Diabetic Nephropathy

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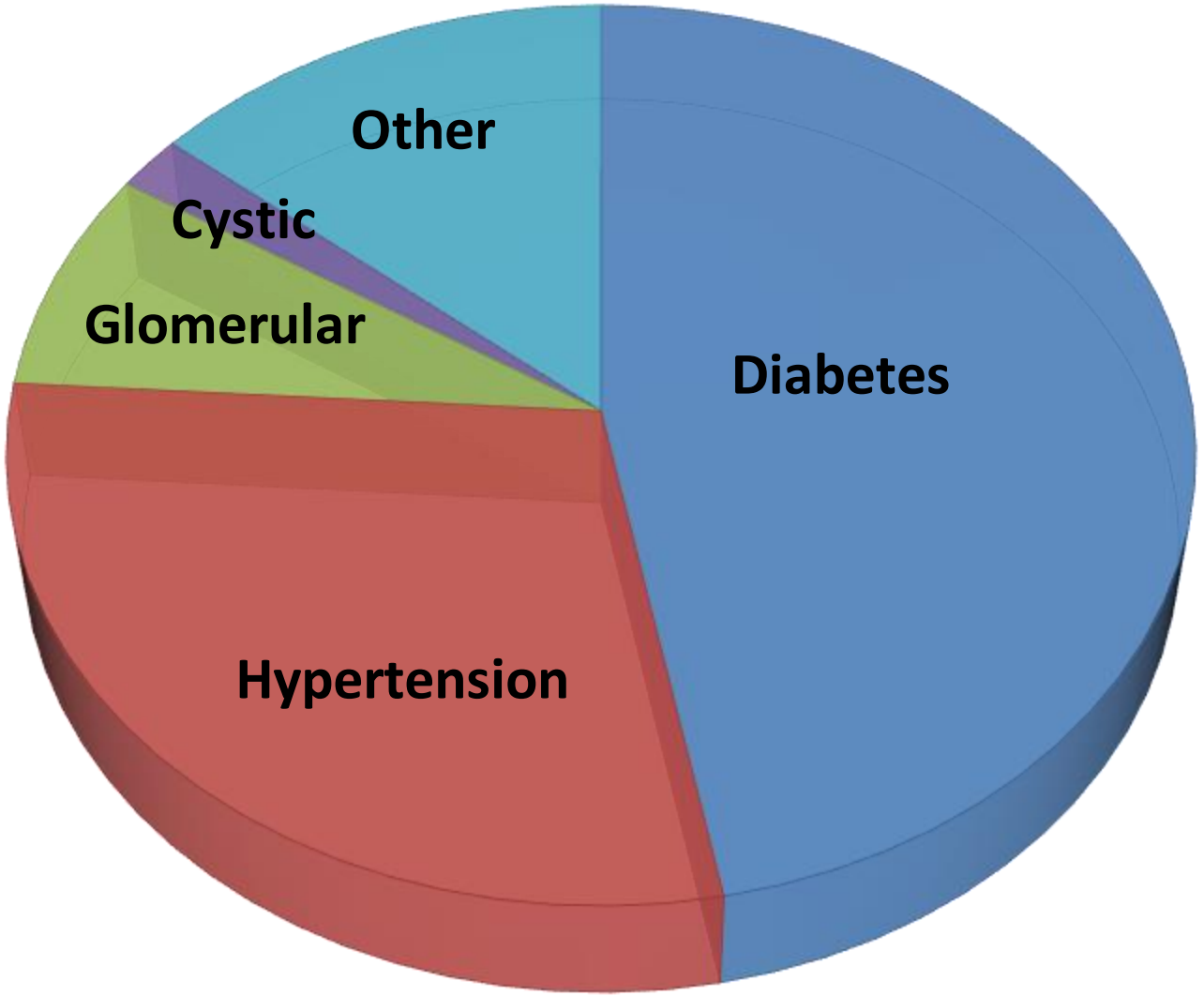
Faculty Title: Assistant Professor of Medicine
Faculty Title: Staff Physician, Nephrology. Dallas VA

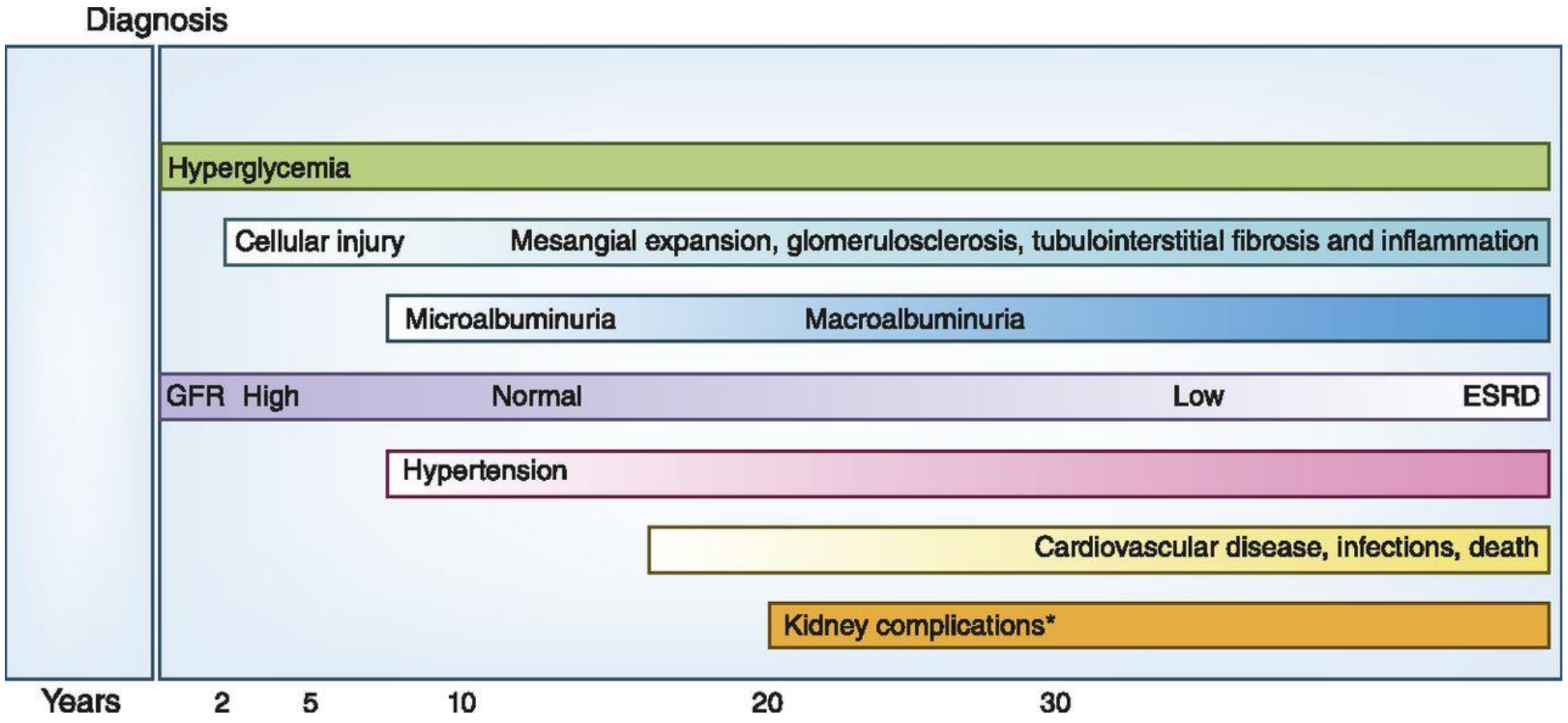
Disclosures

- I have no actual or potential conflict of interest in relation to this presentation

Diabetes is the #1 cause of ESRD

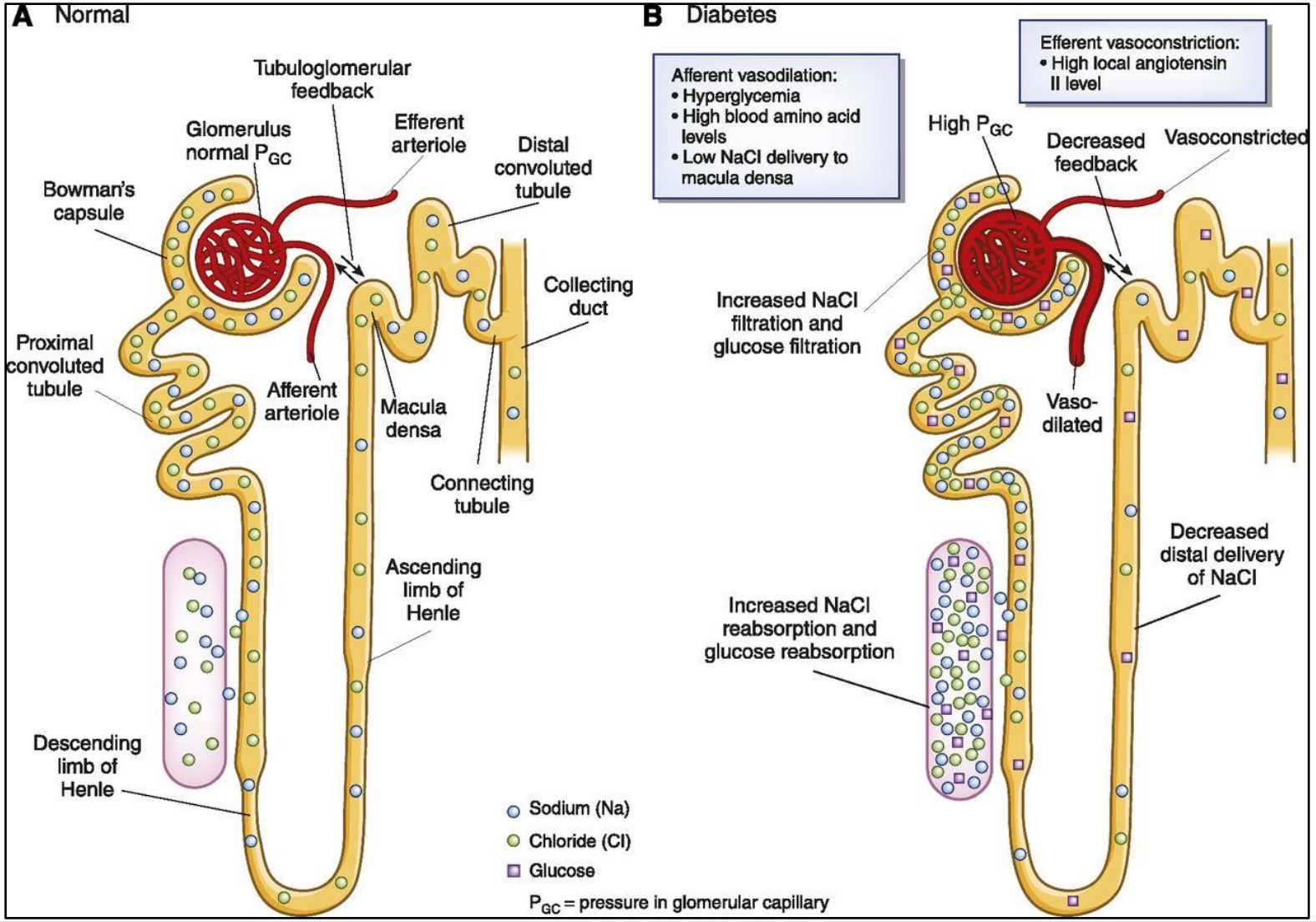


Timeline of Disease Progression



Alicic, et al. CJASN 2017

Pathogenesis



Alicic, et al. CJASN 2017

Diagnosis

Screening:

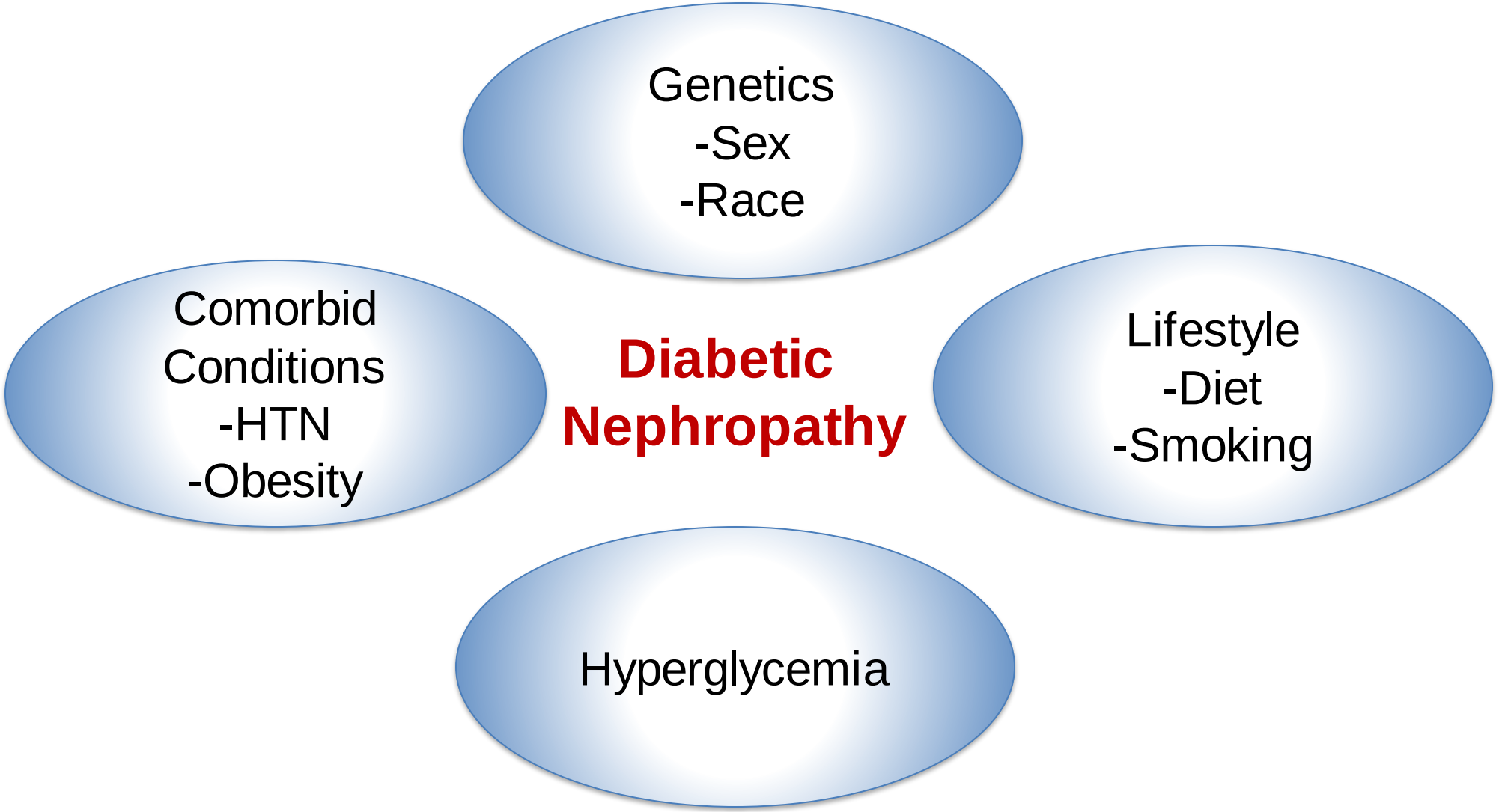
- Type 1: Starting 5 years after diagnosis
- Type 2: Starting immediately at diagnosis

Diagnostic Criteria:

- Albuminuria (>300mg/24h)
- Diabetic Retinopathy
- No evidence of alternative diagnosis

Parving, NEJM. 1996

Risk Factors



Alicic, et al. CJASN. 2017

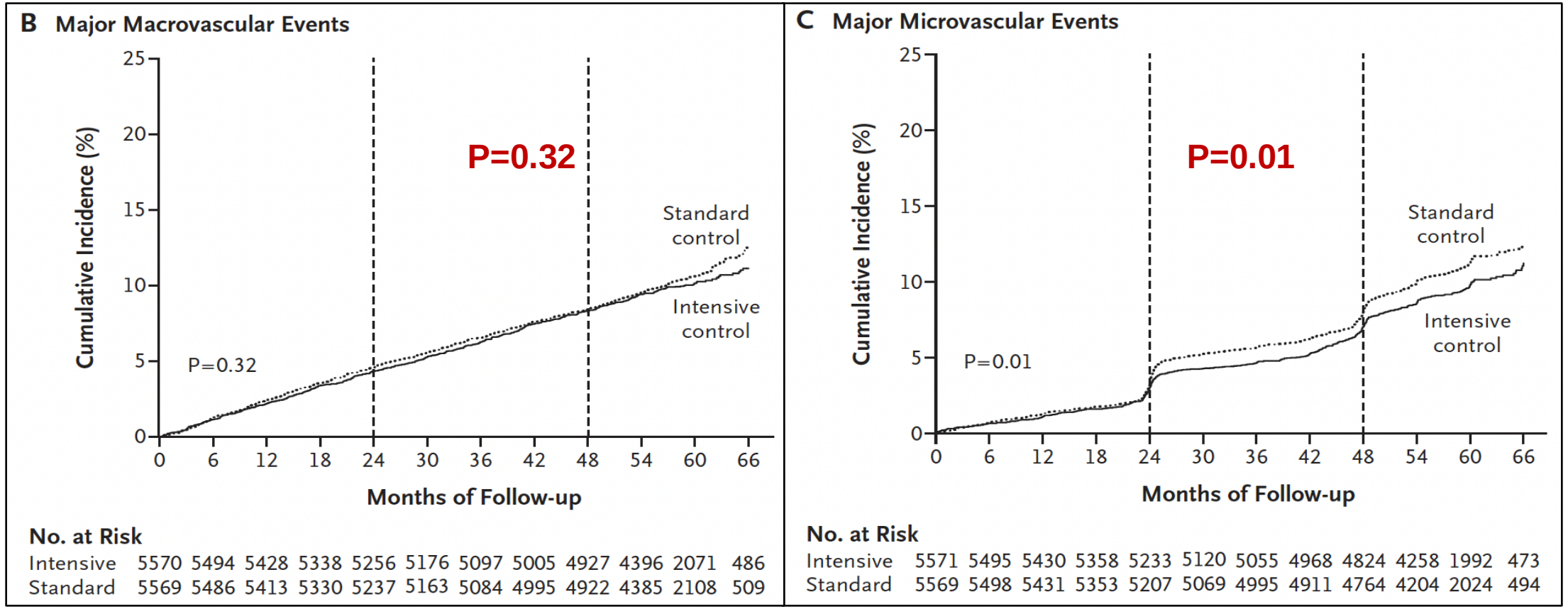
Slowing the Progression

Multifaceted Approach

Lifestyle Changes	Glycemic Control	Blood Pressure Management	Novel Therapeutics
• Low Sodium Diet • Smoking Cessation • Weight Loss	• A1C < 7.0	• Goal < 130/80 • RAAS Blockade	• SGLT2 I • Finerenone • GLP-1 Agonists • DPP-4 Inhibitors

Treatment: Glycemic Control

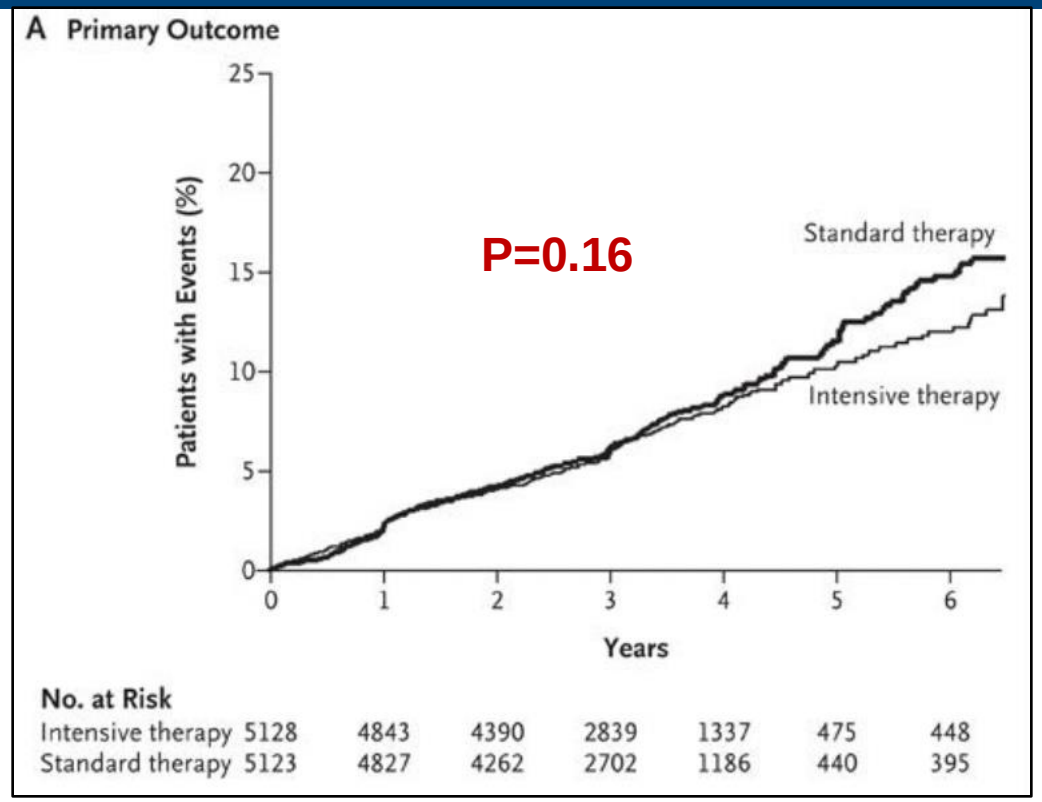
Intensive Glycemic Control: ADVANCE 2008

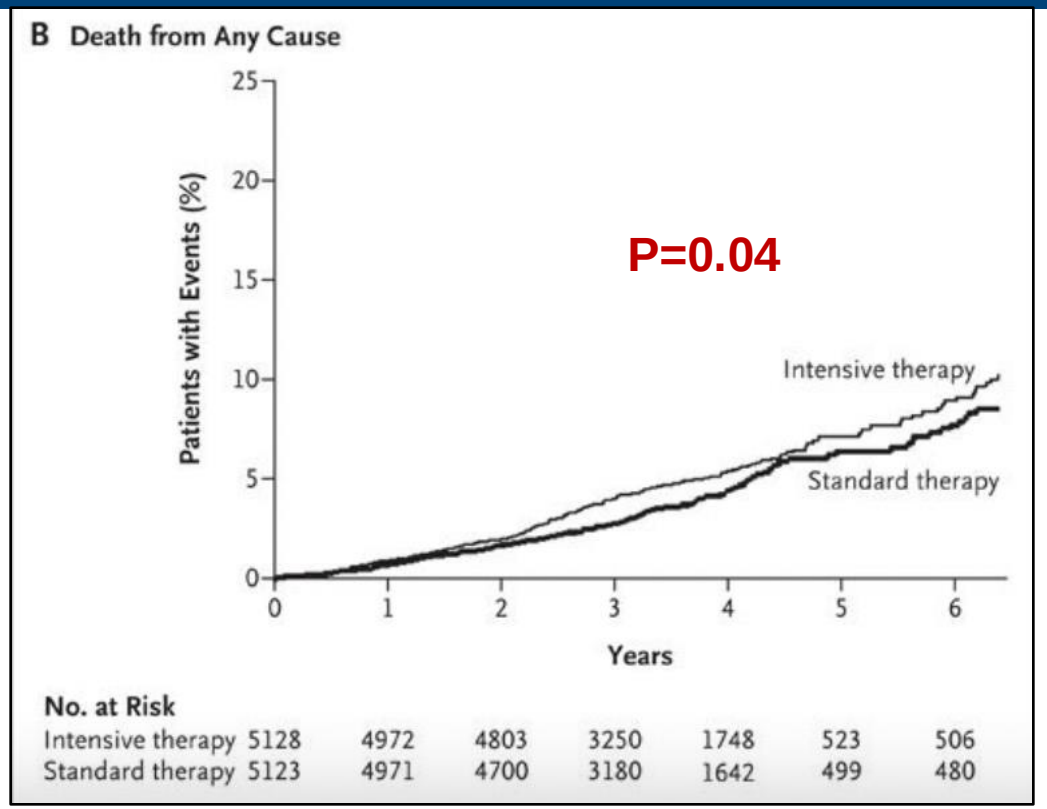


Control group A1C (7.3) vs Intensive A1C (6.5)

The ADVANCE Collaborative Group, NEJM. 2008

Intensive Glycemic Control: ACCORD 2008

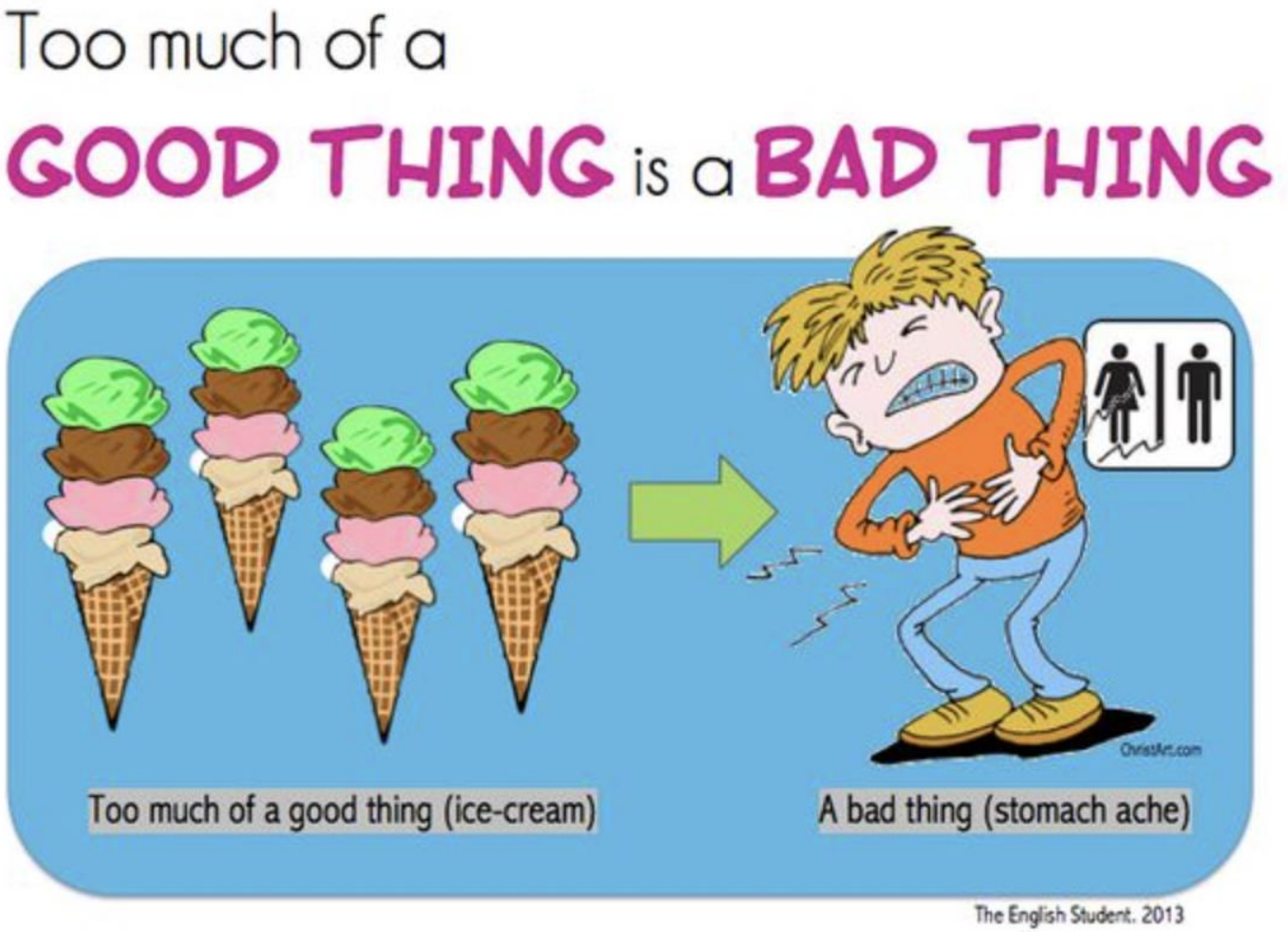




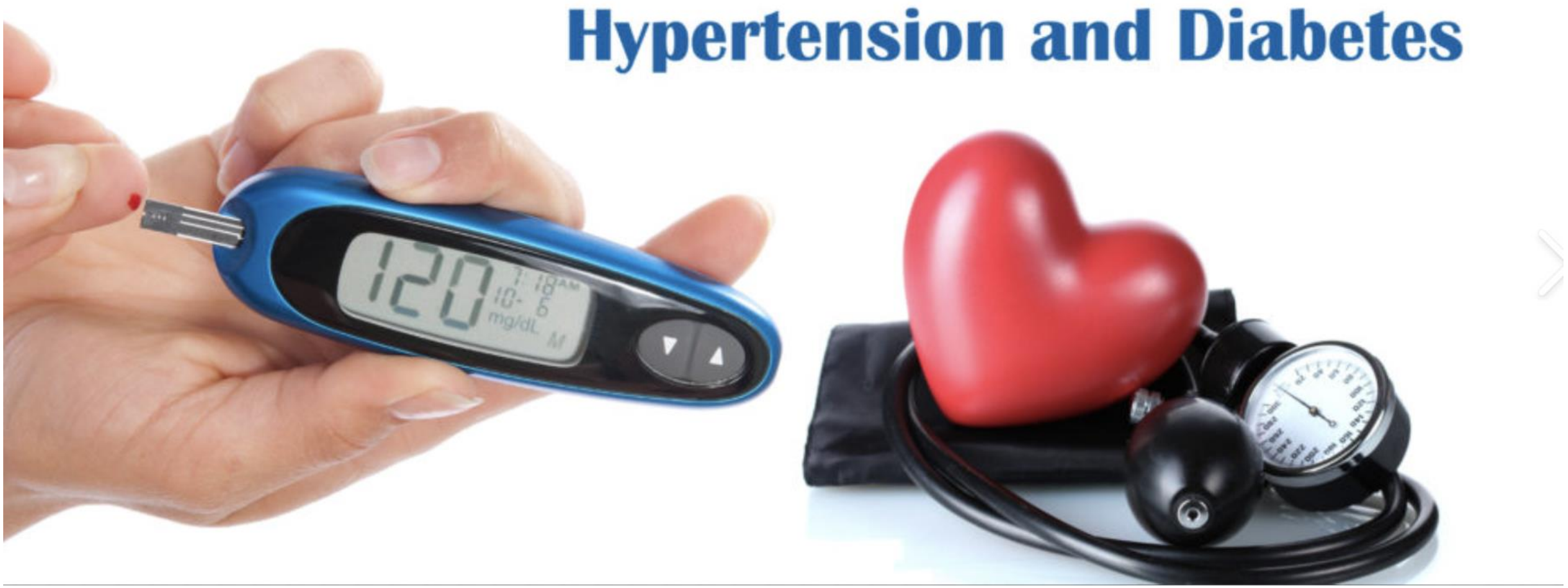
Control group A1C (7.5) vs Intensive A1C (6.4)

Accord Study Group, 2008. NEJM

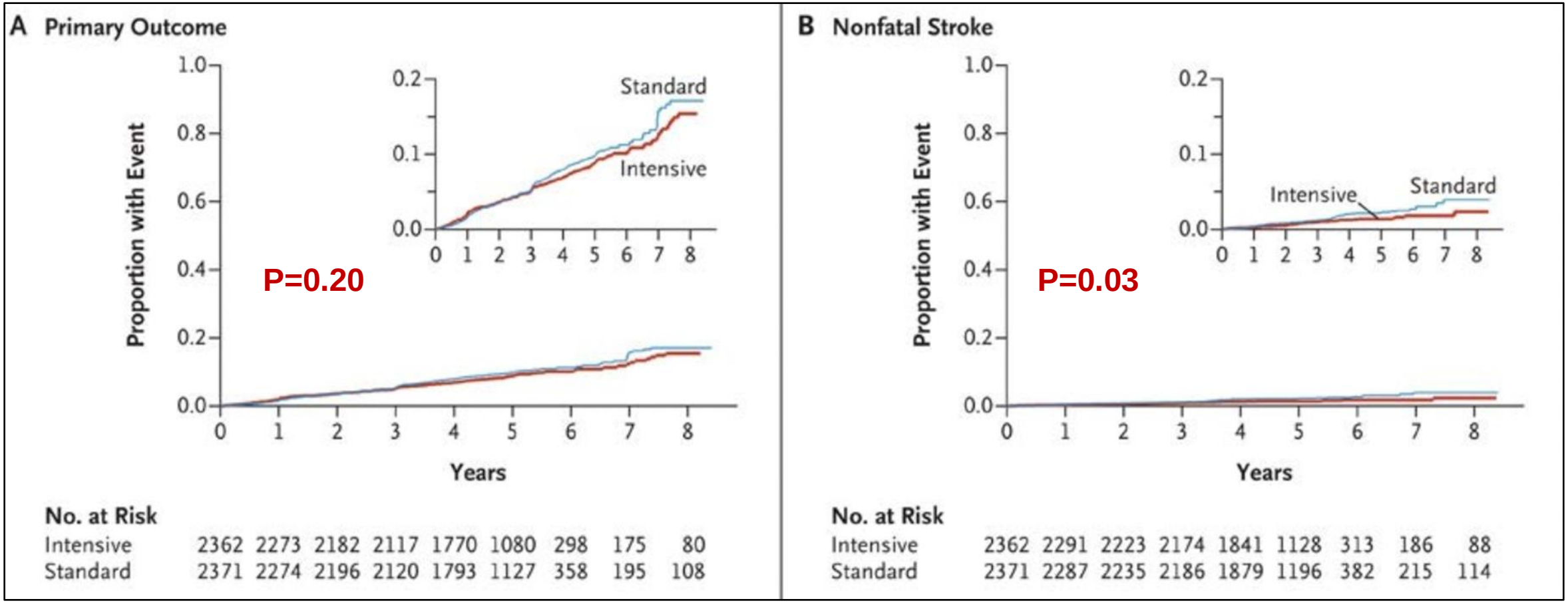
Intensive Glycemic Control



Management of Hypertension



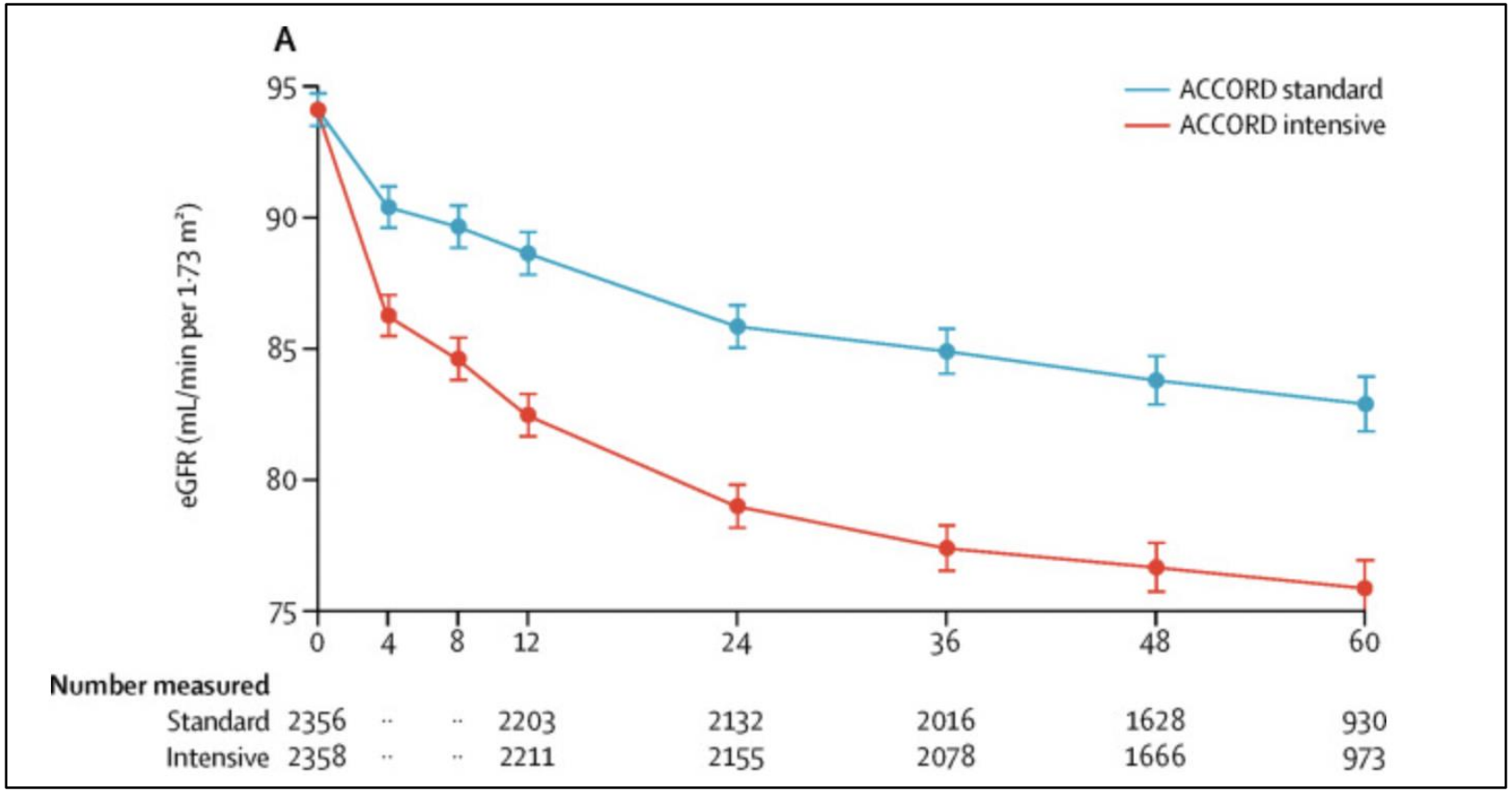
Intensive BP Control: ACCORD 2010



Standard BP (133.5/70.5) vs. Intensive BP (119/64.4)

The Accord Study Group, NEJM. 2010

Intensive BP Control: ACCORD 2010



WORSE RENAL OUTCOMES with intensive BP arm!

Standard BP (133.5/70.5) vs. Intensive BP (119/64.4)

The Beddhu, Lancet. 2018
Accord Study Group, NEJM. 2010

Clinical Case

- A 65 year old male with a past medical history of diabetes, hypertension, OSA, and obesity is managed on the current medicine regimen: losartan 100mg, chlorthalidone 25mg, and metformin 1000mg BID. His BMI is 31, BP 133/78, and he has trace pitting edema on exam. His laboratory parameters are pertinent for:

140 110 15 143 A1C 7.3

5.1 24 1.3. Urine albumin/creatinine 1200mg/gm

Clinical Case

All of the following are recommended strategies in the management of this patient EXCEPT:

A. Start empagliflozin

B. Encourage weight loss

C. Recommend a low salt diet

D. Start finerenone

Clinical Case

All of the following are recommended strategies in the management of this patient EXCEPT:

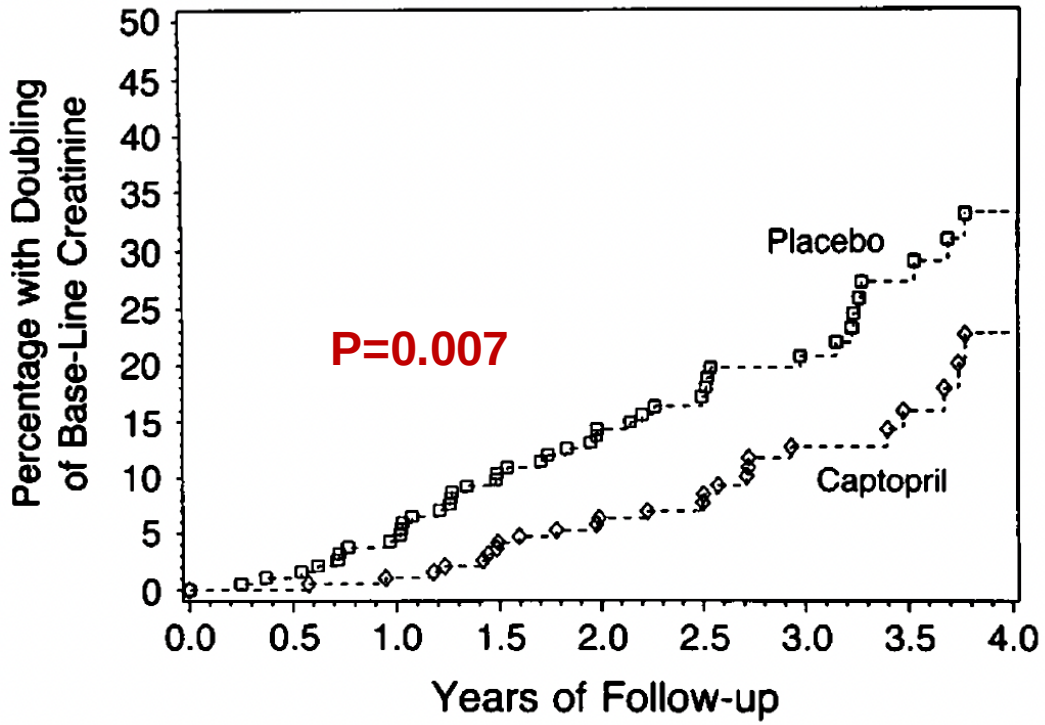
A. Start empagliflozin

B. Encourage weight loss

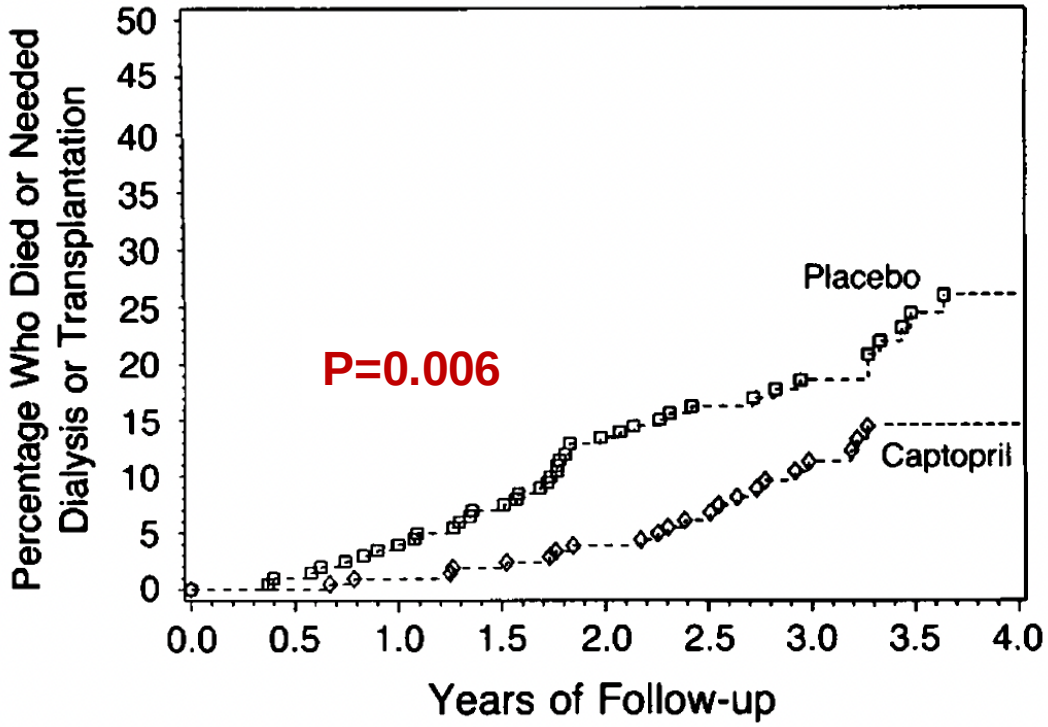
C. Recommend a low salt diet

D. Start finerenone

ACE Inhibitor Breakthrough



Placebo	202	184	173	161	142	99	75	45	22
Captopril	207	199	190	180	167	120	82	50	24



Placebo	202	198	192	186	171	121	100	59	26
Captopril	207	207	204	201	195	140	103	64	37

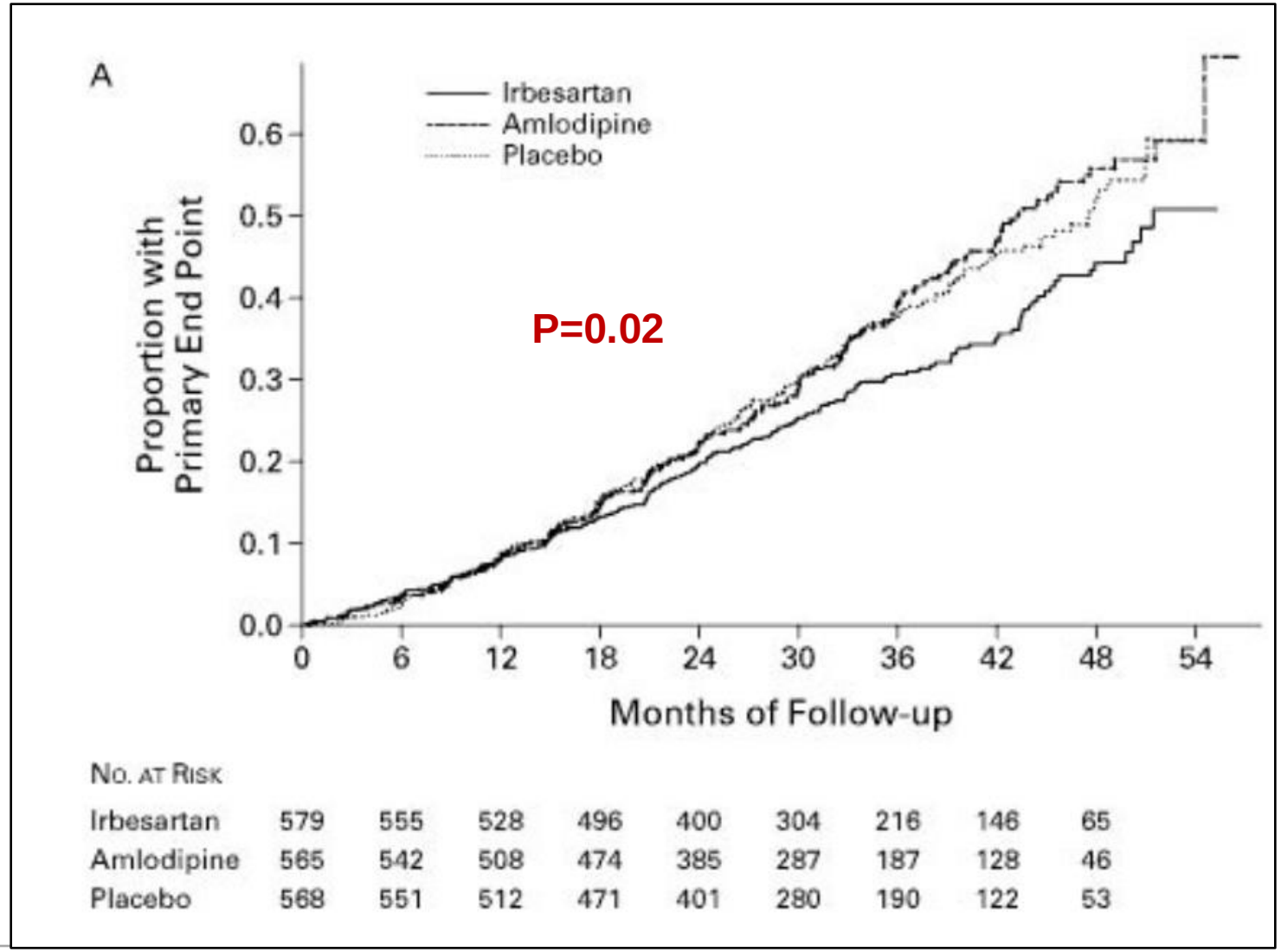
Lewis, et al. NEJM. 1193

Irbesartan vs Amlodipine vs Placebo

Target BP: 135/85

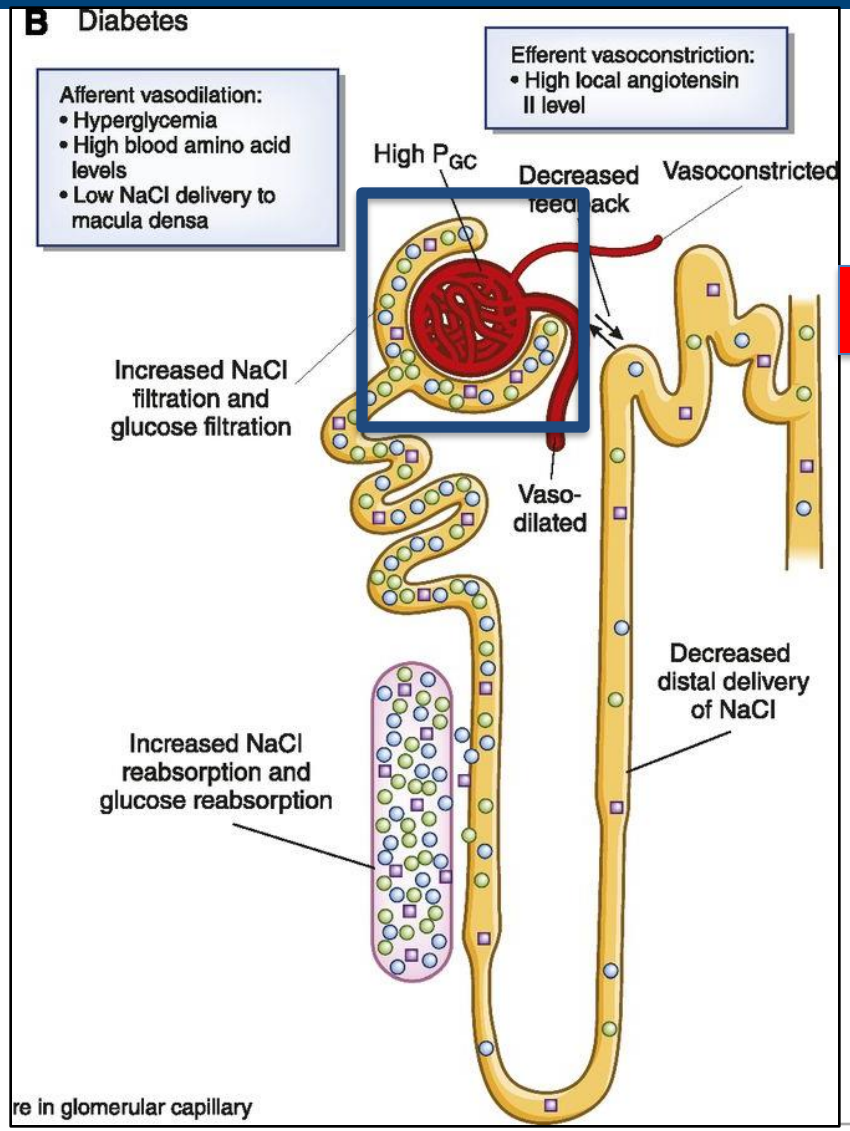
Results:

- 20% reduction in doubling of serum creatinine, ESRD, or death compared to placebo.
- 23% reduction compared to amlodipine.

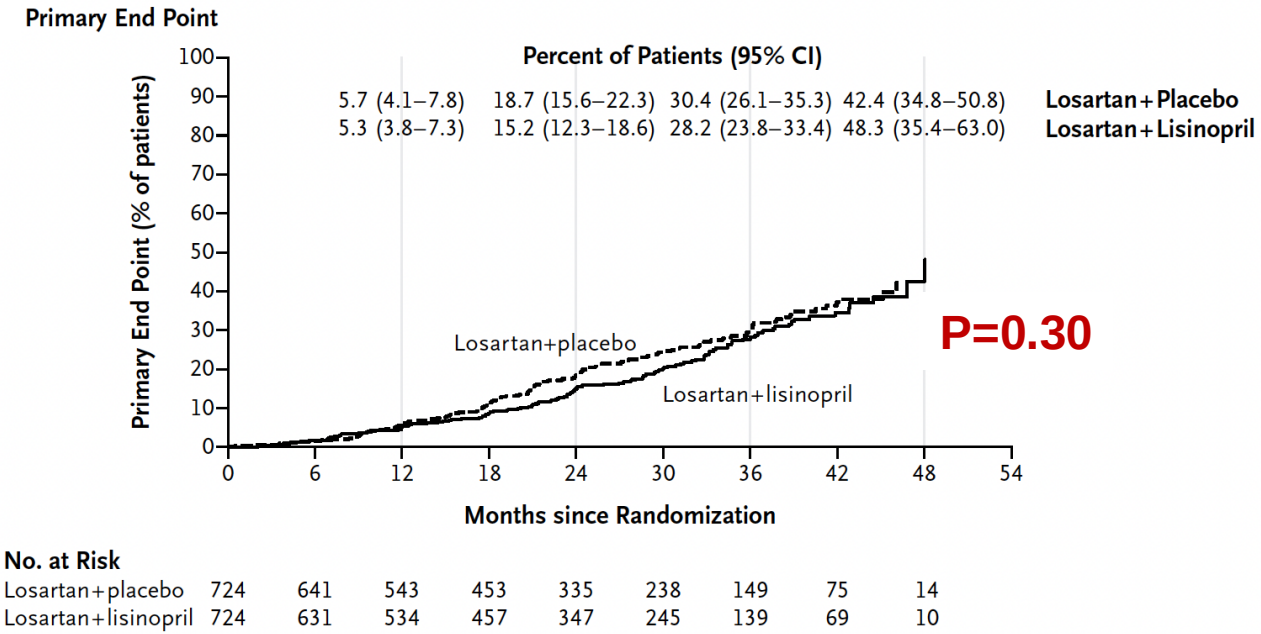


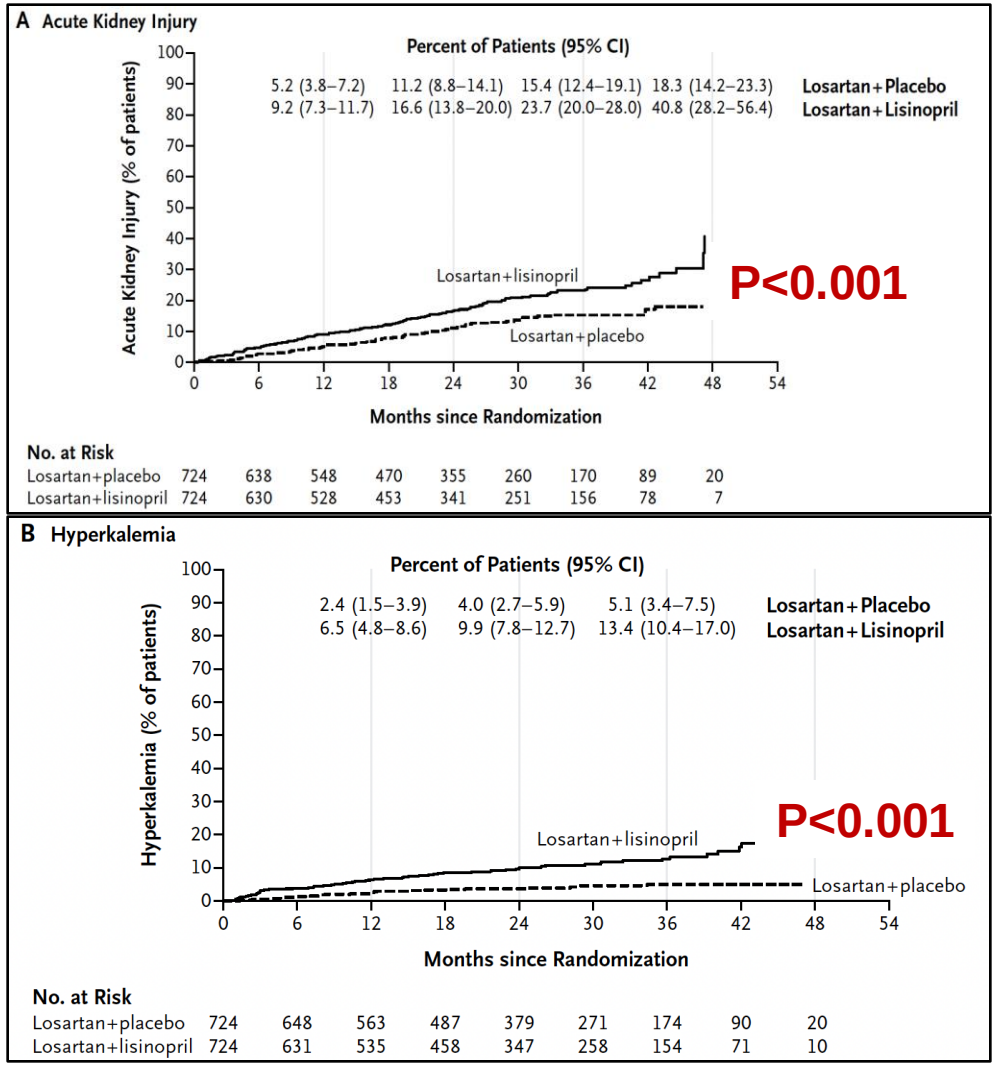
Lewis, et al. NEJM. 2001

RAAS Blockade



Intensive RAAS Blockade: ACE + ARB





- No difference: GFR decline, ESRD, Death
- More AKI
- More hyperkalemia

Fried, et al. NEJM. 2013

Intensive RAAS Blockade

Nephron D: Losartan + Lisinopril

ALTITUDE: ACE + Aliskiren (Direct Renin Inhibition)

ONTARGET: Ramipril + Telmisartan

TRANSCEND: Post hoc analysis of ONTARGET for high-risk patients

Combination therapy consistently produces reduced albuminuria but fails to improve clinical outcomes and increases adverse events

Novel Therapeutic Agents

Diabetic Therapy

Insulin

Giguanides

Sulfonureas

Meglitinides

TZDs

GLP-1 Receptor Agonists

Amylin

Bile acid sequestrants

Dopamine-2 agonists

SGLT2 Inhibitors

Alpha-glucosidase Inhibitors

DPP-4 inhibitors

Diabetic Therapy

Insulin

Giguanides

Sulfonureas

Meglitinides

TZDs

GLP-1 Receptor Agonists

- Reduction in proteinuria
- Improved CVS outcomes

Amylin

Bile acid sequestrants

Dopamine-2 agonists

SGLT2 Inhibitors

Alpha-glucosidase Inhibitors

DPP-4 inhibitors

- Reduction in proteinuria
- No persuasive difference in CVS or renal outcomes

Kristensen, et al. Lancet Diabetes/Endocrinology. 2019
Cornel, et al. Diabetes Care. 2016

SGLT2 Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

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*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire,

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

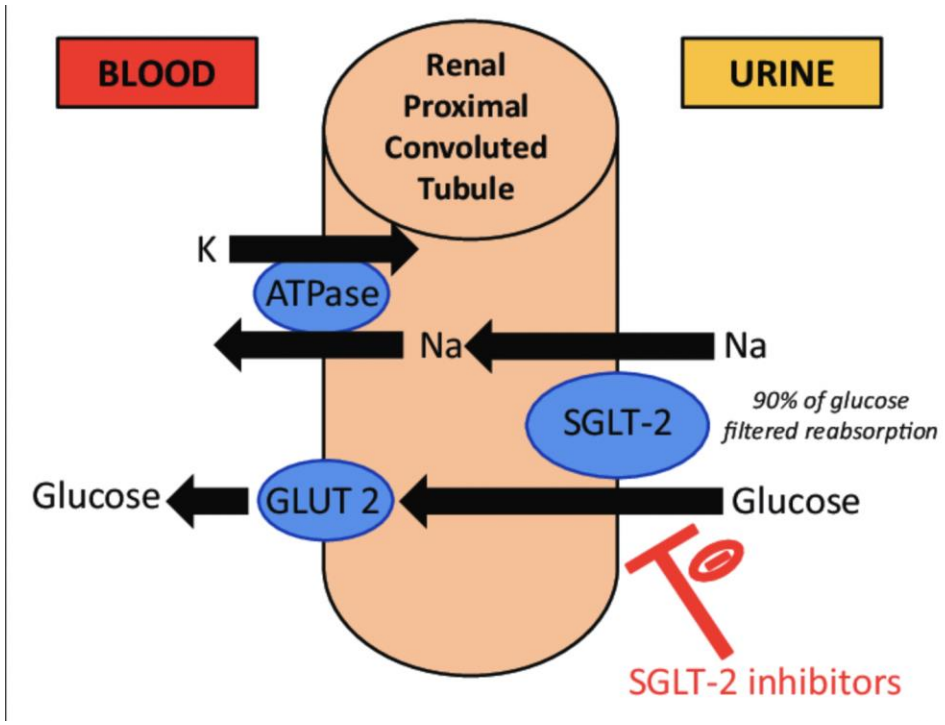
Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

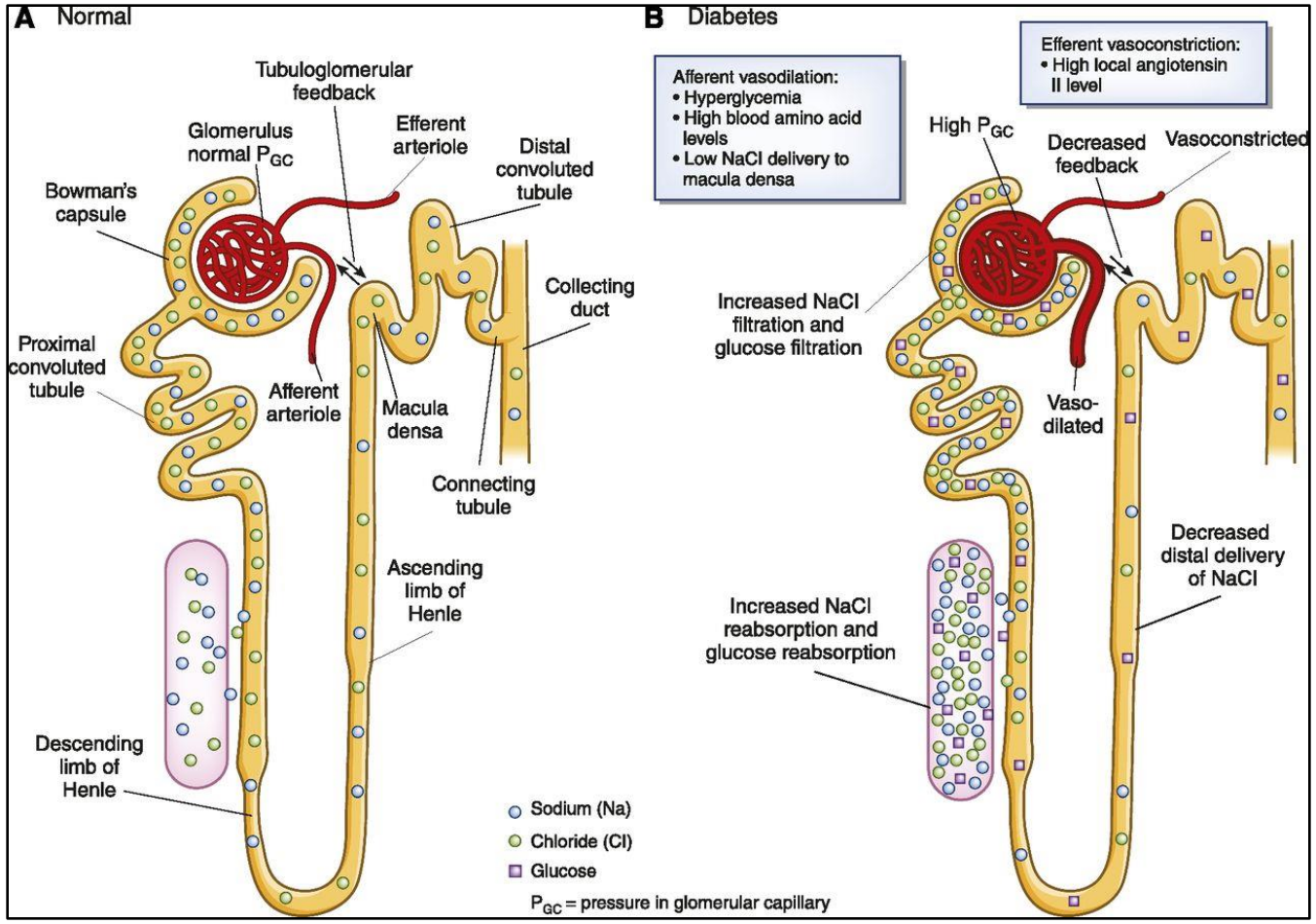
ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., Bertram Pitt, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., David Z.I. Cherney, M.D., Ph.D., Jamie P. Dwyer, M.D., Benjamin M. Scirica, M.D., M.P.H., Clifford J. Bailey, Ph.D., Rafael Díaz, M.D., Kausik K. Ray, M.D., Jacob A. Udell, M.D., M.P.H., Renato D. Lopes, M.D., Ph.D., Pablo Lapuerta, M.D., and P. Gabriel Steg, M.D., for the SCORED Investigators*

Mechanism of Action: SGLT2





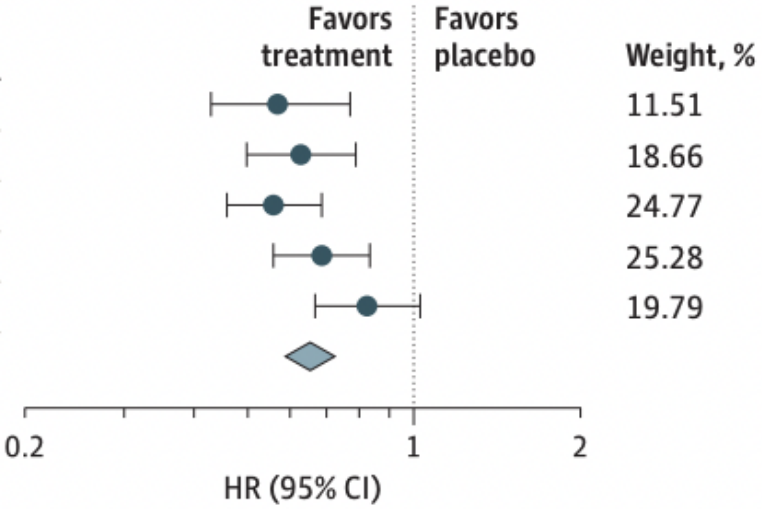
Turner, et al. J. of Investigative Medicine. 2016
Alicic, et al. CJASN 2017

SGLT-2 Inhibitors: Renal Outcomes

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

A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
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)



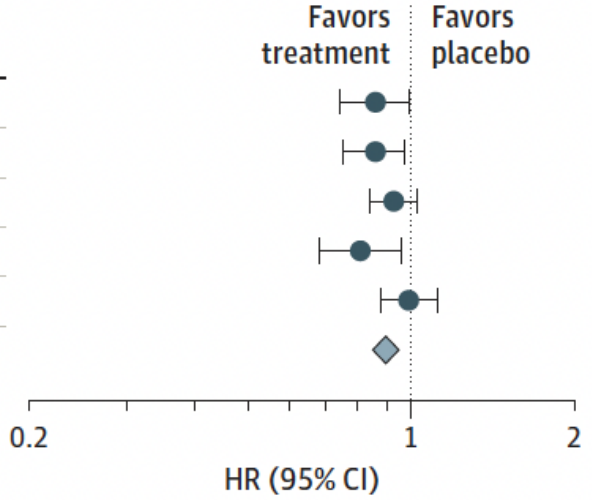
McGuire, et al. JAMA-Cardiology 2021

SGLT2 Inhibitors: MACE Outcomes

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

A Overall MACEs

	Treatment		Placebo			Favors treatment	Favors placebo	Weight, %
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)			
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)			20.12
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)			32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)			10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			21.23
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)			



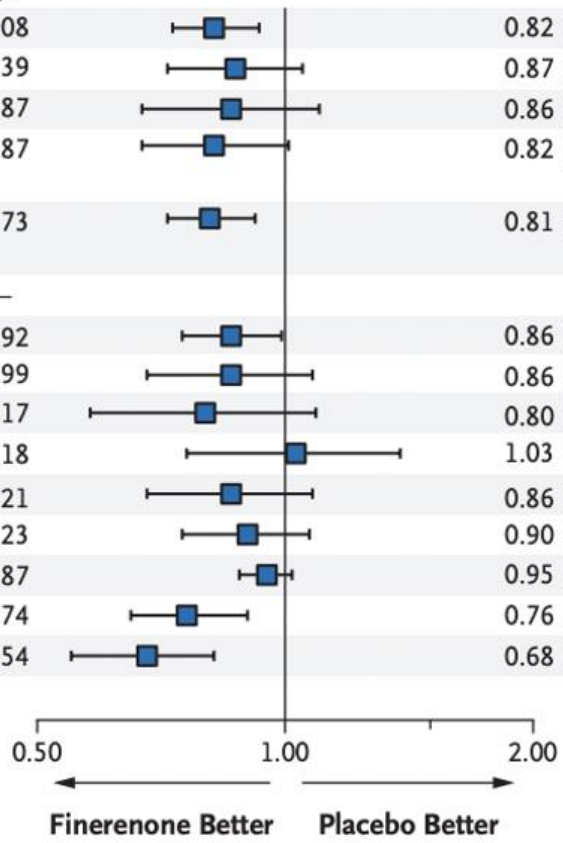
McGuire, et al. JAMA-Cardiology 2021

A new MRA: Finerenone

- Selective mineralocorticoid receptor antagonist (MRA)
  - More selective and potent.
  - More anti-fibrotic and anti-inflammatory effects
  - Less hyperkalemia

RAAS Blockade + Finerenone

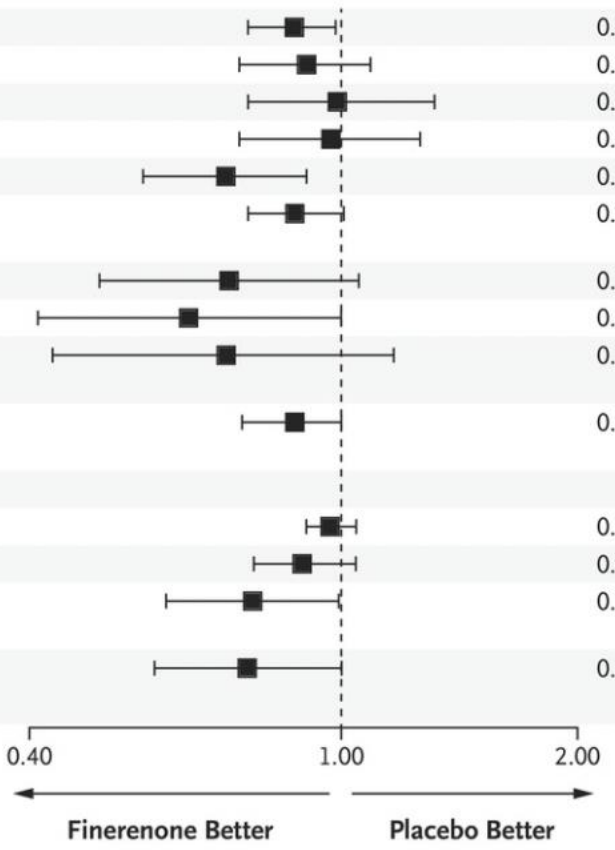
Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



Bakris, et. Al. NEJM. 2020

RAAS Blockade + Finerenone

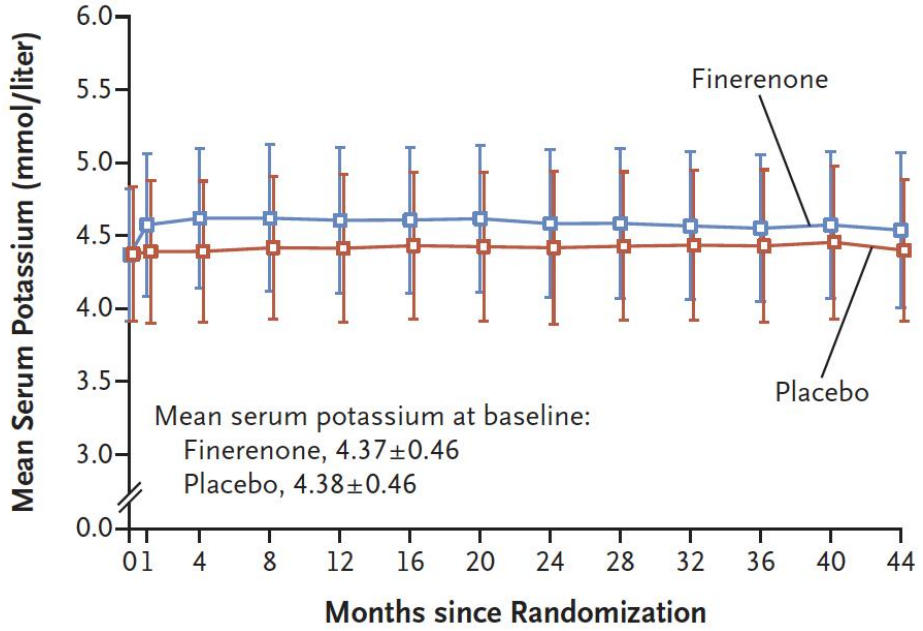
Outcome	Finerenone (N=3686)	Placebo (N=3666)	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	458 (12.4)	519 (14.2)	3.87	4.45	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	1.56	1.74	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.85	0.85	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.89	0.92	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.96	1.36	0.71 (0.56–0.90)	—
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.15	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.995)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m^2	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	333 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—



Pitt, et al. NEJM. 2021

RAAS Blockade + Finerenone

B Mean Serum Potassium

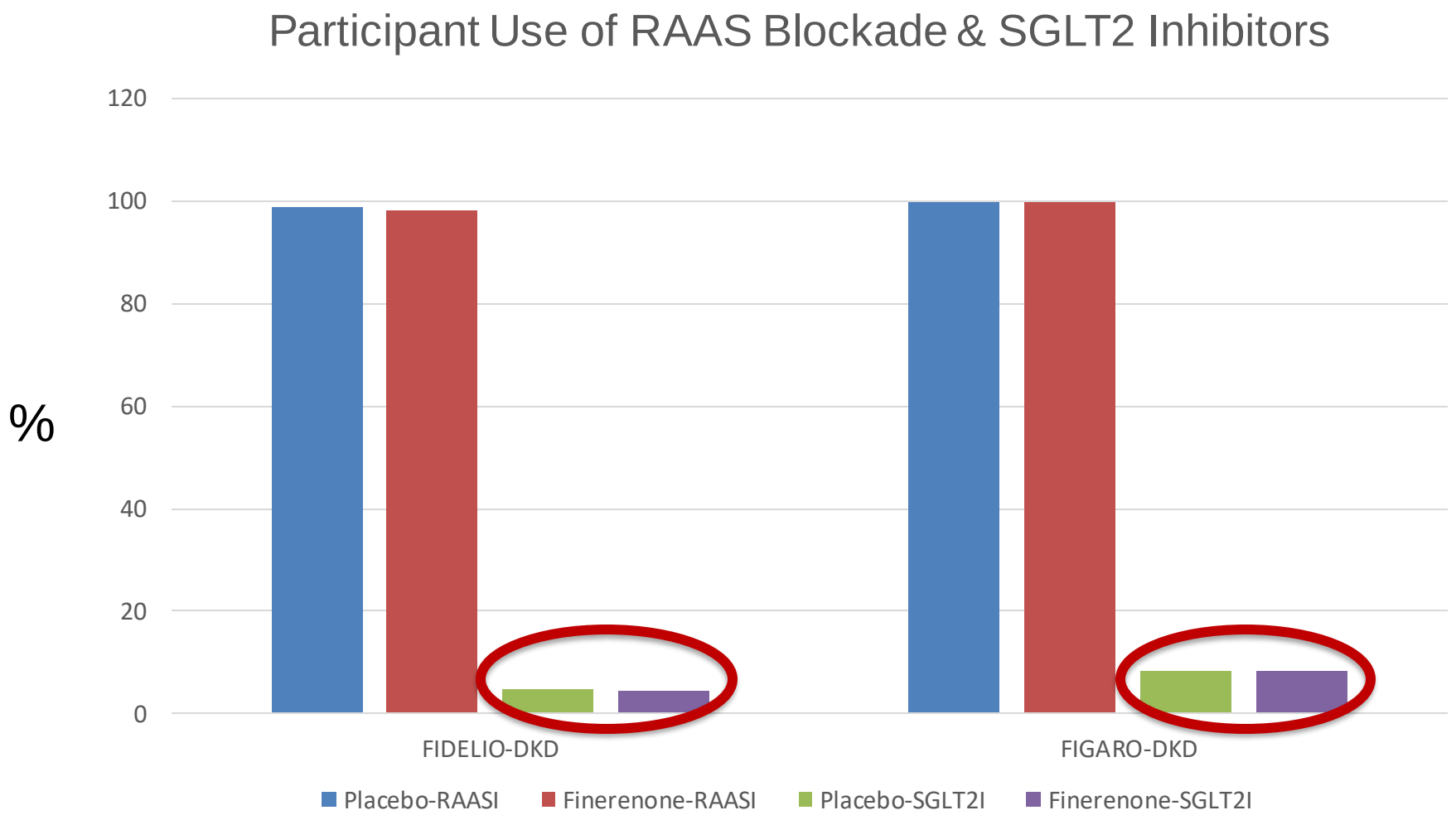


No. of Patients						
Finerenone	2827	2708	2600	1872	882	344
Placebo	2831	2709	2596	1865	862	348
Mean Change from Baseline (mmol/liter)						
Finerenone	Ref.	0.25	0.24	0.21	0.21	0.20
Placebo	Ref.	0.02	0.04	0.05	0.07	0.07

- More hyperkalemia but no difference in AKI or hospitalization.

Bakris, et. Al. NEJM. 2020

Limitations: More Studies Needed



Take Home Points

Multifaceted Approach

Lifestyle Changes	Glycemic Control	Blood Pressure Management	More Data Needed
• Low Sodium Diet • Smoking Cessation • Weight Loss	• A1C < 7.0 • **SGLT2 Inhibitor**	• Goal < 130/80 • **Single agent RAAS blockade**	• Finerenone • GLP-1 Agonists • DPP-4 Inhibitors