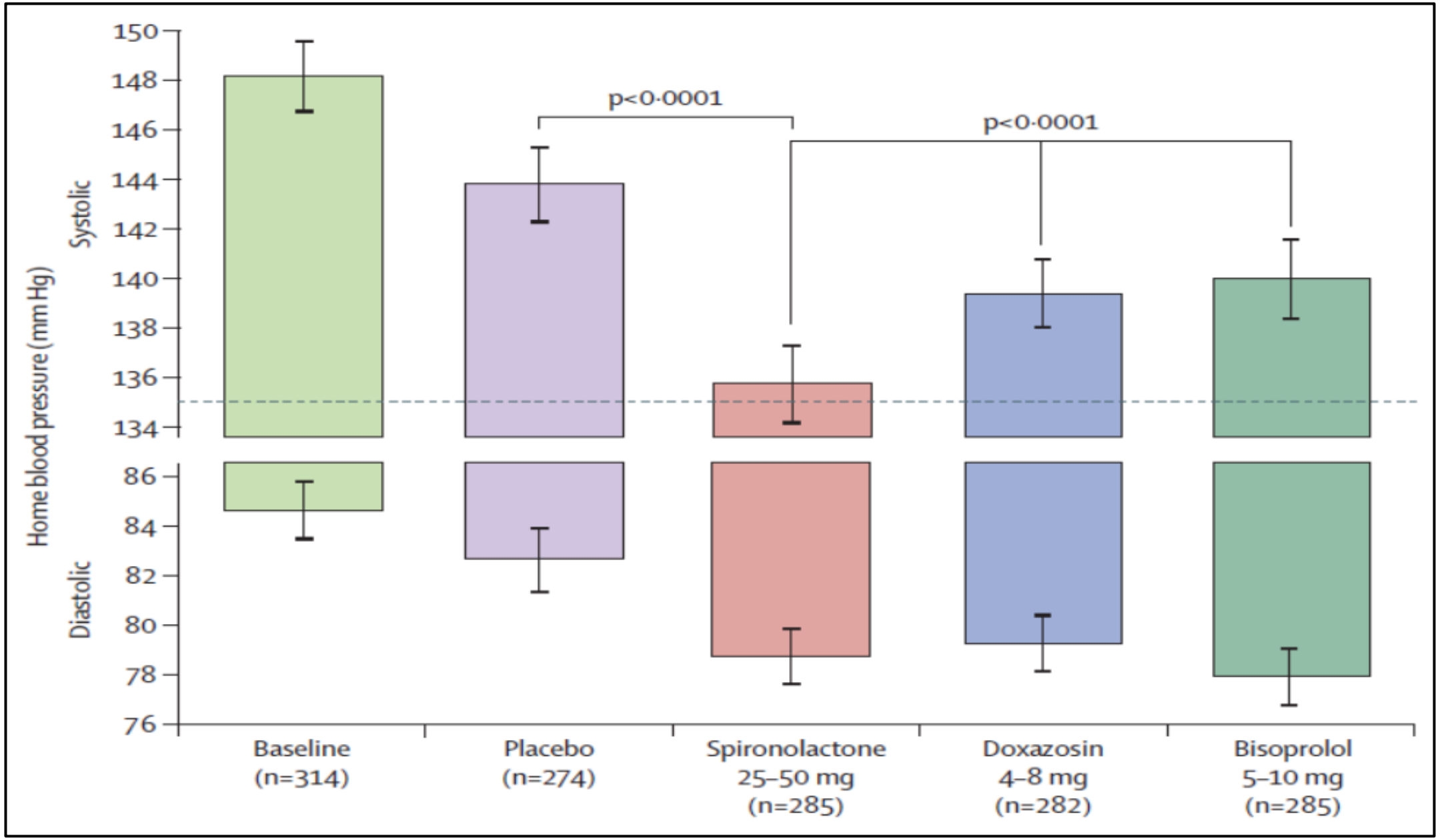
Thiazide Use and Cardiovascular Events in Type 2 Diabetic Patients With Well-Controlled Blood Pressure. Hypertension. 2019

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Lancet 2015; 386:2059-68

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

- In this 12-month double-blind, placebo-controlled, crossover phase 4 trial, patients were enrolled from12 secondary care and 2 primary care sites in the UK.
- The trial enrolled patients aged 18–79 years with SBP 140 mm Hg or greater (or ≥135 mm Hg for patients with diabetes) and home SBP 130 mm Hg or greater, despite treatment for at least 3 months with maximally tolerated doses of three drugs. These had to be an ACE inhibitor or an ARB; (A), a CCB (C), and diuretic (D).
- After a month's single-blind placebo run-in, patients rotated through four cycles of once daily oral treatment with: (1) spironolactone 25–50 mg, (2) doxazosin modified release 4–8 mg, (3) bisoprolol 5–10 mg, and (4) placebo.



Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015

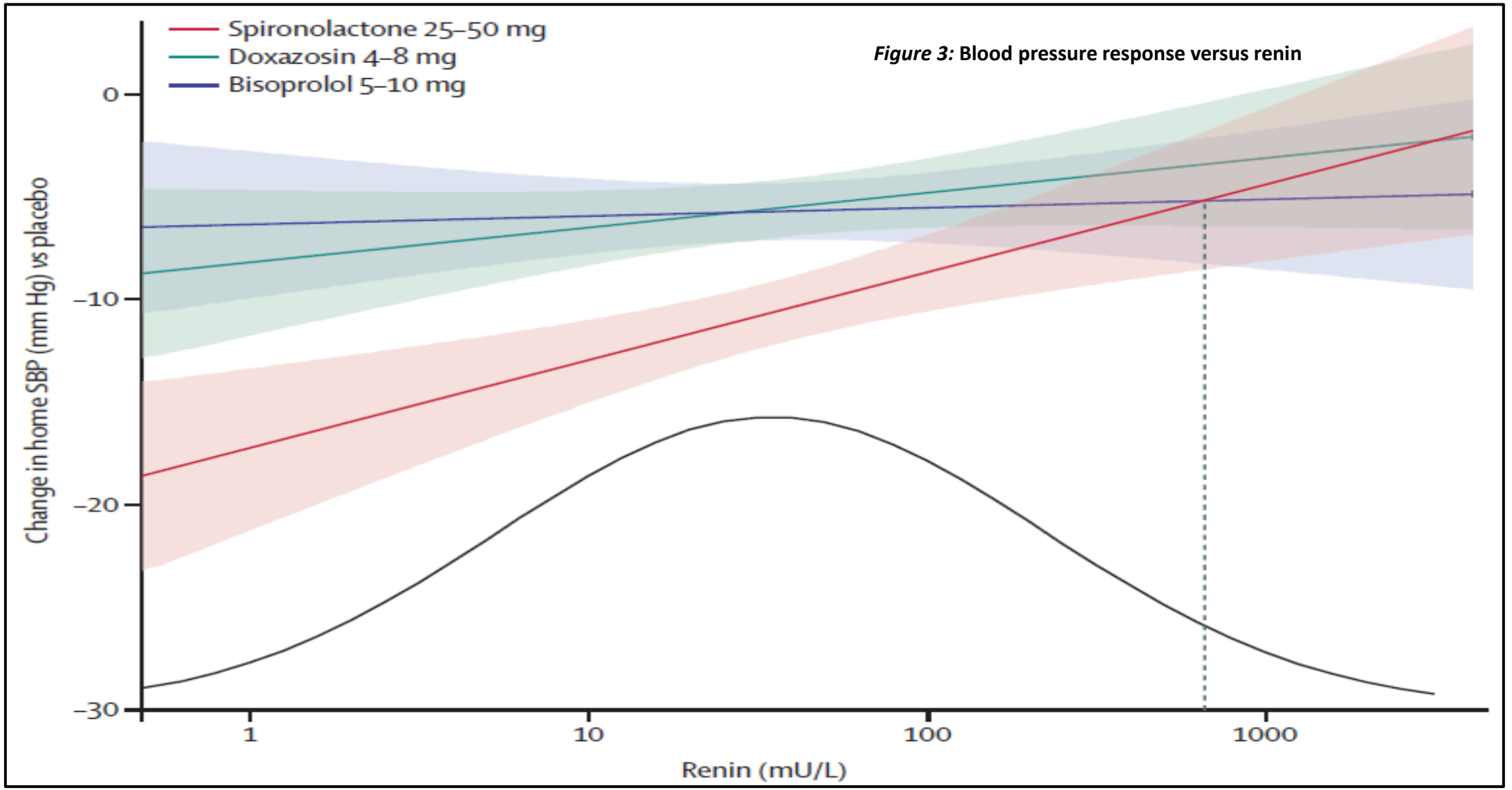


Figure 3: **Blood pressure response versus renin**

Figure 3 shows the relation between plasma renin (measured at baseline whilst patients were receiving their usual medication, A + C + D) and the blood pressure-lowering response to each active treatment corrected for the placebo effect.

Key messages

- Study shows that spironolactone was by far the most effective blood pressure-lowering treatment for patients with resistant hypertension.
- These findings suggest that the predominant underlying pathophysiological cause of resistant hypertension is Na retention, despite existing baseline diuretic therapy.
- Mineralocorticoid receptor antagonists spironolactone, eplerenone can also be effective antihypertensive agents (particularly for those with borderline or low potassium levels), and are important for morbidity and mortality reduction in patients with left ventricular dysfunction.

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015

In people with diabetic kidney disease, hyperkalemia risk dramatically increases when the eGFR is < 45 mL/min/1.73 m^2 or serum K is > 4.5 mEq/L while the patient is already receiving a diuretic. The combination of reduced eGFR and elevated K in a given patient can raise the risk ***8*** fold for hyperkalemia development if spironolactone and an ACE inhibitor or ARB are added.

Diabetes and Hypertension: A Position Statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284

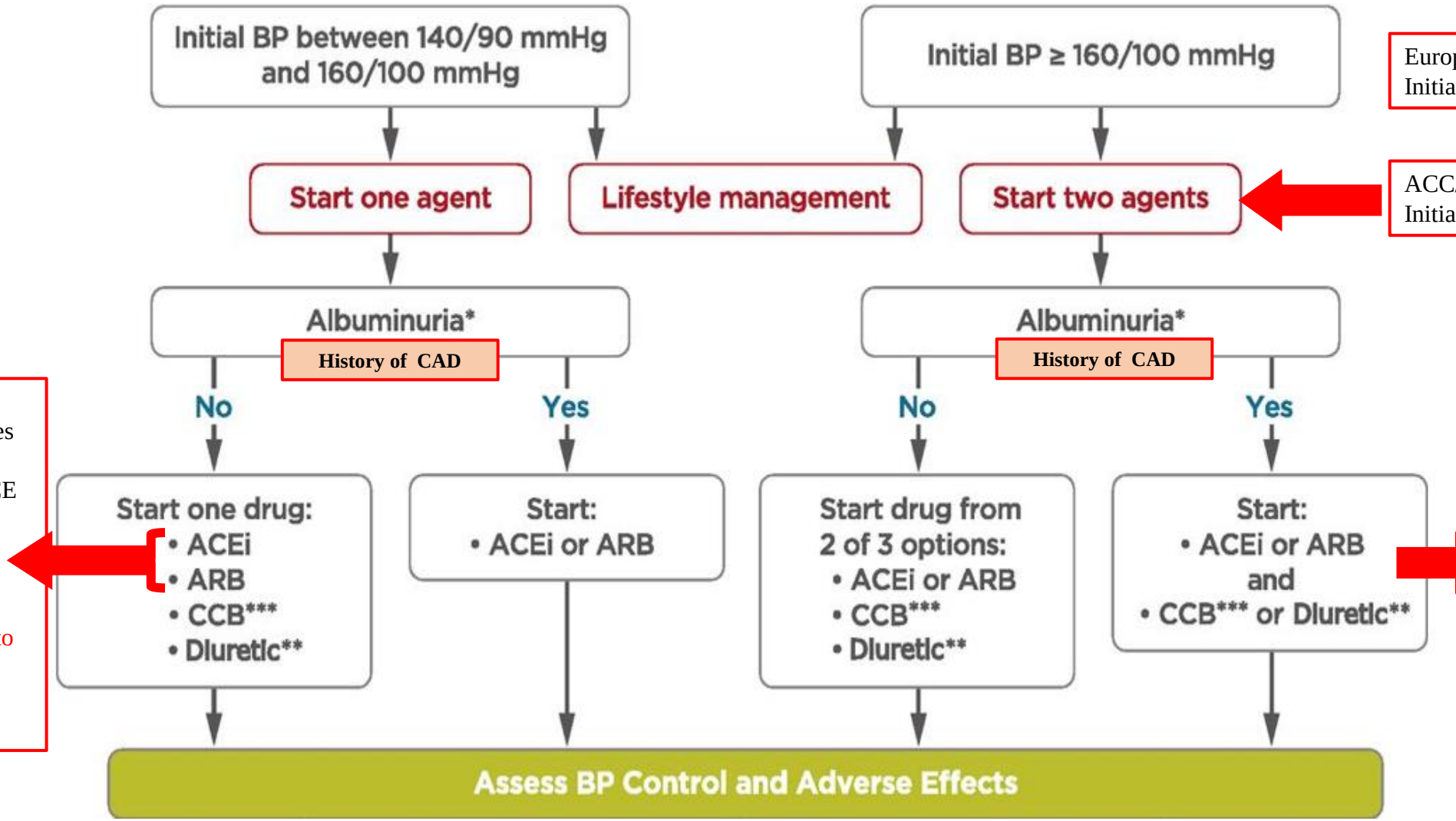
Management of the Patient with Hypertension

Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension*

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP		
			Hypertension	Normotension	Reference
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	−5 mm Hg	−2/3 mm Hg	(S6.2-1)
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	−11 mm Hg	−3 mm Hg	(S6.2-6,S6.2-7)
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	−5/6 mm Hg	−2/3 mm Hg	(S6.2-9,S6.2-10)
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	−4/5 mm Hg	−2 mm Hg	(S6.2-13)
Physical activity	Aerobic	• 90–150 min/wk • 65%–75% heart rate reserve	−5/8 mm Hg	−2/4 mm Hg	(S6.2-18,S6.2-22)
	Dynamic resistance	• 90–150 min/wk • 0%–80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	−4 mm Hg	−2 mm Hg	(S6.2-18)
	Isometric resistance	• 4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk • 8–10 wk	−5 mm Hg	−4 mm Hg	(S6.2-19,S6.2-31)
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: • Men: ≤2 drinks daily • Women: ≤1 drink daily	−4 mm Hg	−3 mm Hg	(S6.2-22—S6.2-24)

DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.

Confirmed Hypertension in People With Diabetes



European guideline
Initial BP ≥ 140/90 mmHg

ACC/AHA
Initial BP ≥ 150/90 mmHg

To prevent inadvertent declines in eGFR, patients treated with an ACE inhibitor or ARB should be aware of volume status and avoid volume depletion to reduce the risk for acute kidney injury

Thiazide-like diuretics are only effective down to an eGFR of 30 mL/min/1.73 m^2. Below an eGFR of 30mL/min/1.73 m^2, a long-acting loop diuretic should be prescribed.

ADA 2023

- In patients with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first line therapy for hypertension.
- In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers.
- β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF, arrhythmia but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions.

It is optimal to select a β-blocker with a concomitant vasodilatory effect (eg. carvedilol, labetalol) which will have fewer adverse metabolic effects.

Frequently Used Medications and Other Substances That May Cause Elevated BP*

Agent	Possible Management Strategy
Decongestants (e.g., phenylephrine, pseudoephedrine)	• Use for shortest duration possible, and avoid in severe or uncontrolled hypertension • Consider alternative therapies (e.g., nasal saline, intranasal corticosteroids, antihistamines) as appropriate
Oral contraceptives	• Use low-dose (e.g., 20–30 mcg ethinyl estradiol) agents or a progestin-only form of contraception, or consider alternative forms of birth control where appropriate (e.g., barrier, abstinence, IUD) • Avoid use in women with uncontrolled hypertension (S5.4.1-16)
NSAIDs	• Avoid systemic NSAIDs when possible • Consider alternative analgesics (e.g., acetaminophen, tramadol, topical NSAIDs), depending on indication and risk
Systemic corticosteroids (e.g., dexamethasone, fludrocortisone, methylprednisolone, prednisone, prednisolone)	• Avoid or limit use when possible • Consider alternative modes of administration (e.g., inhaled, topical) when feasible

Conditions to exclude before making the diagnosis of resistant hypertension

Conditions	Definition
Secondary hypertension (136)*	Hypertension elicited or exacerbated by other drugs or diseases
Pseudoresistance (136,137)	Apparent hypertension due to lack of medication adherence, **poor blood pressure measurement technique**
Masked hypertension (137)	Clinic blood pressure <140/90 mmHg; daytime blood pressure **≥135 or ≥85 mmHg**
White-coat hypertension (137)	Clinic blood pressure ≥140 or ≥90 mmHg; daytime blood pressure <135/85 mmHg

* Secondary causes of hypertension include endocrine issues, renal arterial disease, excessive edema in advanced kidney disease, and hormones, such as testosterone. Drugs that increase blood pressure include NSAIDs, decongestants, and some illicit substances.

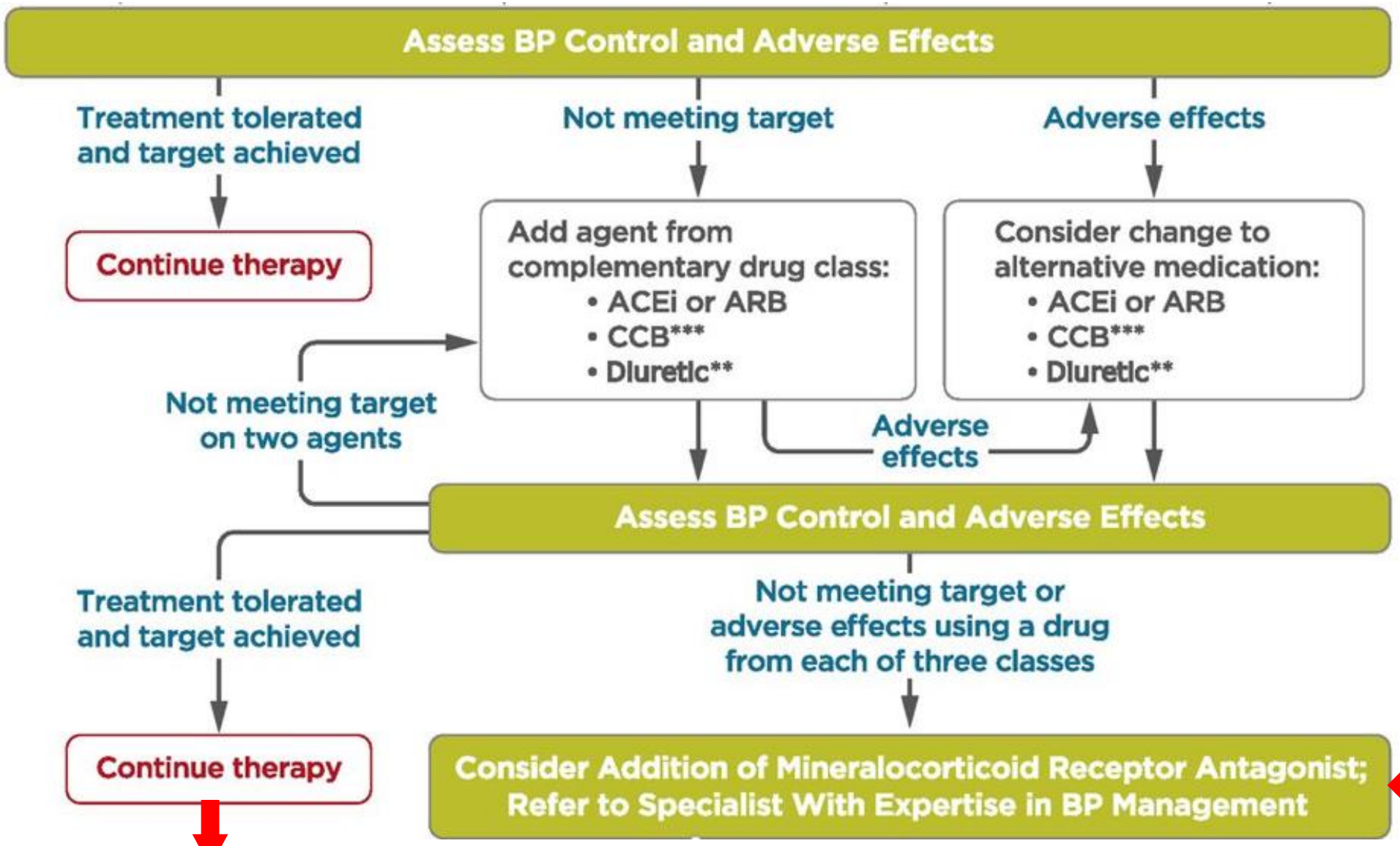


Figure 1: Recommendations for the treatment of confirmed hypertension in people with diabetes. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine. BP, blood pressure.

Reduce sympathetic nerve activity Reduce albuminuria in short term and have additional cardiovascular benefits

In patients receiving pharmacologic antihypertensive treatment, home blood pressure should be measured to promote patient engagement in treatment and adherence and may better correlate with ASCVD risk than office measurements .B

Oral Antihypertensive Medication

Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5–25	1	• Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD. • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid–lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–5	1	
ACE inhibitors	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with ACE inhibitors. • Avoid in pregnancy.
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–20	1 or 2	
	Trandolapril	1–4	1	

Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
ARBs	Azilsartan	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor. • There is an increased risk of hyperkalemia in CKD or in those on K^+supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema • with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	

Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Primary agents				
CCB—dihydropyridines	Amlodipine	2.5–10	1	• Avoid use in patients with HF*r*EF; amlodipine or felodipine may be used if required. • They are associated with dose-related pedal edema, which is more common in women than men.
	Felodipine	2.5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	60–120	2	
	Nifedipine LA	30–90	1	
	Nisoldipine	17–34	1	
CCB—nondihydropyridines	Diltiazem ER	120–360	1	• Avoid routine use with beta blockers because of increased risk of bradycardia and heart block. • Do not use in patients with HF*r*EF. • There are drug interactions with diltiazem and verapamil (*CYP3A4* major substrate and moderate inhibitor).

Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency	Comments
Secondary agents				
Diuretics—loop	Bumetanide	0.5–2	2	• These are preferred diuretics in patients with symptomatic HF. They are preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR <30 mL/min).
	Furosemide	20–80	2	
	Torsemide	5–10	1	
Diuretics—potassium sparing	Amiloride	5–10	1 or 2	• These are monotherapy agents and minimally effective antihypertensive agents. • Combination therapy of potassium-sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy. • Avoid in patients with significant CKD (e.g., GFR <45 mL/min).
	Triamterene	50–100	1 or 2	
Diuretics—aldosterone antagonists	Eplerenone	50–100	1 or 2	• These are preferred agents in primary aldosteronism and resistant hypertension. • Spironolactone is associated with greater risk of gynecomastia and impotence as compared with eplerenone. • This is common add-on therapy in resistant hypertension. • Avoid use with K^+ supplements, other K^+-sparing diuretics, or significant renal dysfunction. • Eplerenone often requires twice-daily dosing for adequate BP lowering.
	Spironolactone	25–100	1	
Beta blockers—cardioselective	Atenolol	25–100	2	▪ Beta blockers are not recommended as first-line agents unless the patient has IHD or HF. ▪ These are preferred in patients with bronchospastic airway disease requiring a beta blocker. ▪ Bisoprolol and metoprolol succinate are preferred in patients with HFrEF. ▪ Avoid abrupt cessation.
	Betaxolol	5–20	1	
	Bisoprolol	2.5–10	1	
	Metoprolol tartrate	100–200	2	
	Metoprolol succinate	50–200	1	

Diabetic Kidney Disease

Diabetic kidney disease (DKD) is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage. Diabetic kidney disease typically develops after diabetes duration of 10 years in type 1 diabetes, but may be present at diagnosis of type 2 diabetes. Screening for albuminuria can be most easily performed by urinary albumin–to– creatinine ratio (UACR) in a random spot urine collection.

Normal UACR is generally defined as , <30 mg/g Cr, and increased urinary albumin excretion is defined as ≥30 mg/g Cr.

Because of high biological variability > 20% , 2 of 3 specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have albuminuria.

Exercise within 24 h, infection, fever, CHF, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage.

eGFR should be calculated from serum Cr using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred.(http://www.nkdep.nih.gov.)

Diagnosis of Diabetic Kidney Disease

- Diabetic kidney disease is usually **a clinical diagnosis** made based on the presence of albuminuria **and/or** reduced eGFR in the **absence** of signs or symptoms of other primary causes of kidney damage.
- The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without hematuria, and gradually progressive kidney disease.
- Signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes, ***and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time.***

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 11.1
Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal estimated GFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. (121).

Indications for referring the patients to nephrologist for possible kidney biopsy

1- Presence of an ACTIVE urinary sediment (containing red or white blood cells or cellular casts),

2- Rapidly increasing albuminuria or nephrotic syndrome,

3- Rapidly decreasing eGFR,

4- Absence of retinopathy in type 1 diabetes, but not type 2 DM

may suggest alternative or additional causes of kidney disease.

Acute Kidney Injury (AKI)

- Acute kidney injury (AKI) is usually diagnosed by a rapid increase in serum Cr, which is also reflected as a rapid decrease in eGFR, over a relatively short period of time.
- Risk factors for AKI include;
- Diabetes per se , pre –existing CKD
- Medications that cause kidney injury (e.g., NSAID)
- Medications that alter renal blood flow and intra-renal hemodynamics (i.e. many antihypertensive medications e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration.
- SGL2 –I and nonsteroidal mineralocorticoid anatagonists (MRAs) do not significantly increase risk of AKI.

Important notes for ACEI/ARBs

- Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI.
- ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.
- Outcome benefits on both mortality and slowed CKD progression in people with diabetes on ACE/ARB who have an eGFR<30 mL/min/1.73 m^2.

Surveillance

- Albuminuria and eGFR should be monitored regularly to enable timely diagnosis of diabetic kidney disease, monitor progression of diabetic kidney disease, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed.
- Serum K should also be monitored for patients treated with ACE inhibitors, ARBs, and diuretics because these medications can cause hyperkalemia or hypokalemia, which are associated with cardiovascular risk and mortality.
- Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy
- In clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria from levels ≥300 mg/g Cr or by >30% from baseline has been associated with improved renal and cardiovascular outcomes.

When eGFR is , <60 mL/min/1.73 m^2, screening for complications of CKD is indicated

Table 10.2: Selected complications of CKD

Complication	Medical and laboratory evaluation
Elevated blood pressure	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of CKD generally become prevalent when eGFR falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every possible clinical contact; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Interventions (Nutrition)

- For people with non-dialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance) Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time.
- Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided.
- Restriction of dietary sodium (<2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk.

Interventions (blood pressure and use of RASS inhibitors)

- Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to **delay** **the onset and progression of** ALBUMINURIA and REDUCTION of eGFR in patients with type 1 diabetes and type 2 diabetes.
- There is a lag time of **at least 2 years in type 2 diabetes to over 10 years in type 1**
- **diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes**.
- Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive.

Cardiovascular Disease and Blood Pressure

- Antihypertensive therapy reduces the risk of albuminuria;
- And among patients with type 1 or 2 diabetes with established diabetic kidney disease (eGFR<60 mL/min/1.73 m^2 & UACR >300 mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD.
- Antihypertensive therapy reduces risks of cardiovascular events.
- BP<130/80 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among people with diabetes.

Cardiovascular Disease and Blood Pressure

- ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes and hypertension, **eGFR<60mL/min/1.73 m^2 and UACR> 300 mg/g Cr** because of their **proven benefits** for prevention of CKD progression.
- In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy has been demonstrated to reduce **progression to more advanced albuminuria (>300 mg/g Cr) and CVD** but **not progression to ESRD**.

An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in people with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate.

Effects on the kidney that are Direct, i.e., not Mediated Through Glycemia, Role of SGL2-I and GLP1- Analogue

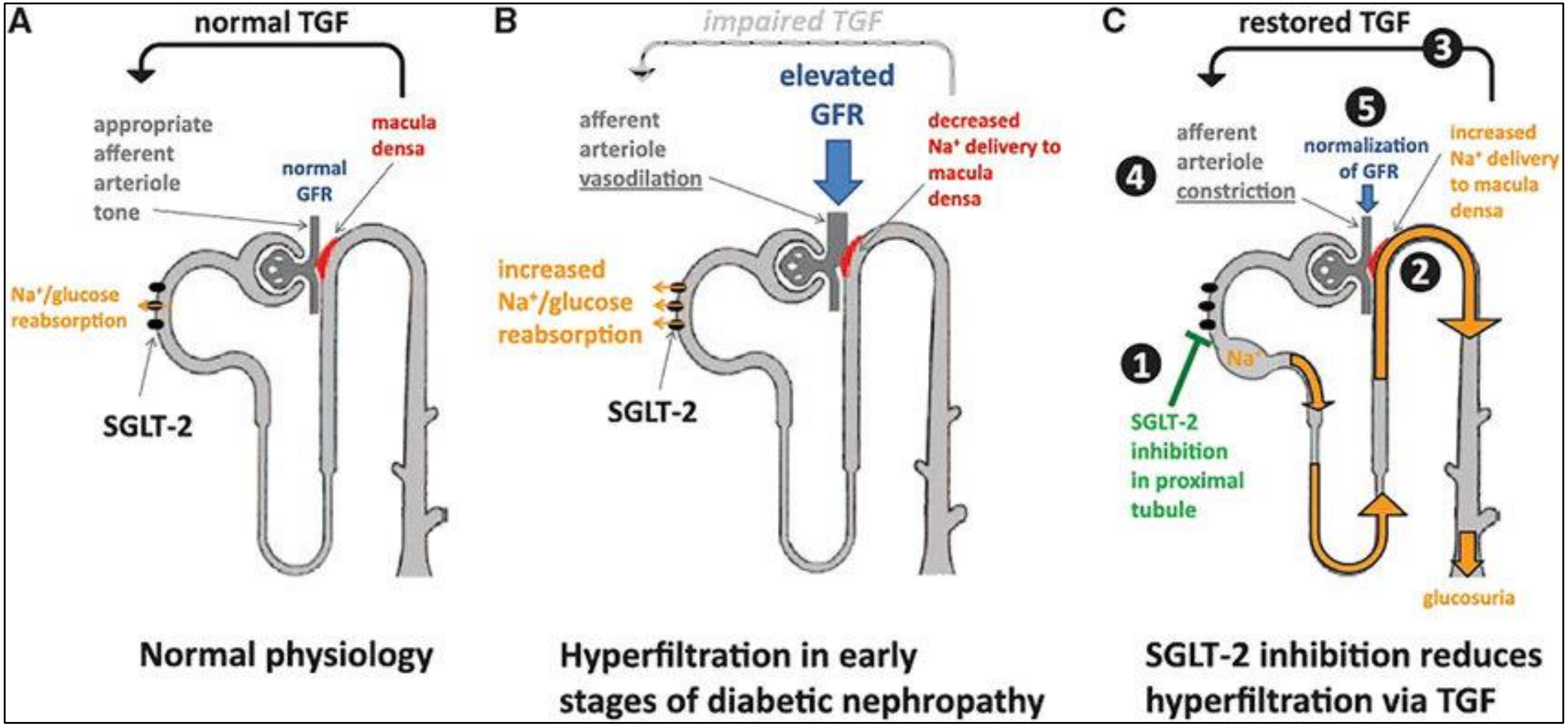


FIGURE 2: Actions of SGLT-2 inhibitors on the renal microcirculation in patients with DM. Under physiological conditions, SGLT-2 co-transporters reabsorb around 90% of the filtered glucose and relevant amounts of sodium, the macula densa is orchestrating normal tubuloglomerular feedback and GFR is normal. In patients with DM, the **number and activity of SGLT-2 co-trasporters are increased**, **thus the macula densa senses relatively lower sodium and chloride concentrations, leading to afferent arteriole vasodilation and hyperfiltration**. Inhibition of SGLT-2 blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium and chloride delivery to the macula densa, restoration of normal tubulo-glomerular feedback and afferent vasoconstriction, which in turn reduces renal plasma flow and GFR.

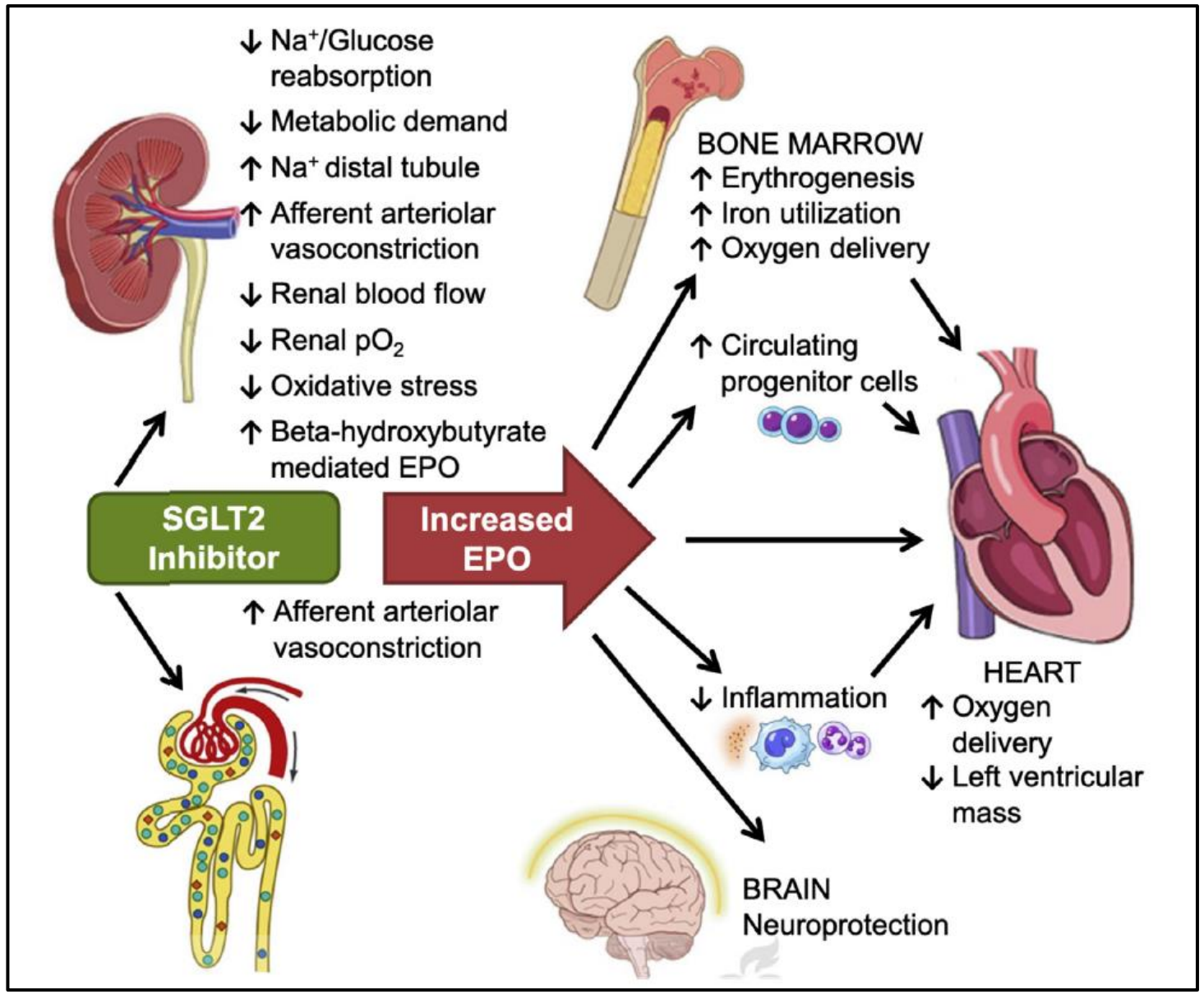
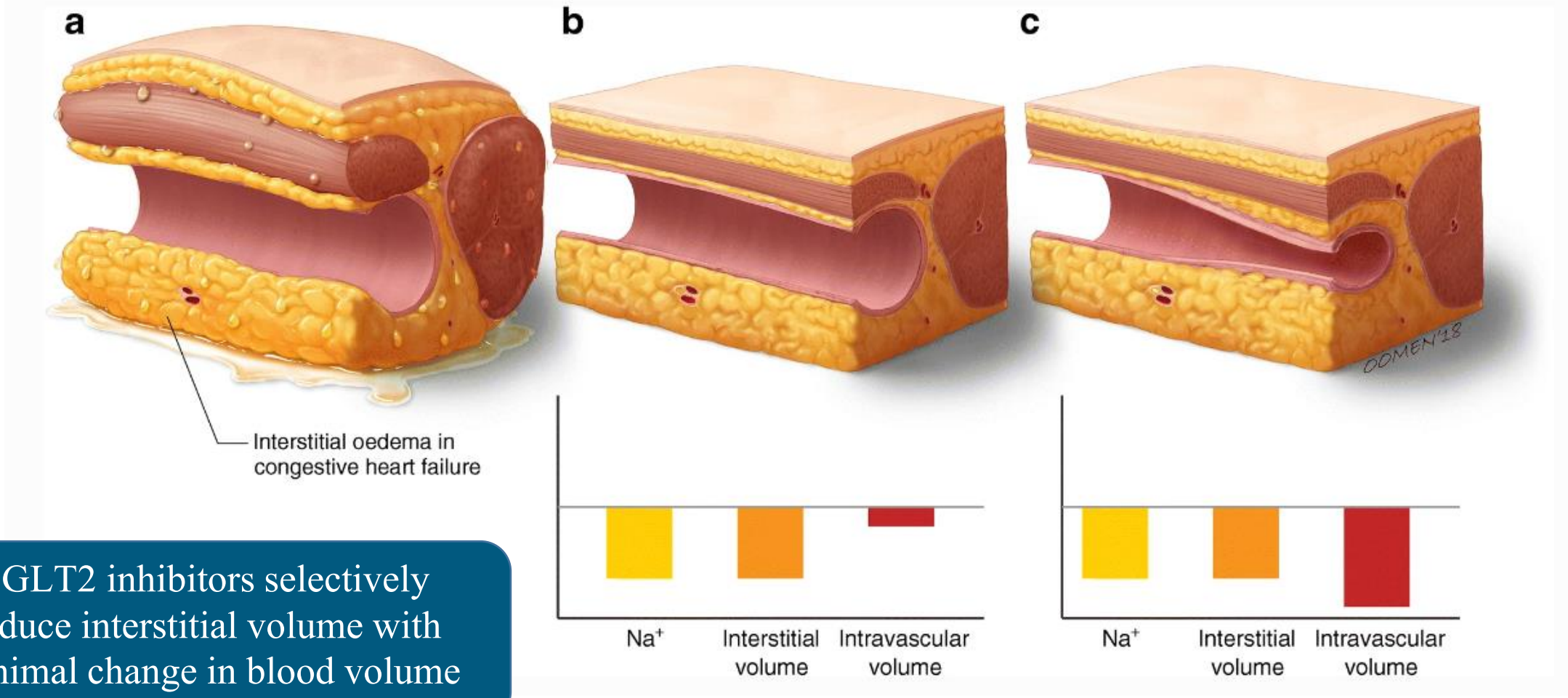


Fig 3:
Multiple Sites for the Beneficial Effects of SGLT2 Inhibition.
Proposed renal mechanisms for increased erythropoietin (EPO) with sodium glucose co-transporter 2 (SGLT2) inhibitors.
Reproduced with
permission from Mazer et al. (95).

SGLT2 Inhibitors Work Differently Than Diuretics



SGLT2 inhibitors selectively reduce interstitial volume with minimal change in blood volume

Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61:2108-17.

Lancet 2019; 393: 31–39

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

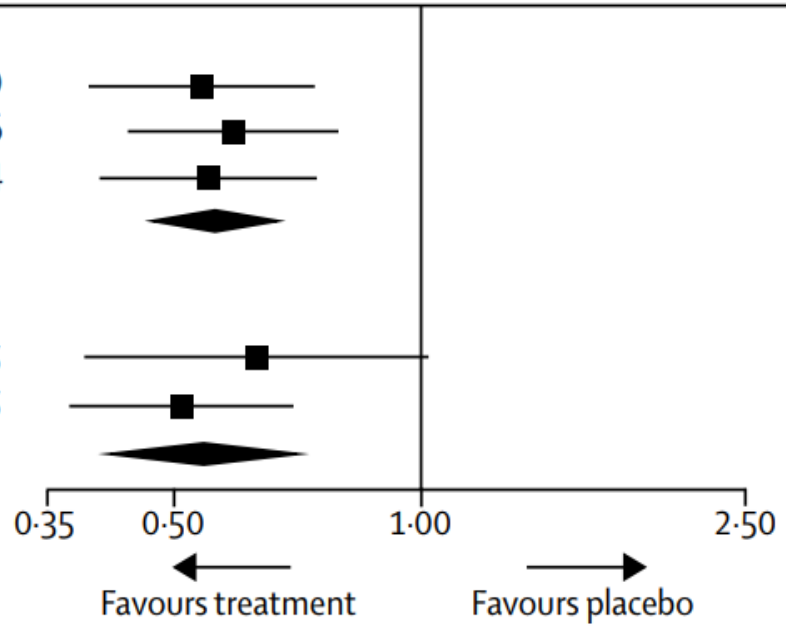
	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m^2	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

SGLT2 inhibitors reduced the composite of worsening of renal function, end-stage renal disease, or renal death by 45% , both in patients with atherosclerotic CVD and those with multiple risk factors

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



p for interaction=0.71

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systemic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019; 393: 31–39

CREDENCE

2019 Jun 13;380(24):2295-2306.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

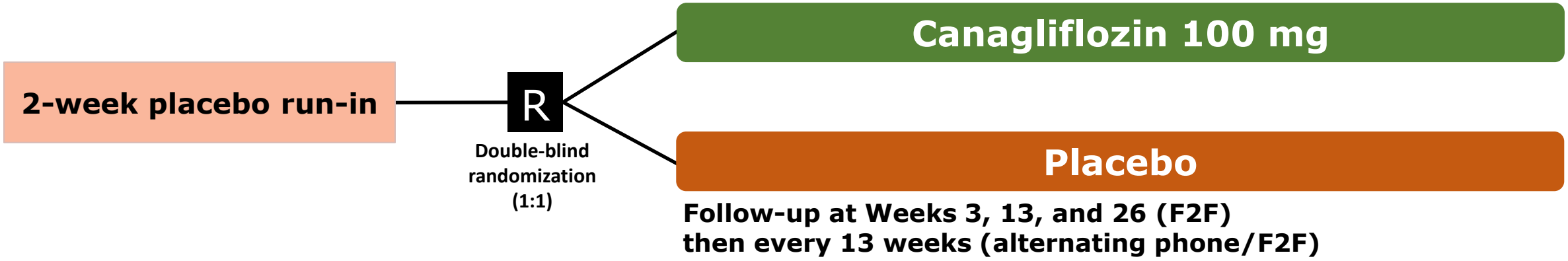
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Aim : To assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients **with type 2 diabetes and albuminuric chronic kidney disease**

Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c **6.5% to 12.0%**
- **eGFR 30 to 90 mL/min/1.73 m²**
- **UACR 300 to 5000 mg/g**
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM



Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred

Primary Endpoint Definitions

ESKD

- Chronic dialysis for ≥30 days
- Kidney transplantation
- eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment

Doubling of serum creatinine

- Doubling from the baseline average sustained for ≥30 days by central laboratory assessment

Renal death

- Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated

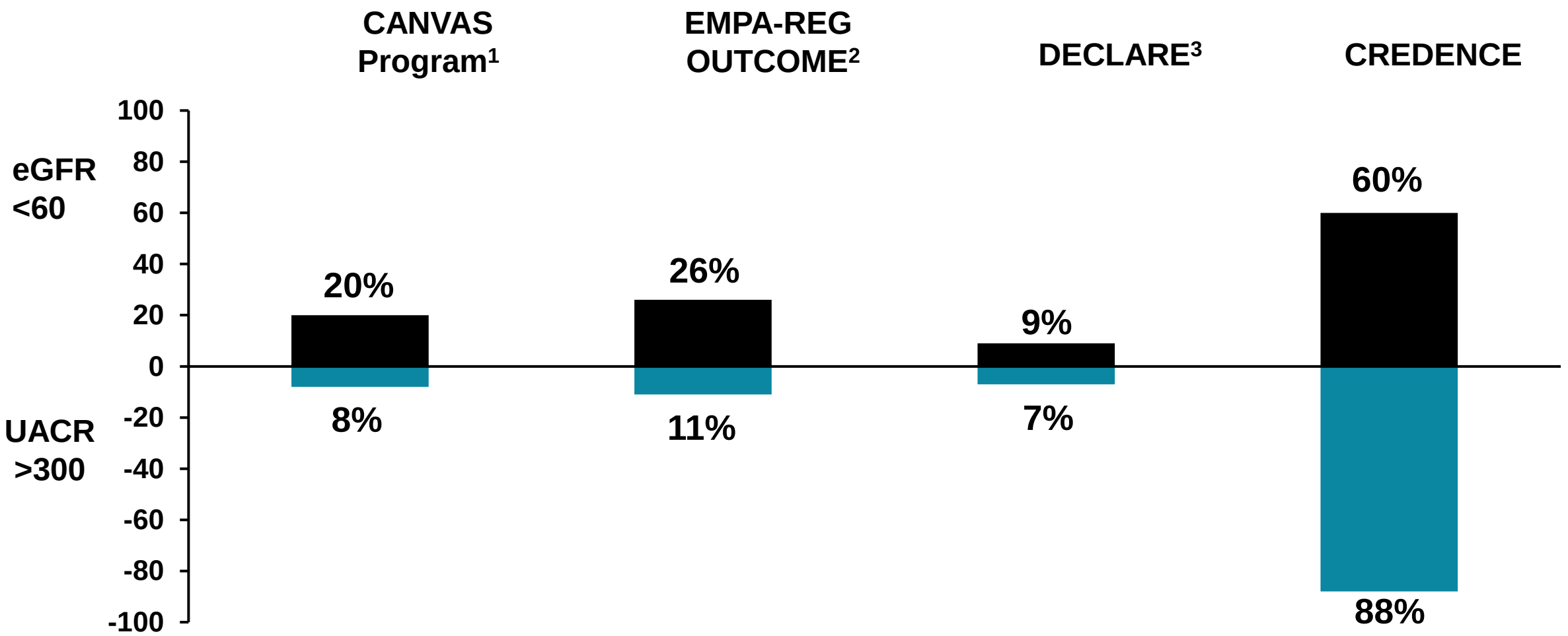
CV death

- Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Canagliflozin (N = 2202)	Placebo (N = 2199)	All Patients (N = 4401)
Age — yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex — no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group — no. (%)†			
White	1487 (67.5)	1444 (65.7)	2931 (66.6)
Black	112 (5.1)	112 (5.1)	224 (5.1)
Asian	425 (19.3)	452 (20.6)	877 (19.9)
Other	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker — no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension — no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure — no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes — yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease — no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation — no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
Body-mass index‡	31.4±6.2	31.3±6.2	31.3±6.2
Blood pressure — mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin — %	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR — ml/min/1.73 m^2§	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)¶	923 (459–1794)	931 (473–1868)	927 (463–1833)

Lower Baseline Renal Function in CREDENCE Participants

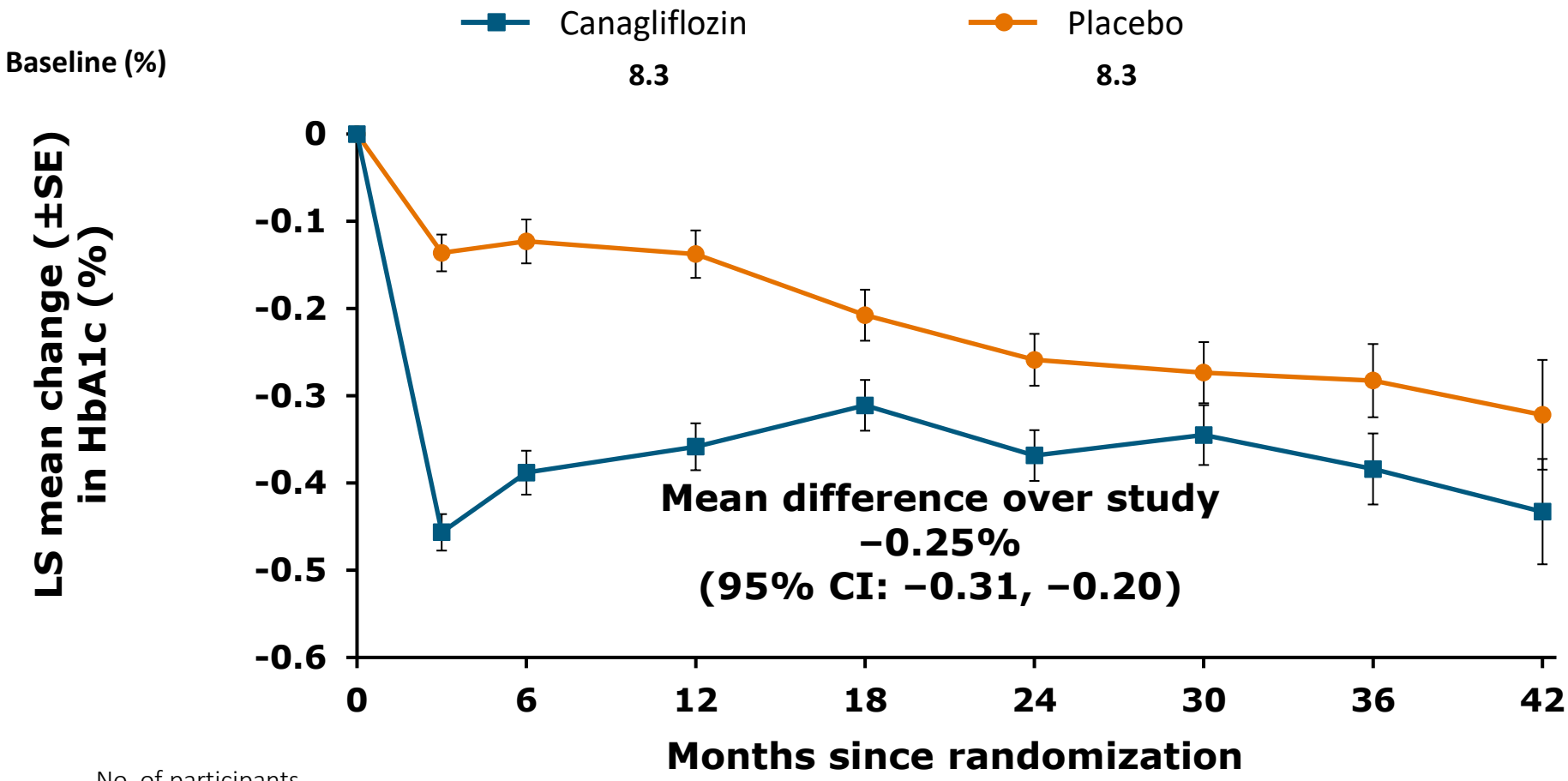


1. Neal B, et al. N Engl J Med. 2017;377(7):644-657. 2. Zinman B, et al. N Engl J Med. 2015;373(22):2117-2128. 3. Raz I, et al. Diabetes Obes Metab. 2018;20(5):1102-1110.

Baseline Therapies

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Glucose-lowering agents, %			
Insulin	66	65	66
Metformin	58	58	58
Sulfonylurea	28	30	29
DPP-4 inhibitor	17	17	17
GLP-1 receptor agonist	4	4	4
Renal and CV protective agents, %			
RAAS inhibitor	>99.9	99.8	99.9
Statin	70	68	69
Antithrombotic	61	58	60
Beta blocker	40	40	40
Diuretic	47	47	47

Effects on HbA1c

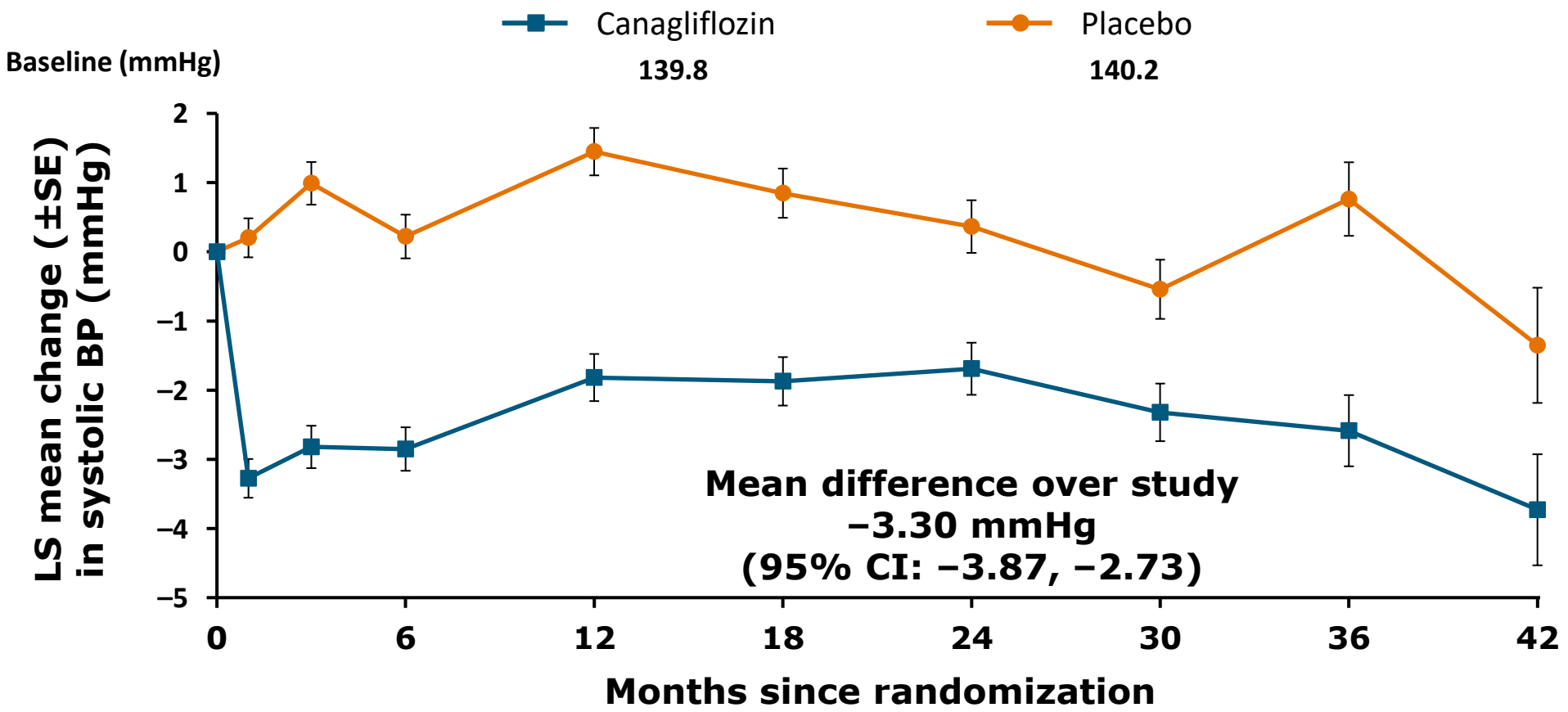


No. of participants

Placebo	2150	2103	2066	1981	1882	1728	1172	688	252
Canagliflozin	2154	2108	2074	2024	1909	1817	1254	729	274

ITT analysis

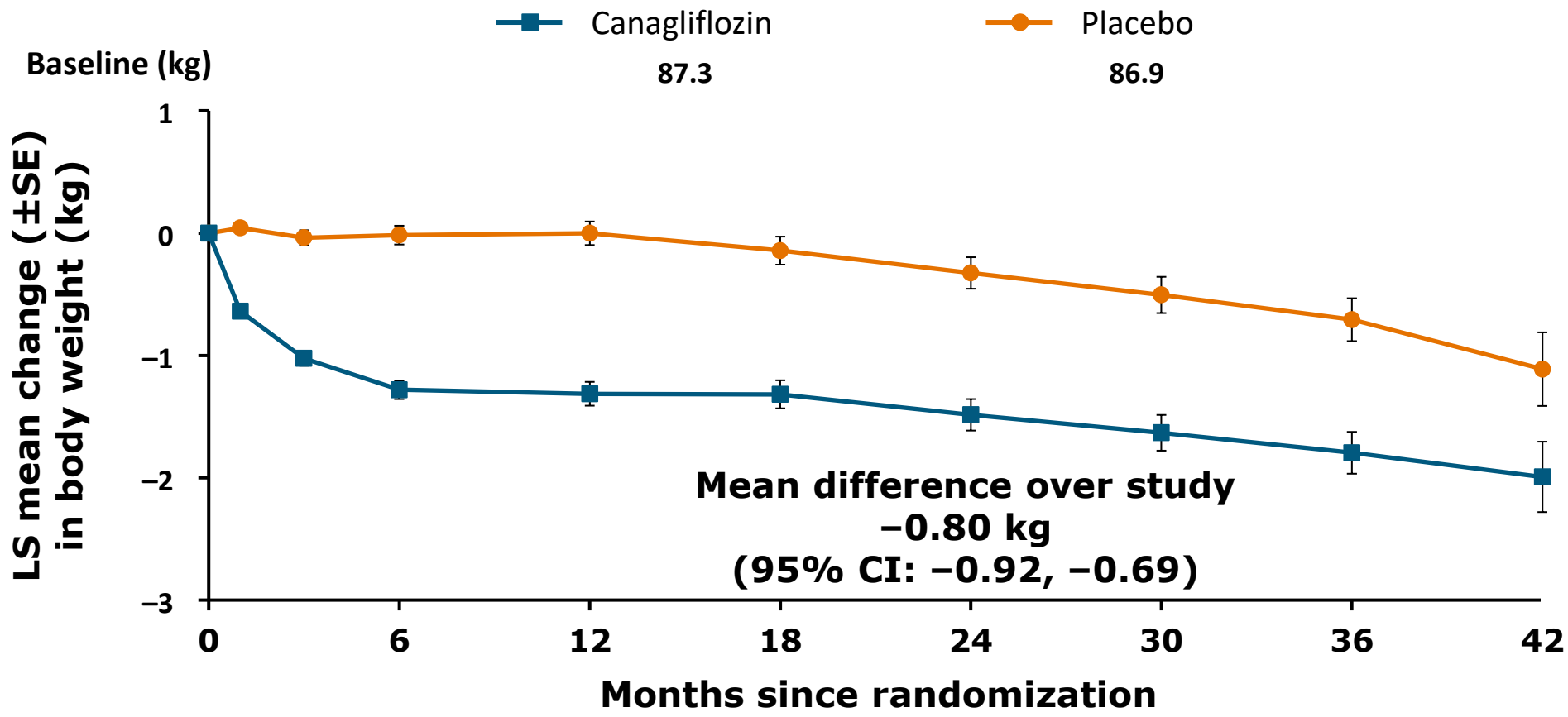
Effects on Systolic BP



No. of participants									
Placebo	2188	2131	2096	2027	1923	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

ITT analysis

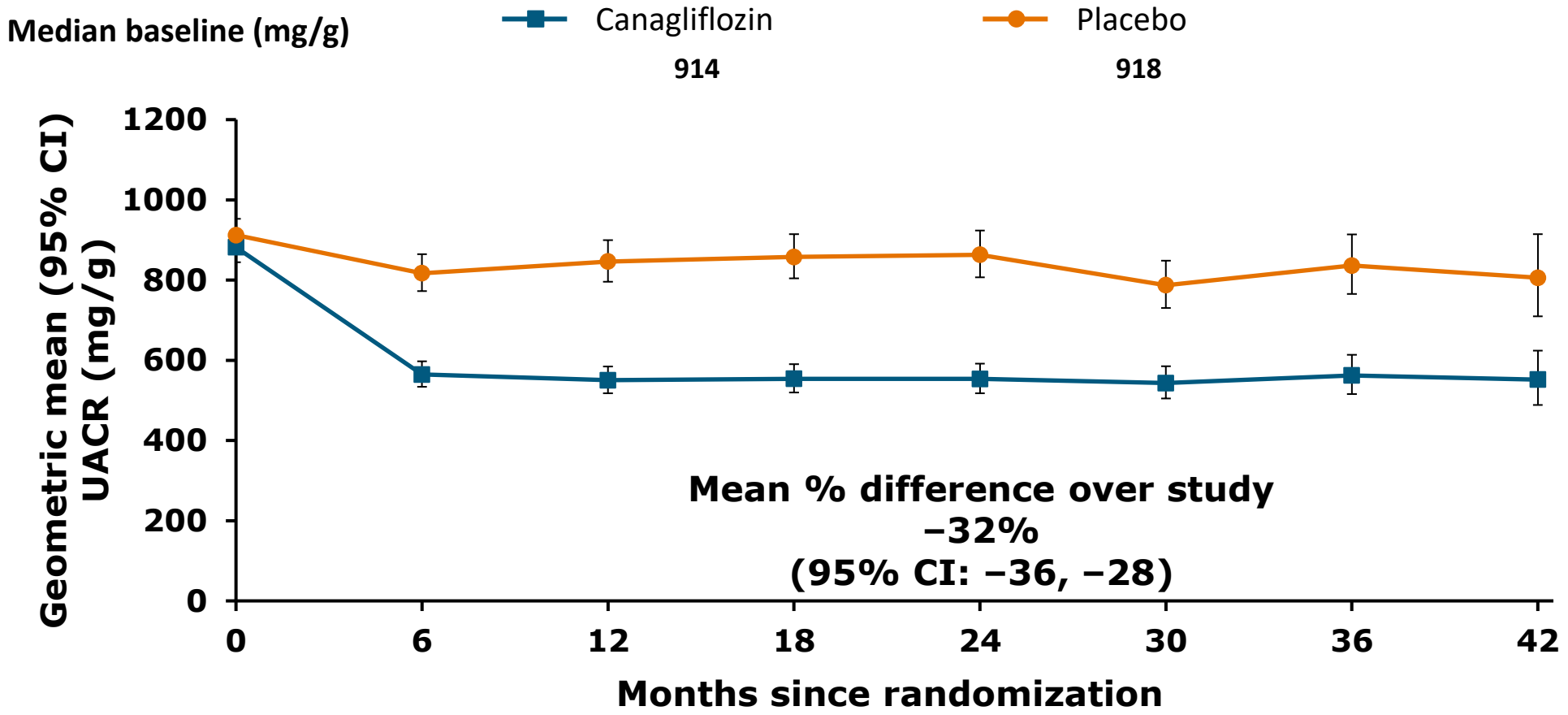
Effects on Body Weight



No. of participants								
Placebo	2187	2126	2092	2005	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1830	1256	731	263

ITT analysis

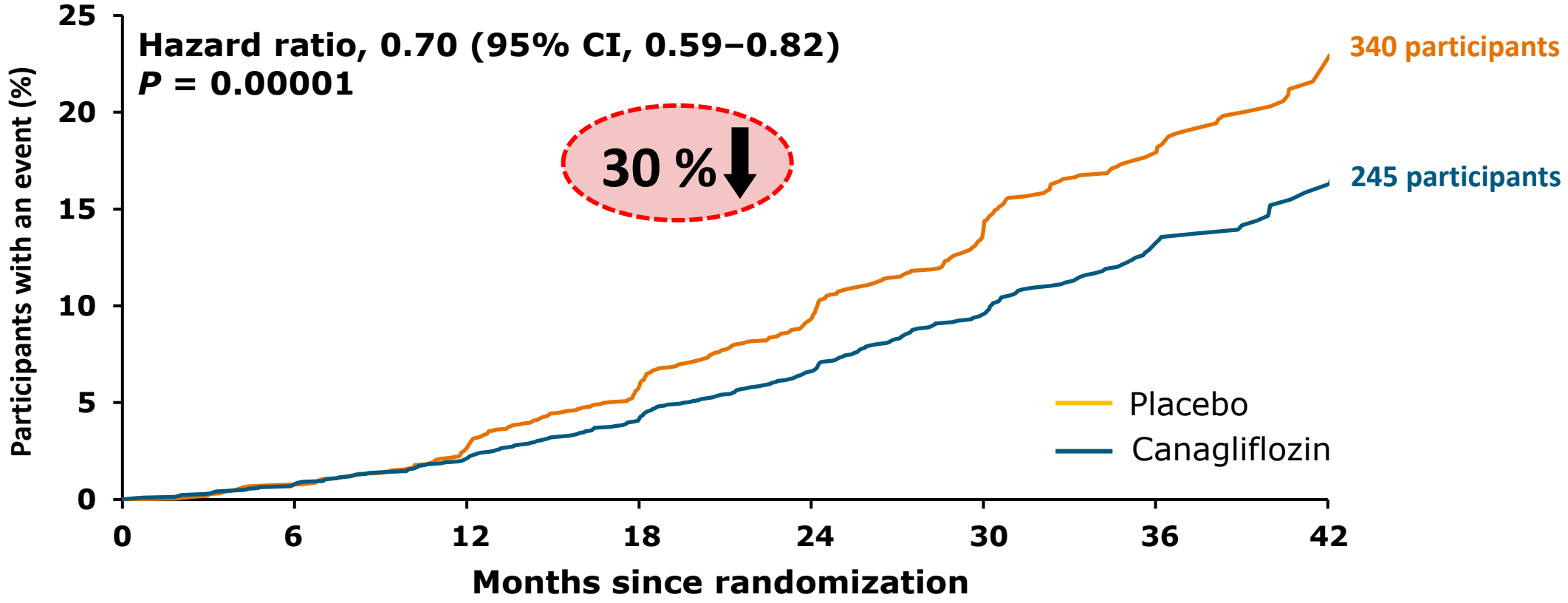
Effects on Albuminuria (UACR)



No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

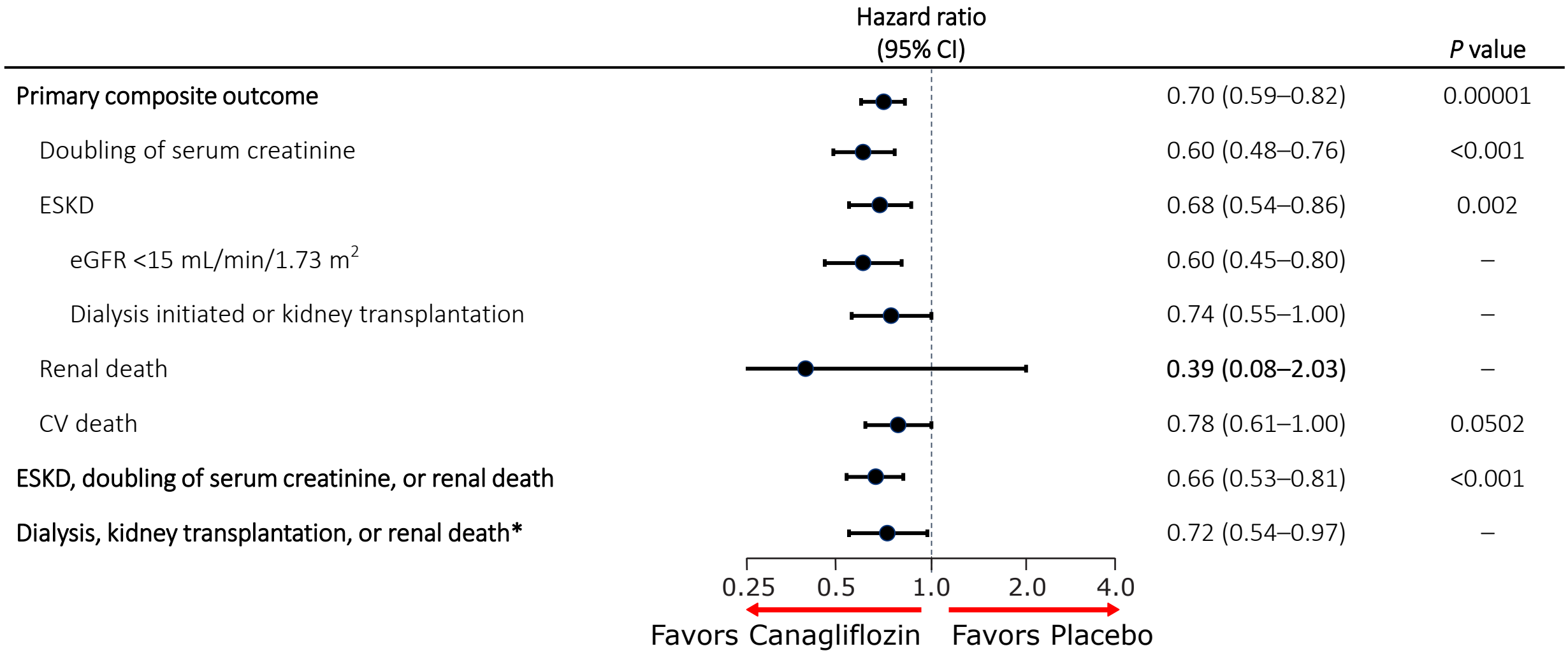
ITT analysis

Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death

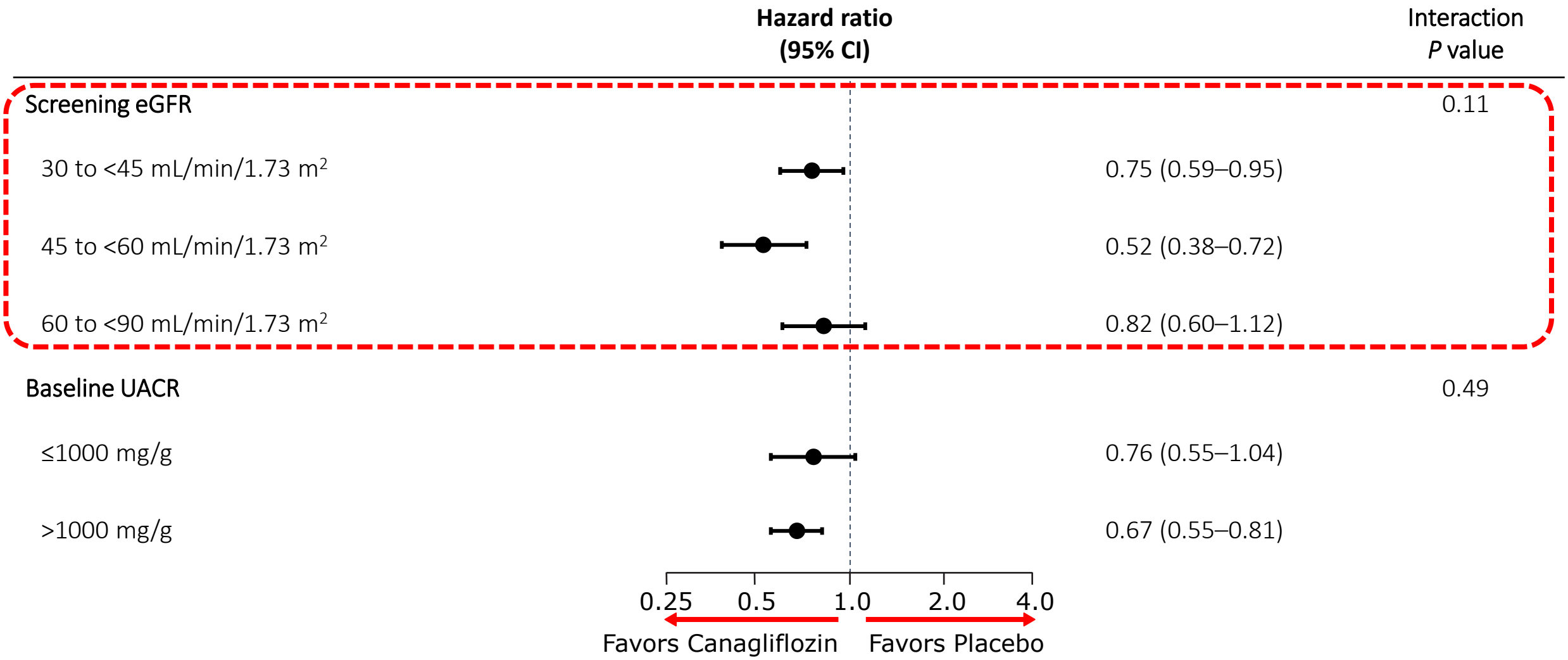


No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Summary Forest Plot



Primary Outcome by Screening eGFR and Albuminuria



DAPA-CKD

The NEW ENGLAND JOURNAL of MEDICINE

2020;383:1436-46

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D.,

- ✓ Participants with an estimated GFR of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine) of 200 to 5000 were randomized to receive dapagliflozin (10 mg once daily) or placebo.
- ✓ The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes
- ✓ 67.5% had received a diagnosis of type 2 diabetes
- ✓ Median follow up: 2.4 years

CREDENCE

Key inclusion criteria

- ✓ ≥30 years of age
- ✓ T2DM and HbA1c **6.5% to 12.0%**
- ✓ **eGFR 30 to 90 mL/min/1.73 m^2**
- ✓ **UACR 300 to 5000 mg/g**
- ✓ Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

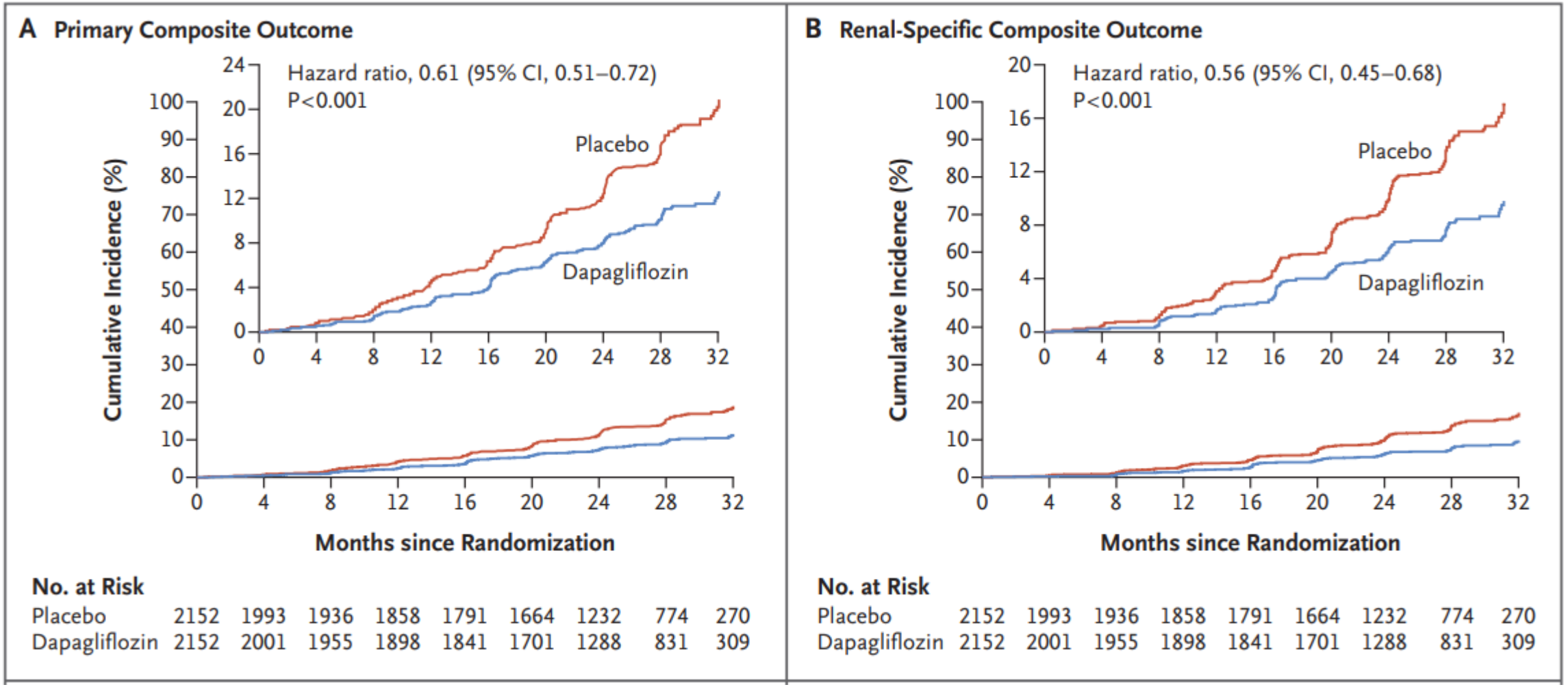


Figure 1. Primary and Secondary Outcomes. The primary outcome was a composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, end stage kidney disease, or death from renal or cardiovascular causes (Panel A). The secondary outcomes of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes (Panel B), were estimated with the use of the Kaplan–Meier method.

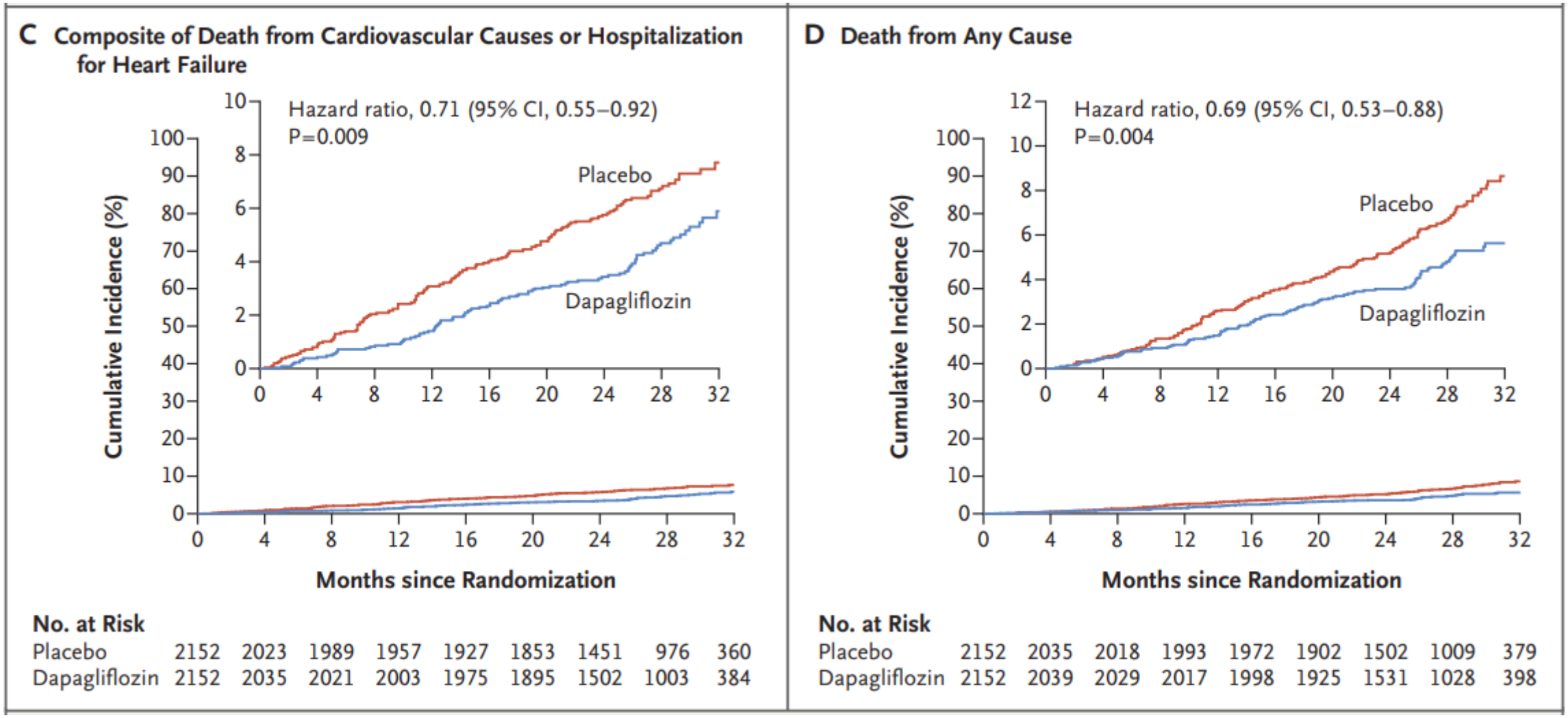


Figure 1. HR were estimated with the use of the Kaplan–Meier method. Hazard ratios, confidence intervals, and P values were estimated with the use of Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and urinary albumin-to creatinine ratio) and adjusted for baseline estimated GFR. Included in these analyses are all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo. The graphs are truncated at 32 months (the point at which <15% of participants remained at risk). The insets show the same data on an expanded y axis.

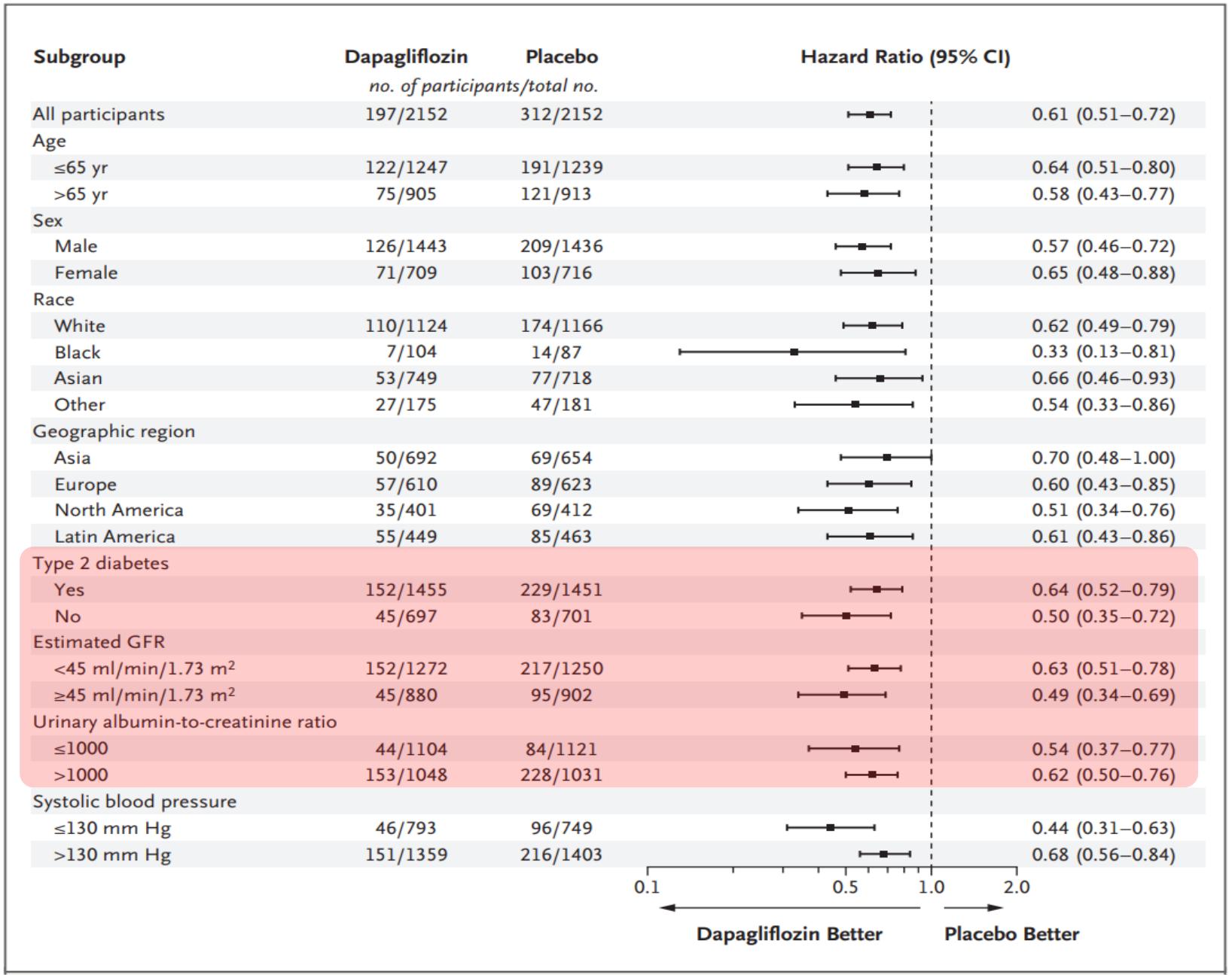


Figure 2.
Primary Outcome According to Prespecified Subgroups at Baseline.
Shown are forest plots of the hazard ratios for the primary outcome (a composite of a sustained decline in the estimated GFR of ≥50%, end-stage kidney disease, or death from renal or cardiovascular causes) according to prespecified baseline subgroups. Hazard ratios and confidence intervals were calculated with a Cox proportional-hazards model with stratification according to diabetes status and urinary albumin-to-creatinine ratio adjusted for baseline estimated GFR, with factors for trial group, subgroup, and the interaction between trial group and the subgroup variable.

ADA 2023

- **11.5a** For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 and urinary albumin ≥ 200 mg/g creatinine. A
- **11.5b** For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥ 20 mL/min/1.73 m^2 and urinary albumin ranging from normal to 200 mg/g creatinine. B

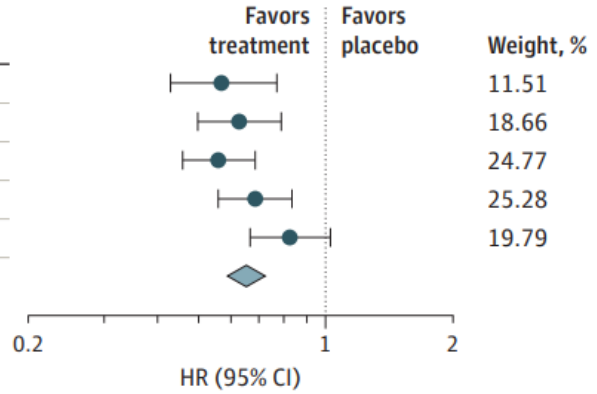
worsening eGFR or creatinine,
end-stage kidney disease with or without requirement
for kidney replacement therapy or transplant,
kidney death,
or CV death.

Figure 4. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Kidney-Related Outcomes

A Overall kidney outcomes

	Treatment		Placebo		Hazard ratio (95% CI)
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)

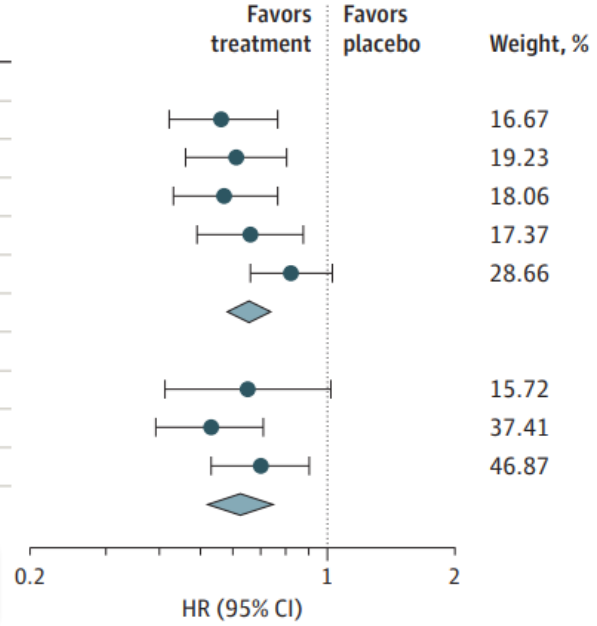
38% ↓



B Kidney outcomes by ASCVD status

	Treatment		Placebo		Hazard ratio (95% CI)
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)

P=0.73 for interaction



Cardiovascular Diabetology (2022) 21:47

ORIGINAL INVESTIGATION Open Access

Association of SGLT2 inhibitors with cardiovascular, kidney, and safety outcomes among patients with diabetic kidney disease: a meta-analysis

Arnaud D. Kaze[1], Min Zhuo[2,3,4,5], Seoyoung C. Kim[2,3], Elisabetta Patorno[2,3] and Julie M. Paik[2,3,4,6*]

Study	SGLT2 inhibitor	No. with DKD	Age, y	Follow-up, y	CKD Definition*	eGFR* Range	HbA_{1C}, %	CVD, %	HF,%
EMPA-REG OUTCOME[6,18]	Empagliflozin	2250	66.0	3.1	eGFR<60 and/or UACR ≥ 300	30-59	8.1	100	14.1
CANVAS Program[11,15,19,20]	Canagliflozin	2039	67.2	2.4	eGFR < 60	30-59	8.2	79.7	17.9
DECLARE- TIMI 58[7]	Dapagliflozin	1265	63.9	4.2	eGFR < 60	NR	8.3	40.6	10.0
CREDENCE[8,21,22]	Canagliflozin	4401	63.0	2.6	eGFR 30-89 and UACR ≥ 300	30-89	8.3	50.4	14.8
DAPA-CKD[9,23]	Dapagliflozin	2906	61.8	2.4	eGFR 25-75 and UACR ≥ 200	25-75	NR	37.4	10.9
VERTIS CV[10,24]	Ertugliflozin	1807	64.4	3.0	eGFR < 60	30-59	8.2	100	23.7
SCORED[16]	Sotagliflozin	10584	69	1.3	eGFR < 60	25-59	8.3	48.6	31.0
SOLOIST- WHF[30]	Sotagliflozin	854	69	0.8	eGFR < 60	30-59	7.1	NR	100

Table S2. Characteristics of Clinical Trials Included in the Meta-analysis

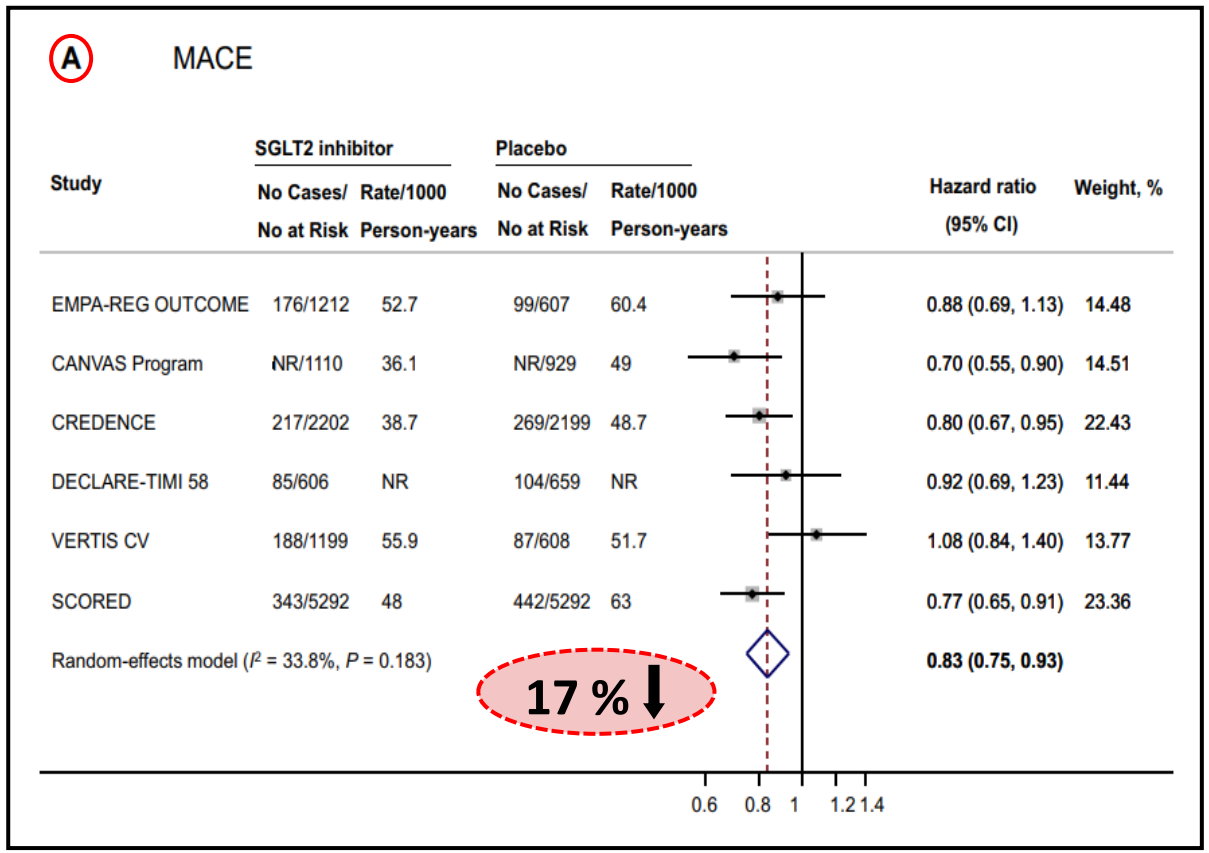
CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

Table 1 Effect of SGLT2 inhibitors on clinical outcomes in adults with diabetic kidney disease

Outcome	No. studies	No. events	Sample size	HR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
MACE	6	2271	21,913	0.83 (0.75–0.93)	33.8	0.183	0.287
Kidney composite	5	1197	21,195	0.66 (0.58–0.75)	0.0	0.949	0.513
HHF	6	1219	22,346	0.62 (0.55–0.71)	0.0	0.844	0.267
Cardiovascular death	5	953	20,539	0.84 (0.74–0.96)	0.0	0.639	0.996
Fatal and nonfatal MI	5	498*	20,108	0.78 (0.67–0.92)	7.7	0.363	0.671
Fatal and nonfatal stroke	5	332*	20,108	0.76 (0.59–0.97)	41.3	0.146	0.564
All-cause mortality	5	1451	21,406	0.86 (0.77–0.96)	14.5	0.322	0.268

*The number of MI events and stroke cases from the SCORED trial were not reported in the primary trials and are not included in the table. CI indicates confidence interval; *HHF* hospitalization for heart failure, *HR* hazard ratio, I^2, I-squared, *MACE* Major Adverse Cardiovascular Events, *MI* myocardial infarction, *SCORED* Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk, *SGLT2* sodium-glucose cotransporter 2; SGLT2, sodium-glucose cotransporter 2, *SOLOIST-WHF* Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure, *VERTIS CV* Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial

Figure 1
Effects of SGLT2 inhibitors on major adverse cardiovascular events (A) and kidney composite outcomes (B) among individuals with diabetic kidney disease.



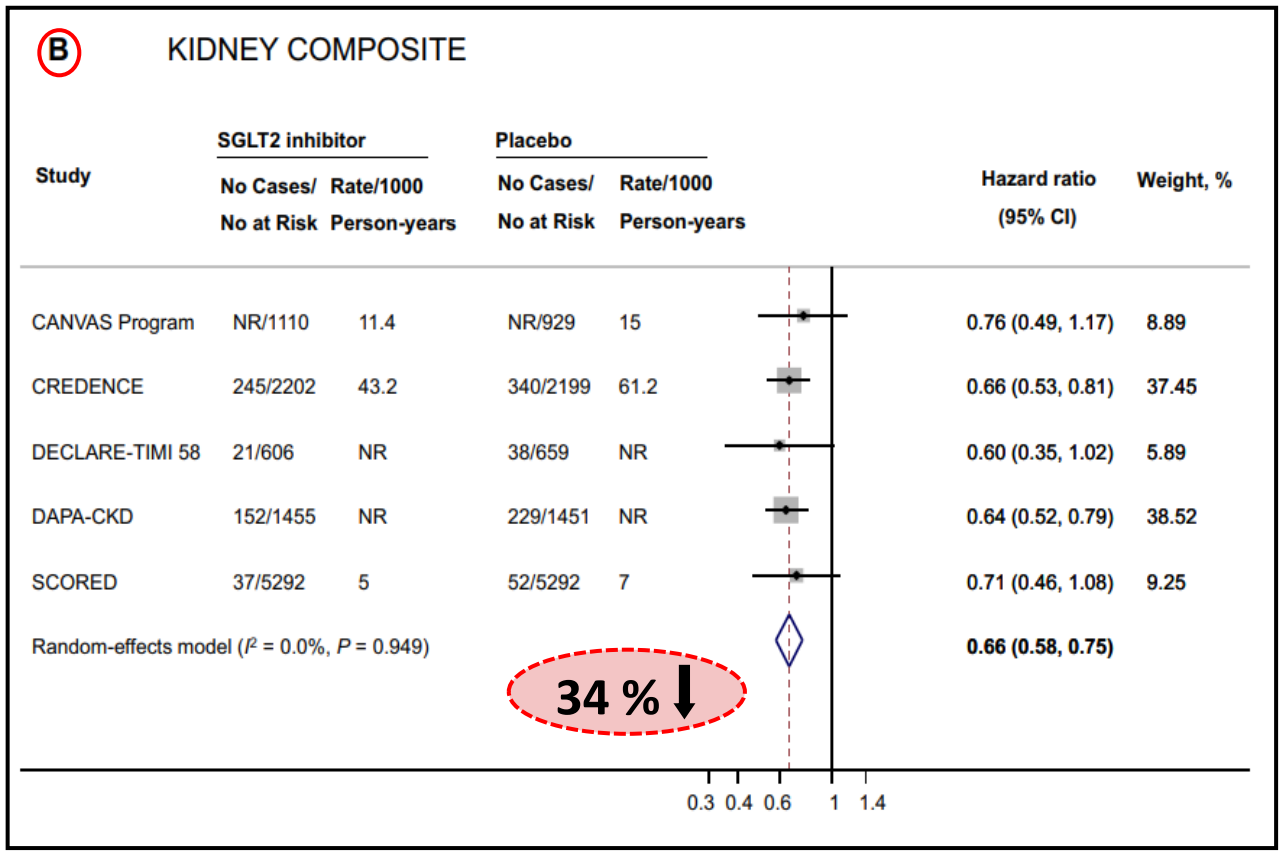


Table 2 Effect of SGLT2 inhibitors on clinical outcomes among participants with reduced eGFR

Outcome	No. studies	No. events	Sample size	HR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
Overall (eGFR < 60 mL/min/1.73m^2)							
MACE	6	2102	20,106	0.82 (0.74–0.91)	8.6	0.363	0.810
Kidney composite	4	530	16,480	0.65 (0.55–0.78)	0.0	0.645	0.771
HHF	6	1125	20,106	0.61 (0.54–0.70)	0.0	0.740	0.099
Cardiovascular death	5	834	18,299	0.86 (0.75–0.98)	0.0	0.912	0.363
Fatal and nonfatal MI	4	320*	15,707	0.75 (0.63–0.90)	0.0	0.480	0.879
Fatal and nonfatal stroke	4	190*	15,707	0.75 (0.55–1.01)	38.3	0.151	0.855
All-cause mortality	3	837	13,668	0.93 (0.81–1.07)	0.0	0.638	0.147
eGFR < 45 mL/min/1.73m^{2}**							
MACE	3	347	2437	0.75 (0.60–0.93)	0.0	0.797	0.921
Kidney composite	2	225	1867	0.70 (0.54–0.92)	0.0	0.841	NA
HHF	3	166	2437	0.60 (0.44–0.82)	0.0	0.522	0.193
Cardiovascular death	3	191	2437	0.83 (0.62–1.11)	0.0	0.699	0.925
Fatal and nonfatal MI	2	71	1124	0.70 (0.39–1.26)	28.3	0.238	NA
Fatal and nonfatal stroke	2	38	1124	0.52 (0.23–1.17)	30.2	0.231	NA
All-cause mortality	1	74	570	0.86 (0.54–1.38)	NA	NA	NA

*The number of MI and stroke events were not reported in SCORED and are therefore not included in the table. Likewise, the number of HHF/cardiovascular death events were not reported in SOLOIST-WHF and are not included in the table. CI indicates confidence interval, *eGFR* estimated glomerular filtration rate, *HHF* hospitalization for heart failure, *MACE* major adverse cardiovascular events, *HR* hazard ratio, *MI* myocardial infarction, *NA* not applicable, *NR* not reported, *SCORED* Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk, *SGLT2* sodium-glucose cotransporter 2, *SOLOIST-WHF* Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure

Table 3 Effect of SGLT2 inhibitors on clinical outcomes among participants with moderate or severe albuminuria

Outcome	No. studies	No. events	Sample size	HR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
Overall							
MACE	4	1284*	17,084	0.80 (0.71–0.90)	25.6	0.234	0.683
Kidney composite	4	1124*	17,208	0.66 (0.58–0.75)	1.4	0.407	0.530
HHF	4	670	13,456	0.61 (0.52–0.71)	0.0	0.916	0.791
Cardiovascular death	3	642	10,209	0.70 (0.55–0.88)	50.9	0.086	0.378
Fatal and nonfatal MI	3	503	10,209	0.89 (0.75–1.07)	0.0	0.679	0.355
Fatal and nonfatal stroke	3	382	10,209	0.92 (0.75–1.14)	0.0	0.457	0.279
All-cause mortality	4	817*	13,115	0.76 (0.66–0.88)	28.8	0.219	0.285
Moderate albuminuria							
MACE	3	520*	7868	0.92 (0.79–1.07)	0.0	0.795	0.342
Kidney composite	2	70*	5855	0.98 (0.62–1.57)	0.0	0.962	NA
HHF	3	261	6771	0.60 (0.47–0.77)	0.0	0.473	0.283
Cardiovascular death	2	229	4279	0.70 (0.35–1.38)	84.2	0.012	NA
Fatal and nonfatal MI	2	233	4279	1.01 (0.77–1.32)	0.0	0.774	NA
Fatal and nonfatal stroke	2	153	4279	1.06 (0.76–1.48)	0.0	0.363	NA
All-cause mortality	2	147*	4279	0.78 (0.47–1.28)	80.4	0.024	NA
Severe Albuminuria							
MACE	4	764*	9216	0.73 (0.65–0.83)	0.0	0.444	0.428
Kidney composite	3	673*	8447	0.63 (0.53–0.76)	0.8	0.365	0.729
HHF	4	409	6685	0.62 (0.51–0.75)	0.0	0.915	0.815
Cardiovascular death	3	413	5930	0.72 (0.59–0.87)	0.0	0.408	0.348
Fatal and nonfatal MI	3	270	5930	0.81 (0.64–1.03)	0.0	0.654	0.389
Fatal and nonfatal stroke	3	229	5930	0.85 (0.65–1.11)	0.0	0.410	NA
All-cause mortality	3	473*	5930	0.77 (0.65–0.90)	0.0	0.415	0.234

*The number of MACE and kidney composite outcomes were not reported in SCORED and are therefore not included in the table. Likewise, the number of all-cause deaths by albuminuria were not reported in the CANVAS program and are not included in the table. CANVAS indicates Canagliflozin Cardiovascular Assessment Study, *CI* confidence interval; *HHF* hospitalization for heart failure, *MACE* major adverse cardiovascular events, *HR* hazard ratio, *MI* myocardial infarction, *NA* not applicable, *NR* not reported, *SCORED* Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk, *SGLT2* sodium-glucose cotransporter 2

Table 4 Effect of SGLT2 Inhibitors on safety events among patients with diabetic kidney disease

Outcome	No studies	No events	Sample size	RR (95% CI)	I^2, %	$P_{Heterogeneity}$	$P_{Egger\ test}$
Male genital mycotic infections	2	98	4091	**3.89 (1.42–10.62)**	62.1	0.072	0.392
Female genital mycotic infections	2	53	2100	**2.50 (1.32–4.72)**	0.0	0.384	NA
Diabetic ketoacidosis	2	56	14,974	3.54 (0.82–15.39)	54.3	0.139	NA
Volume depletion	4	1016*	18,832	**1.29 (1.13–1.48)**	0.0	0.713	0.936
Amputations	4	248*	18,832	1.21 (0.85–1.72)	25.4	0.244	0.767
Bone fractures	4	475*	18,832	1.00 (0.84–1.20)	0.0	0.953	0.447
Urinary tract infections	4	1739*	18,832	1.04 (0.95–1.14)	0.0	0.781	0.339
Acute kidney injury	3	197*	8255	0.85 (0.66–1.11)	0.0	0.975	0.535
Hyperkalemia	3	359*	8255	0.82 (0.67–1.01)	0.0	0.692	0.601

Bold values indicate statistically significant estimates

*The number of events from the EMPA-REG OUTCOME trial were not reported and therefore not included in the table for the following outcomes: volume depletion, amputations, fractures, urinary tract infection, acute kidney injury, and hyperkalemia. CI indicates confidence interval, *EMPA-REG OUTCOME* Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients; I^2, I-squared, *RR* relative risk, *SGLT2* sodium-glucose cotransporter 2

Table 2—Summary of dosing recommendations for FDA-approved SGLT2 inhibitors

Agent	Usual dosing recommendations	Renal dosing recommendations
Canagliflozin	• The recommended starting dose is 100 mg once daily, taken before the first meal of the day. • The dose can be increased to 300 mg once daily in those who require additional glycemic control.	• Assess kidney function before initiating and periodically thereafter. • Limit the dose to 100 mg once daily in patients who have an eGFR of 45 to <60 mL/min/1.73 m^2. • Initiation is not recommended in patients with an eGFR <45 mL/min/1.73 m^2. • Use is not recommended when eGFR is persistently <45 mL/min/1.73 m^2. • Use is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2.
Empagliflozin	• The recommended starting dose is 10 mg once daily, taken in the morning, with or without food. • The dose can be increased to 25 mg once daily.	• Assess kidney function before initiating. • Initiation is not recommended if eGFR is <45 mL/min/1.73 m^2. • Discontinue if eGFR is persistently <45 mL/min/1.73 m^2.

The NEW ENGLAND JOURNAL of MEDICINE

2021 Dec 9;385(24):2252-63

ORIGINAL ARTICLE

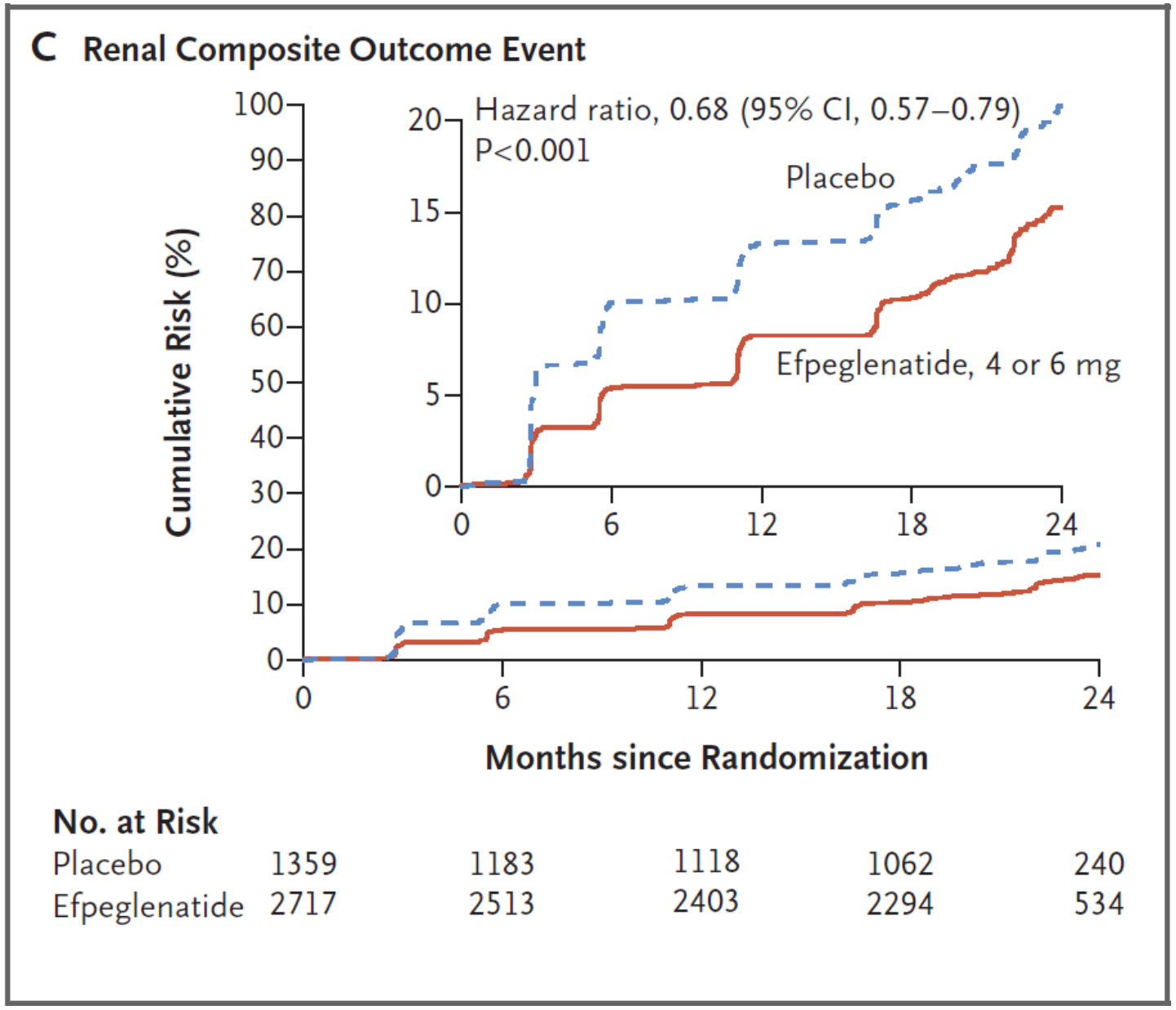
Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes

BACKGROUND

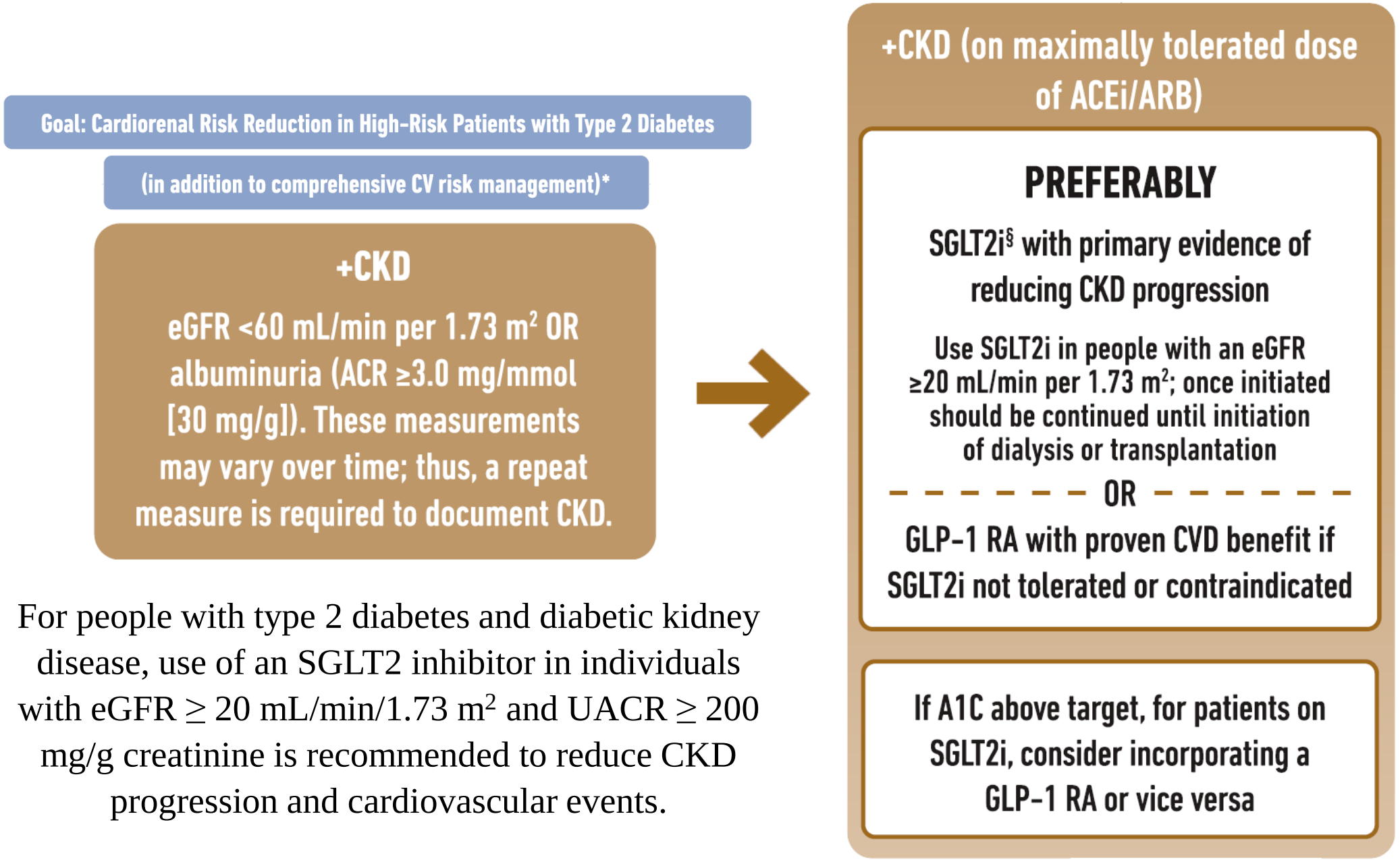
The effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with type 2 diabetes who are also at high risk for adverse cardiovascular events is uncertain.

METHODS

In this randomized, placebo-controlled trial conducted at 344 sites across 28 countries, we evaluated efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease (defined as an estimated glomerular filtration rate of 25.0 to 59.9 ml per minute per 1.73 m^2 of body-surface area) plus at least one other cardiovascular risk factor. Participants were randomly assigned in a 1:1:1 ratio to receive weekly subcutaneous injections of efpeglenatide at a dose of 4 or 6 mg or placebo.

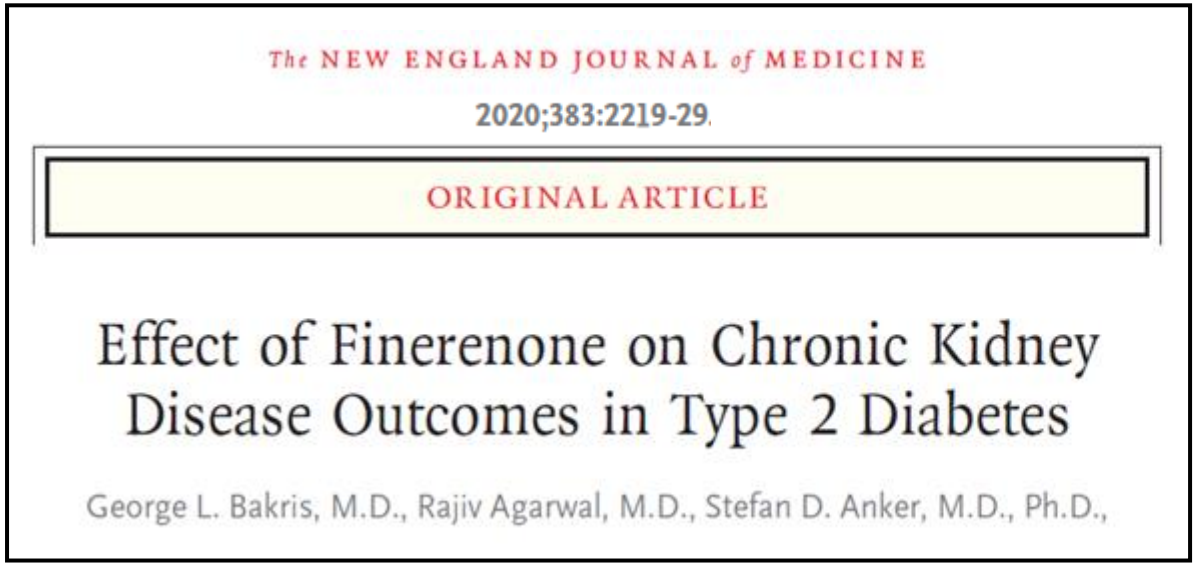


Composite renal outcome (incident macroalbuminuria [defined as a urinary albumin-to-creatinine ratio of >300, as measured in milligrams of albumin to grams of creatinine], plus an increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained decrease in the eGFR of ≥40% for ≥30 days, renal-replacement therapy for ≥90 days, or a sustained eGFR of <15 ml per minute per 1.73 m^2 for ≥30 days).

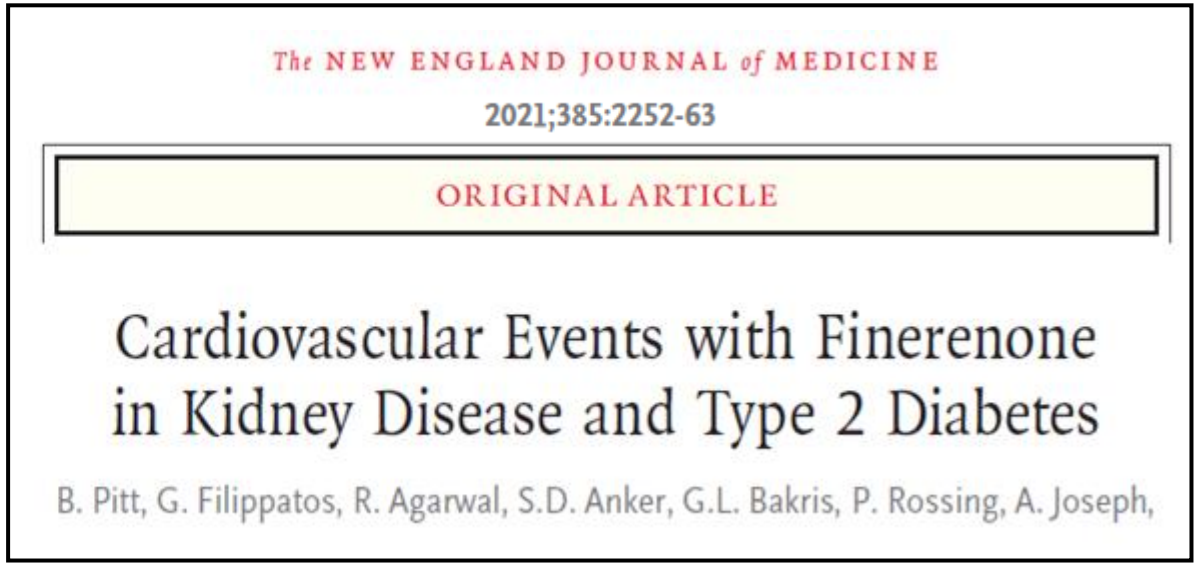


For people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor in individuals with eGFR $\geq$ 20 mL/min/1.73 m^2 and UACR $\geq$ 200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events.

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease



Its long-term effects on kidney and cardiovascular outcomes are unknown.
Eligible patients had a urinary albumin-to-creatinine ratio of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m^2 of body surface area, and diabetic retinopathy, or they had a urinary albumin-to creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2.



The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.
Eligible patients had a urinary albuminto -creatinine ratio of 30 to less than 300 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD).

Inclusion/exclusion

T2D + CKD
eGFR ≥25 mL/min/1.73m²
Serum [K⁺] ≤ 4.8 mmol/L
Maximum tolerated labeled dose of RAS

HFrEF (NYHA class II-IV)

Protocol

6519 → Finerenone 10 mg or 20 mg od

R

Median follow-up 3 years

6507 → Placebo

Outcomes

CV composite:
Time to CV death, non- fatal MI, non-fatal stroke, or HHF

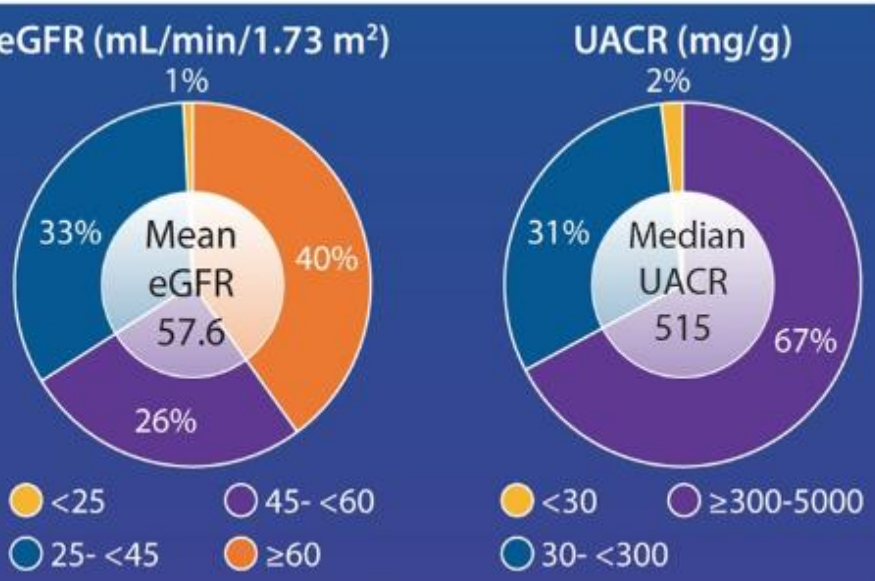
≥57% kidney composite:
Time to kidney failure, sustained ≥57% decrease in eGFR, or renal death

Baseline characteristics

Median age: 65 years
♂ 70% ♀ 30%

RAS inhibitors: 99.8%
Statins: 72.2%

HbA1c: 7.7%
BP: 137/76 mmHg
Prior HF: 7.7%



Few hyperkalemia-related discontinuations occurred

(n=110) 0.66

(n=38) 0.22

Discontinuation rate (IR/100 PY)

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 Feb 10;43(6):474-484.

Results

	HR (95% CI)	p-value	Risk ↓
Endpoint CV composite	0.86 (0.78 – 0.95)	0.0018	14%
HHF	0.78 (0.66 – 0.92)	0.0030	22%
Kidney composite	0.77 (0.67 – 0.88)	0.0002	23%
Dialysis	0.80 (0.64 – 0.99)	0.040	20%

Conclusion

Finerenone on top of standard of care reduces the risk of clinically meaningful cardiovascular and kidney outcomes in patients with type 2 diabetes over a broad spectrum of chronic kidney disease

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 Feb 10;43(6):474-484.

ADA 2023

- **11.5c** In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥ 20 mL/min/1.73m^2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥ 25 mL/min/1.73 m^2) additionally for cardiovascular risk reduction. A
- **11.5d** In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. A

Smoking and Diabetes

ADA 2023

- Data show tobacco use is higher among adults with chronic conditions as well as in adolescents and young adults with diabetes.
- People with diabetes who smoke (and people with diabetes exposed to second-hand smoke) have a heightened risk of CVD, premature death, microvascular complications, and worse glycemic outcomes when compared with those who do not smoke.
- Smoking may have a role in the development of type 2 diabetes.

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Relation of Smoking with Total Mortality and Cardiovascular Events Among Patients with Diabetes: A Meta-Analysis and Systematic Review

An Pan, Yeli Wang, Mohammad Talaei and Frank B. Hu

METHODS:

- We searched Medline and Embase databases through May 2015, and multivariate-adjusted relative risks were pooled by using random-effects models. A total of 89 cohort studies were included

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The pooled adjusted relative risk associated with smoking

- 1.55 (1.46-1.64) for total mortality
- 1.49 (1.29-1.71) for CVD mortality
- 1.44 (1.34-1.54) CVD
- 1.51 (1.41-1.62) CHD
- 1.54 (1.41-1.69) for stroke
- 2.15 (1.62-2.85) for PAD
- 1.43 (1.19-1.72) for heart failure

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In comparison with never smokers, former smokers

- 1.19 (1.11-1.28)for total mortality,
- 1.15 (1.00-1.32,) CVD mortality
- 1.09 (1.05-1.13)for CVD,
- 1.14 (1.00-1.30) for CHD
- 1.04 (0.87-1.23) but not for stroke

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- Active smoking is associated with significantly increased risks of total mortality and cardiovascular events among diabetic patients, whereas smoking cessation is associated with reduced risks in comparison with current smoking.
- The findings provide strong evidence for the recommendation of quitting smoking among diabetic patients.

ADA 2023

- Numerous large RCTs have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of telephone quit lines, in reducing tobacco use.
- Pharmacologic therapy to assist with smoking cessation in people with diabetes has been shown to be effective, and for people who are motivated to quit, the addition of pharmacologic therapy to counseling is more effective than either treatment alone.
- Although some people may gain weight in the period shortly after smoking cessation, recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation.
- Among patients with newly diagnosed type 2 diabetes it was shown that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year.

ADA 2023

- In light of recent Centers for Disease Control and Prevention evidence of deaths related to e-cigarette use, no individuals should be advised to use e-cigarettes, either as a way to stop smoking tobacco or as a recreational drug.
- A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates (>6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline.

در هر حرفه ای که هستید نه اجازه دهید که به بدبینی‌های بی‌حاصل آلوده شوید و نه بگذارید که بعضی لحظات تاسف بار که برای هر ملتی پیش می‌آید شما را به یاس و ناامیدی بکشاند.

در آرامش حاکم بر آزمایشگاه‌ها و کتابخانه‌هایتان زندگی کنید و نخست از خود بپرسید برای یادگیری و خودآموزی چه کرده‌ام؟

سپس همچنانکه پیشتر می‌روید، بپرسید من برای کشورم چه کرده‌ام؟ و این پرسش را آنقدر ادامه دهید تا به این احساس هیجان انگیز برسید که شاید سهم کوچکی در اعتلای بشریت داشته‌اید.

اما هر پاداشی که زندگی به تلاشهایمان بدهد یا ندهد، هنگامیکه به پایان راه نزدیک می‌شویم هر کدام از ما باید حق آن را داشته باشیم که با صدای بلند بگوییم:

من هر آنچه که در توان داشته‌ام انجام داده‌ام