Treatment of Hypertension in people with Diabetes Mellitus

New Insights into Cardiometabolic Wellness in People with Diabetes

CME Programme for Africa

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Erika Jones

Division of Nephrology and Hypertension

University of Cape Town and Groote Schuur Hospital

Declaration and Disclaimer

I declare that I have received financial support from the following pharmaceutical companies, in the form of grants, sponsorship:

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Pharmadynamics
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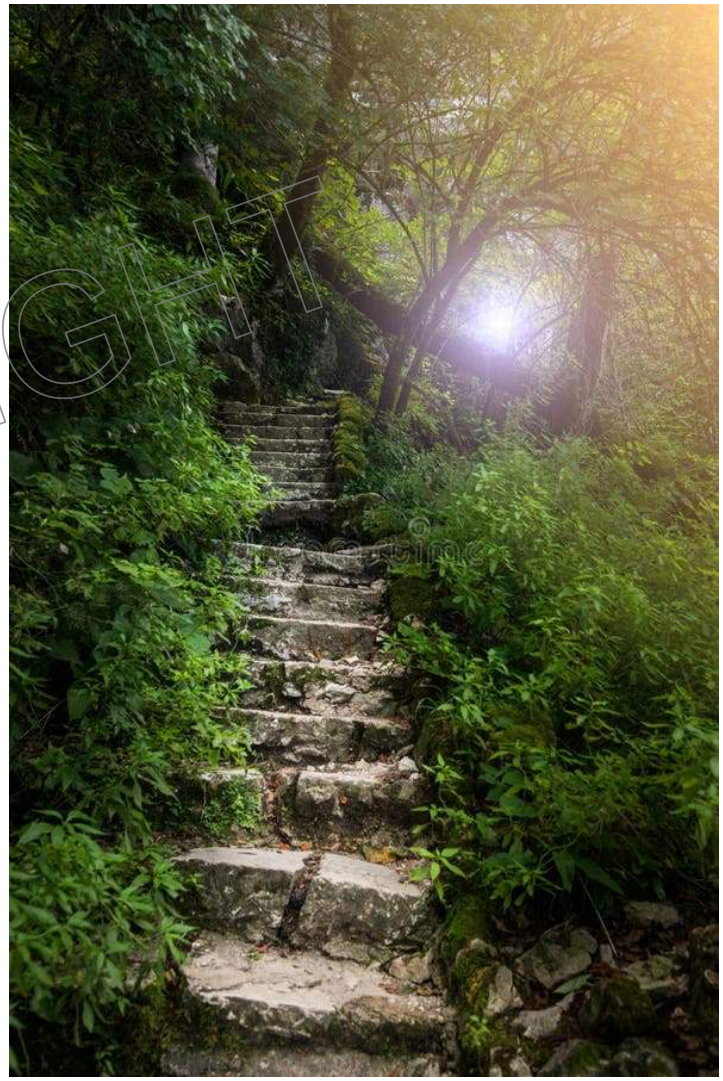
Talk Layout

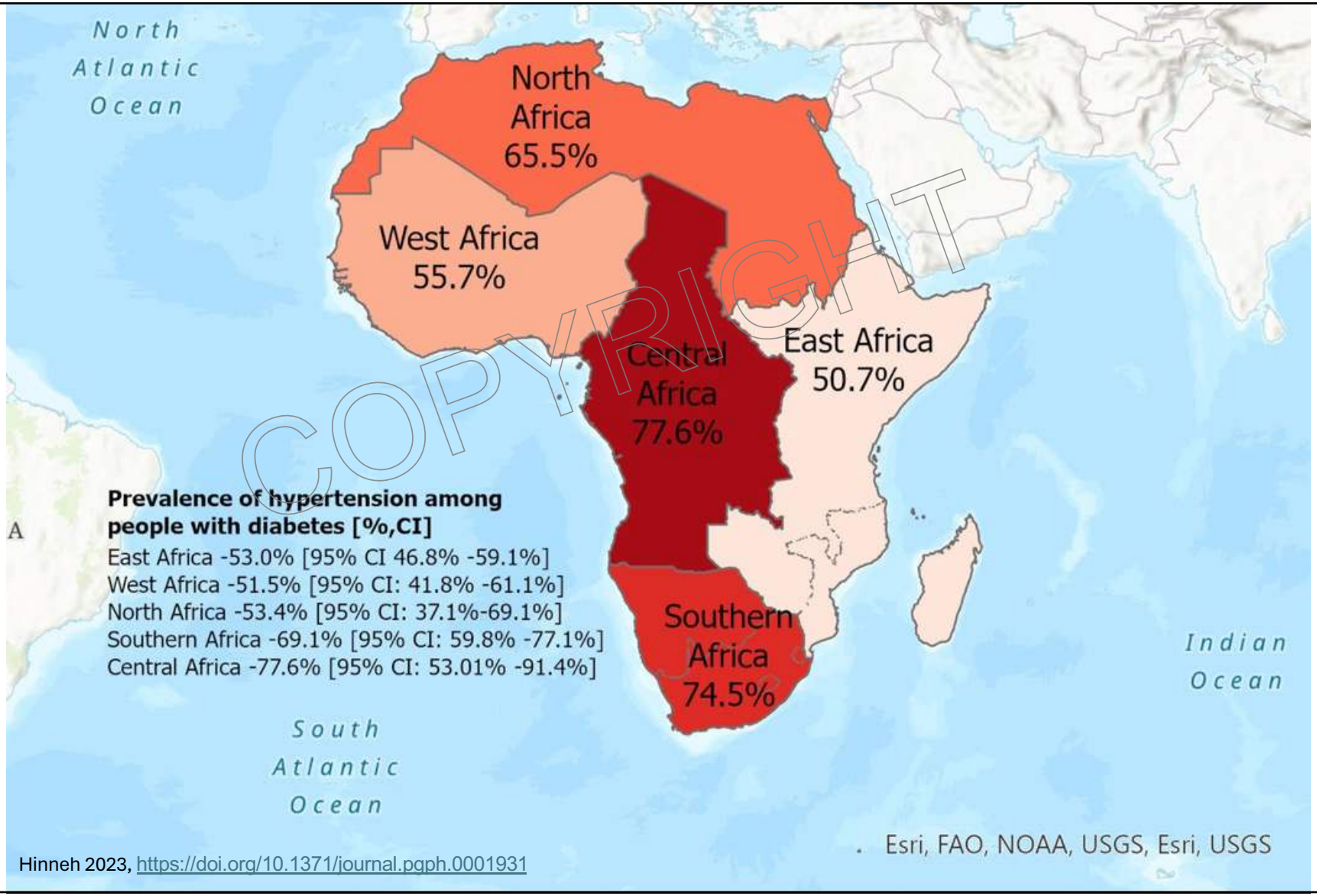
- Epidemiology
- Pathophysiology
- Treatment
- BP targets
- Which antihypertensive
- Screening
- Kidney dysfunction



Epidemiology

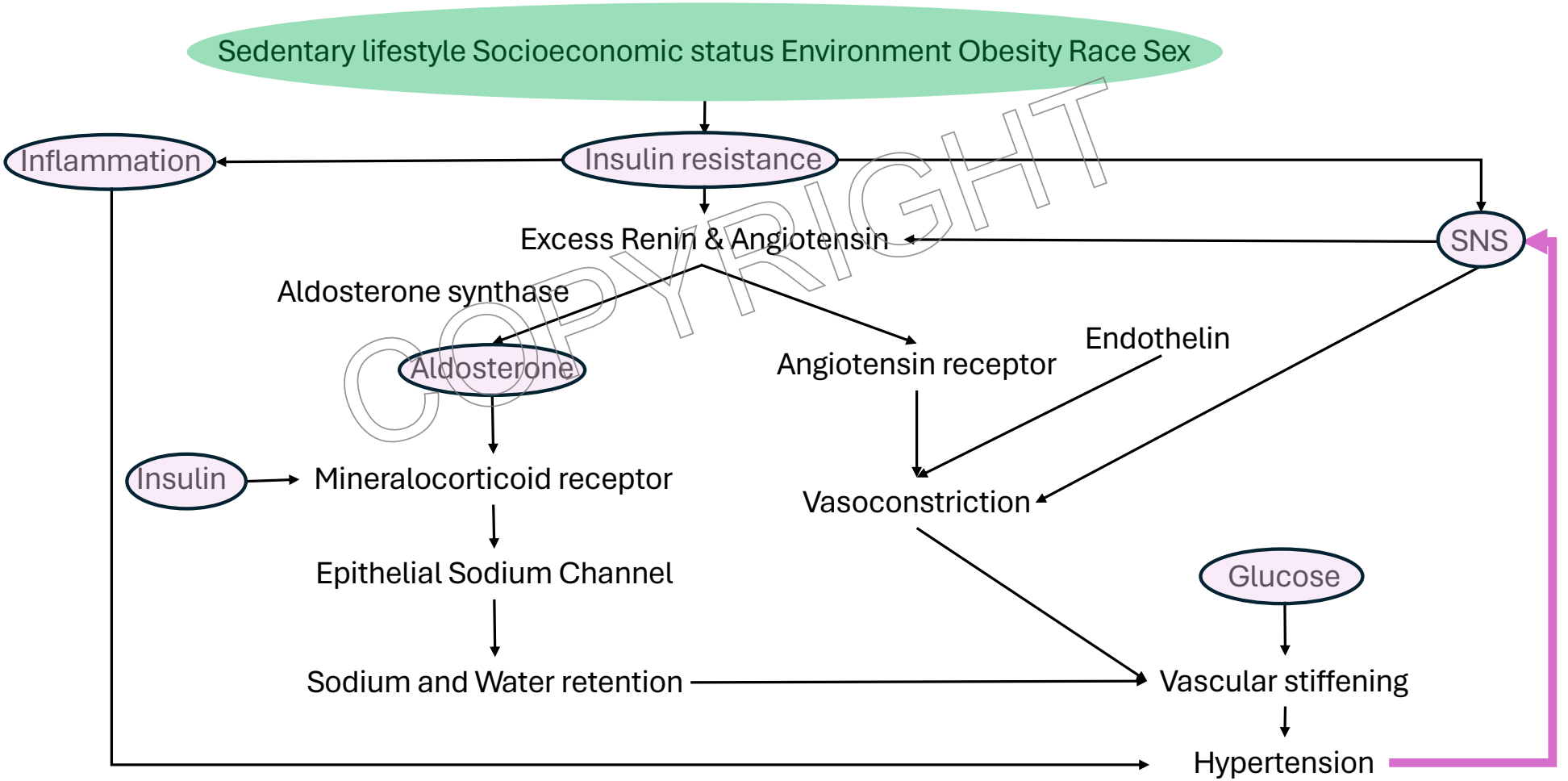
- Diabetics have a 2-4 fold increased risk of hypertension
- In Africa – average prevalence 58%
  - 61% in people with T2DM
- Co-existence of diabetes and hypertension increases mortality and CV risk
- Risks for Hypertension
  - Age
  - Length of DM
  - Body Mass index
  - Employment
  - Sex

Hinneh 2023, https://doi.org/10.1371/journal.pgph.0001931



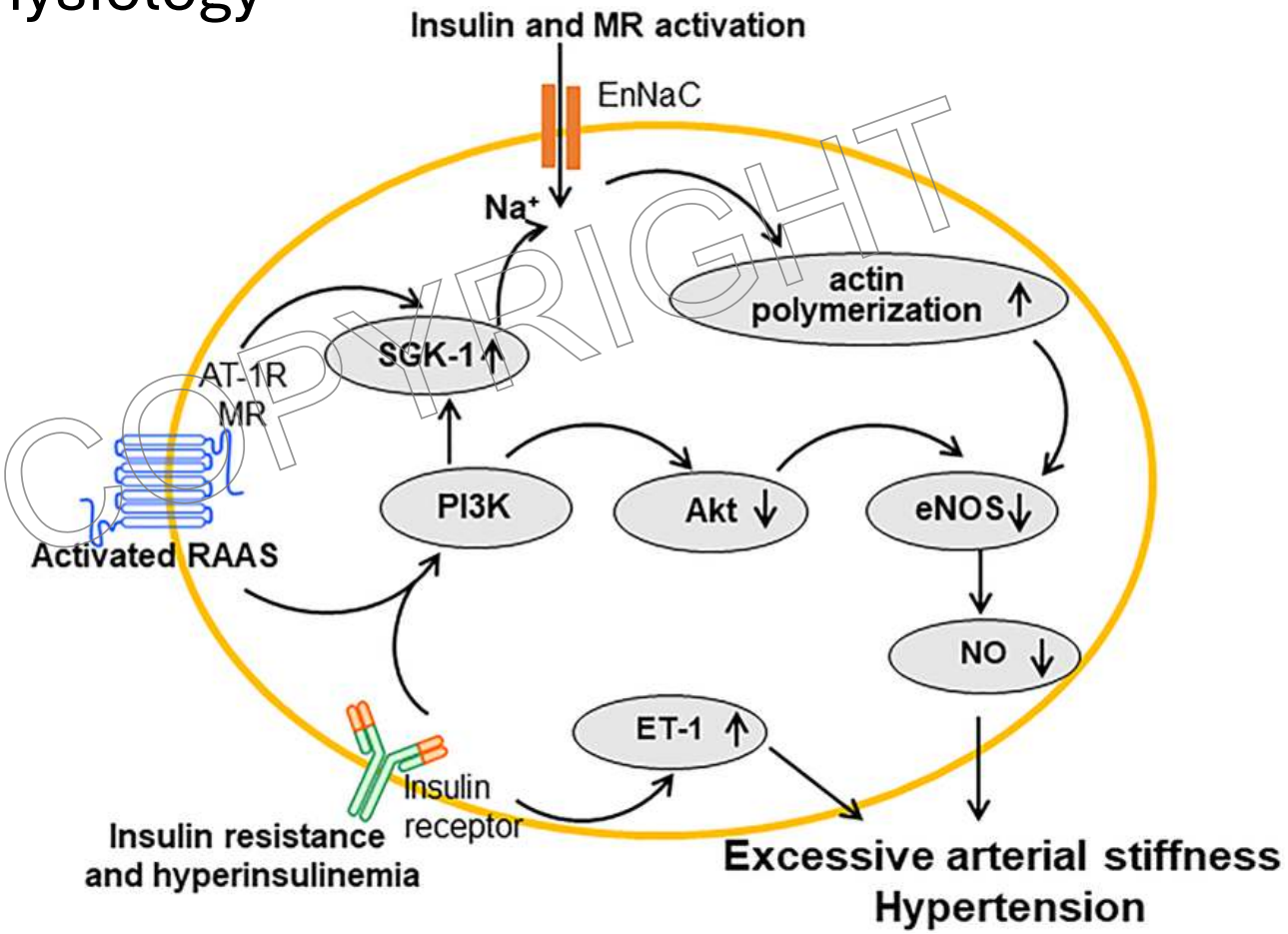
Hinneh 2023, https://doi.org/10.1371/journal.pgph.0001931

Pathophysiology of Hypertension in DM

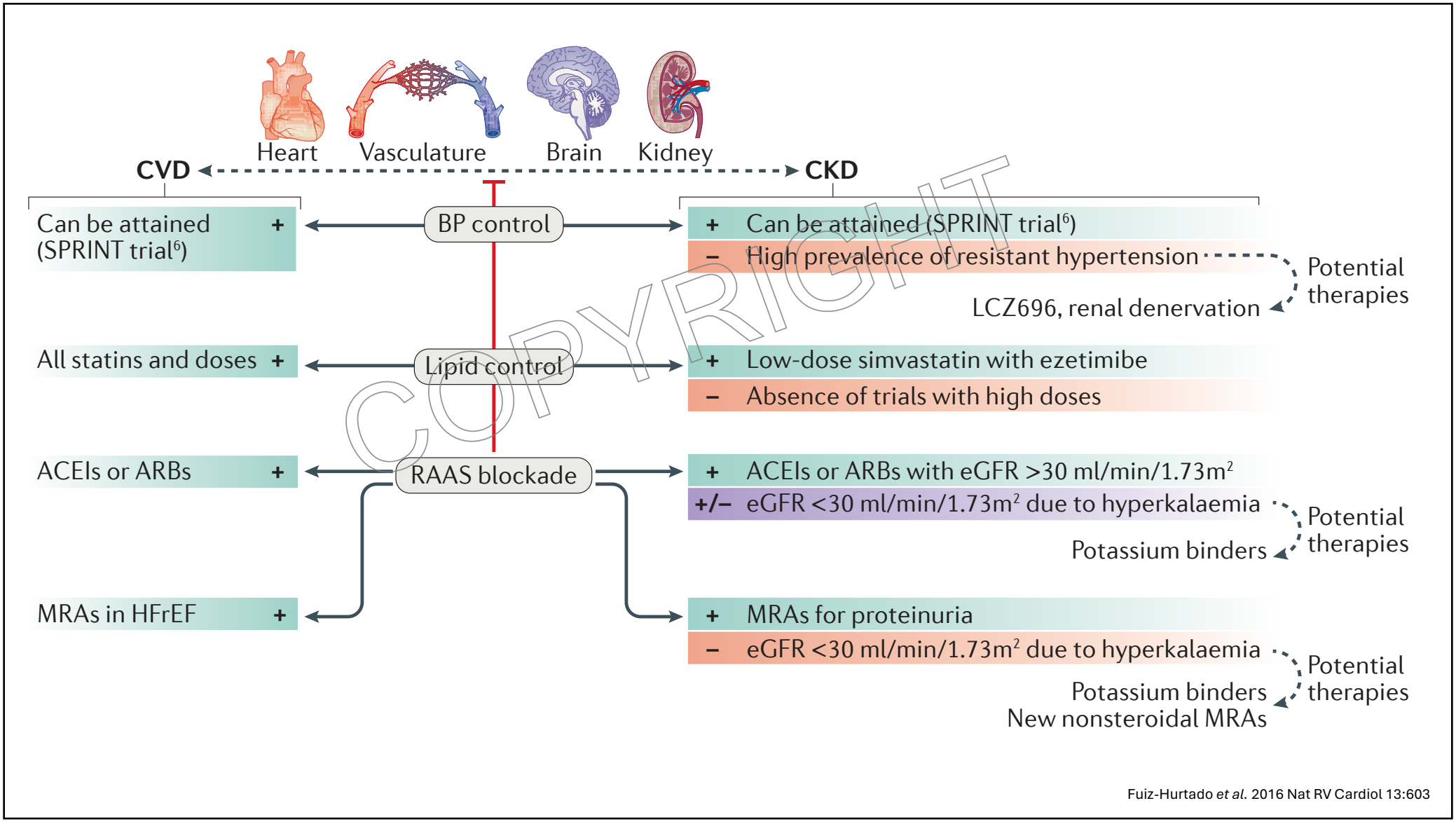


Hypertension. 2021;78:1197–1205. DOI: 10.1161/HYPERTENSIONAHA.121.17981

Endothelial physiology

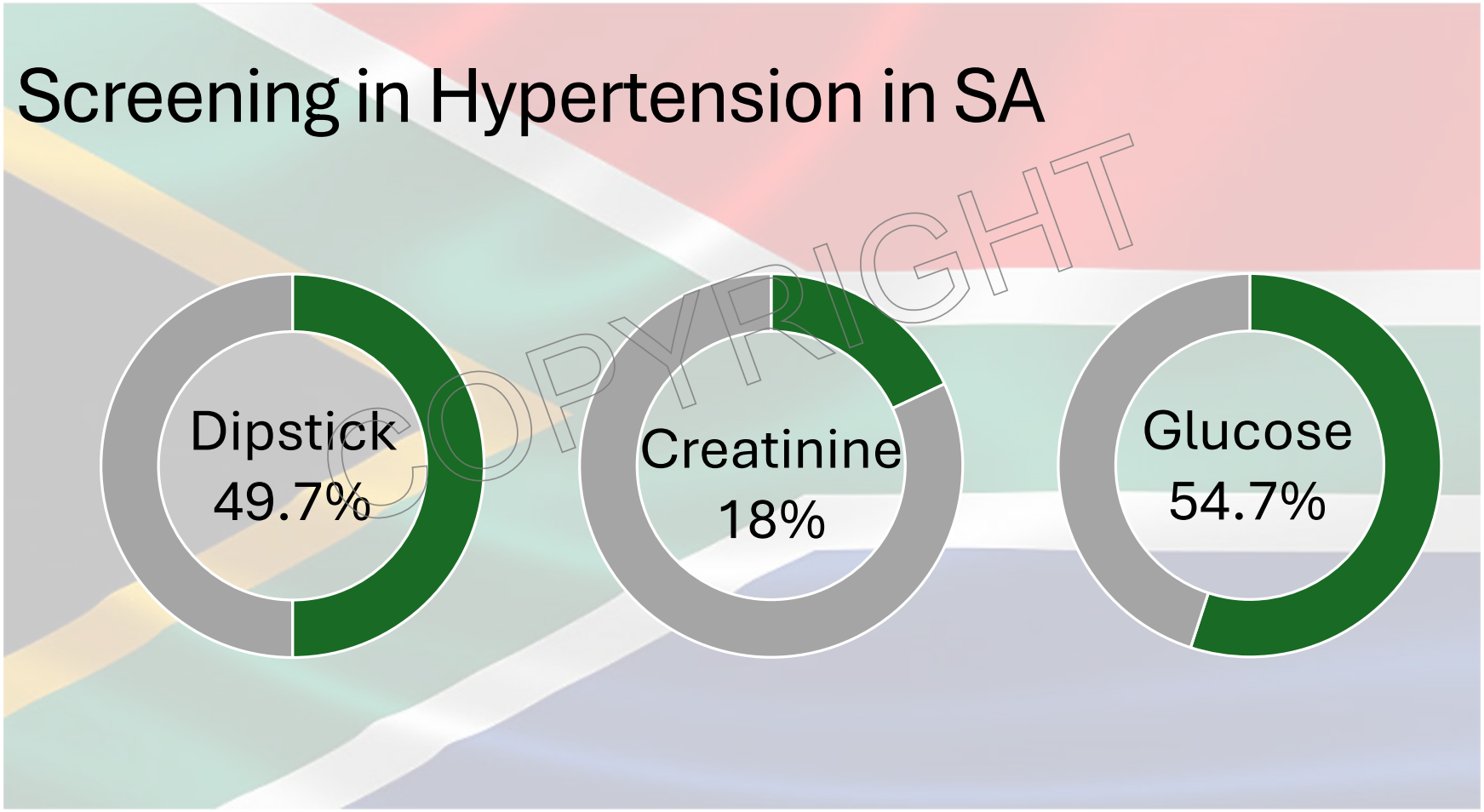


Hypertension. 2021;78:1197–1205. DOI: 10.1161/HYPERTENSIONAHA.121.17981



Fuiz-Hurtado *et al.* 2016 Nat RV Cardiol 13:603

Screening in Hypertension in SA



Rayner et al., SAMJ 2007 97(4)

WHO Risk Scores

Blood pressure

Body Mass Index

Age and sex

Smoking status

±

Diabetes

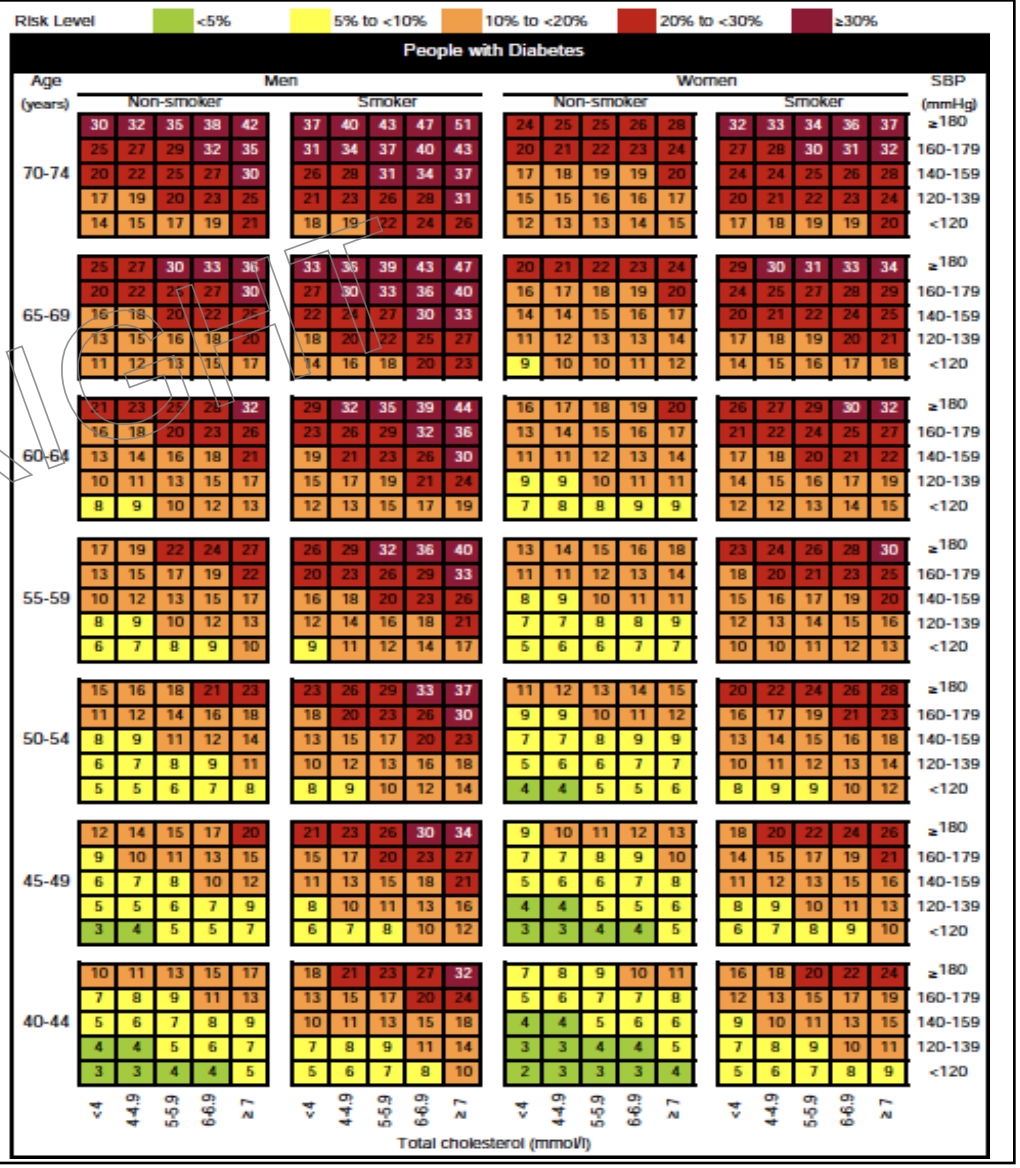
Cholesterol

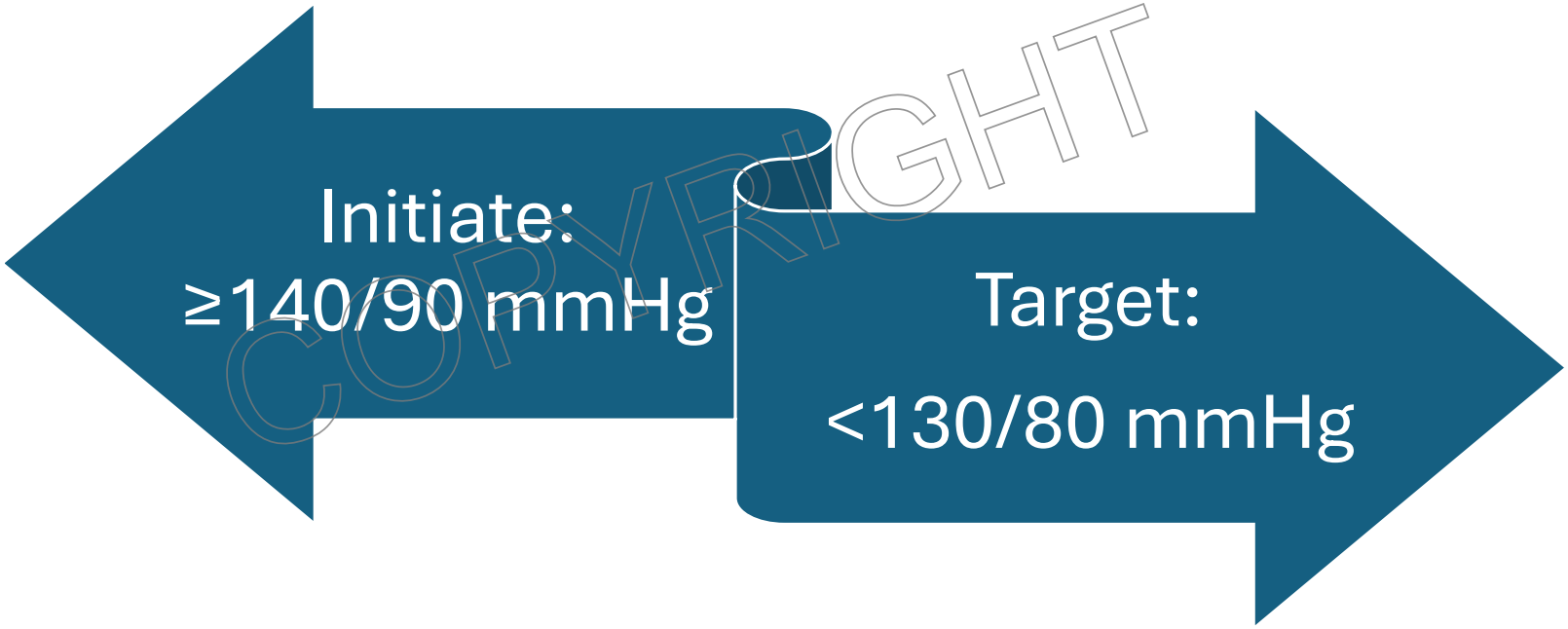
Central Sub-Saharan Africa

Eastern Sub-Saharan Africa

Western Sub-Saharan Africa

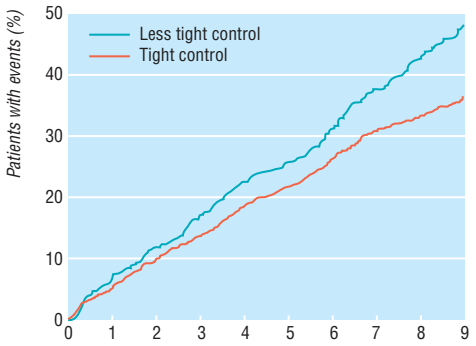
Southern Sub-Saharan Africa





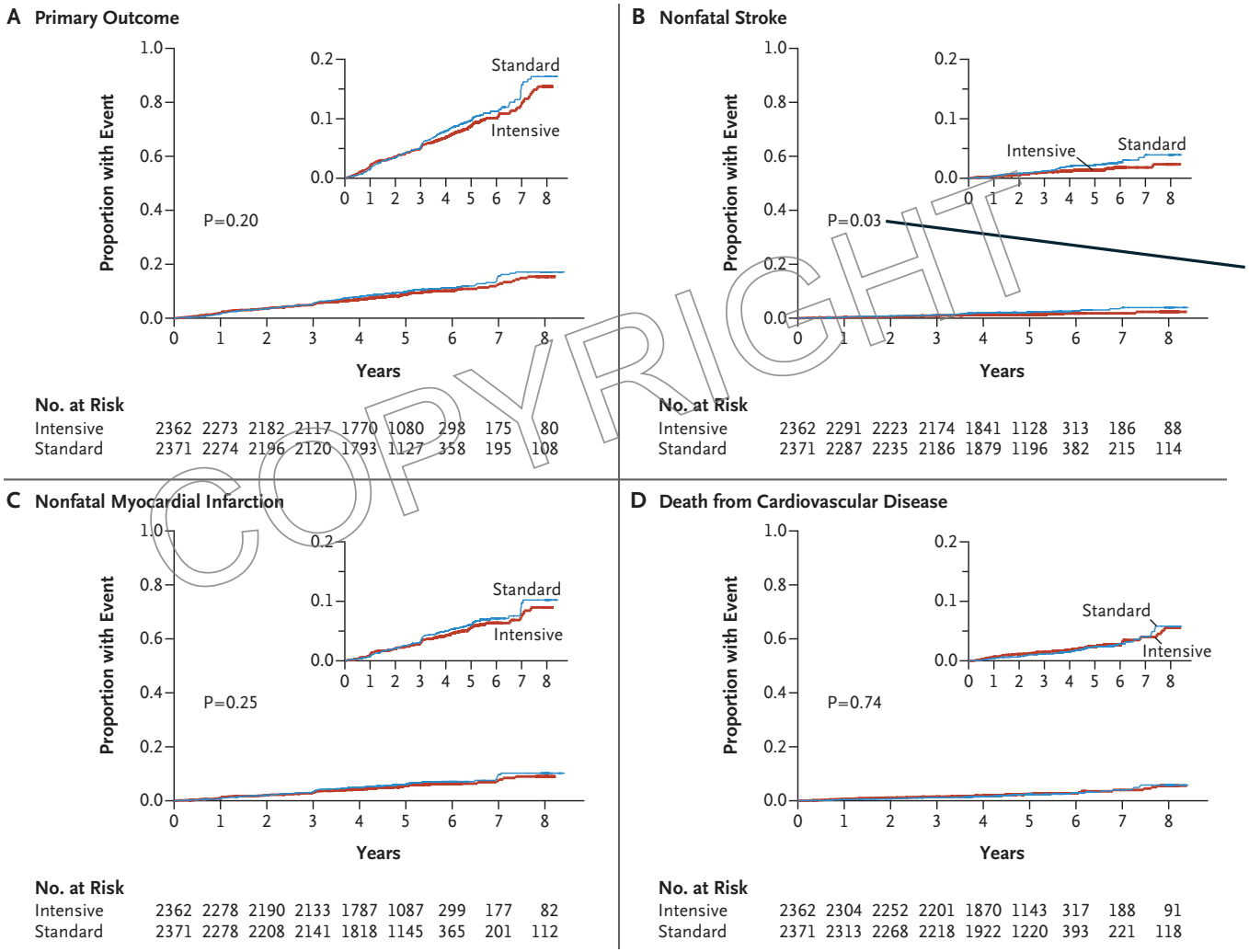
ESH 2023 guidelines Journal of Hypertension

UKPDS



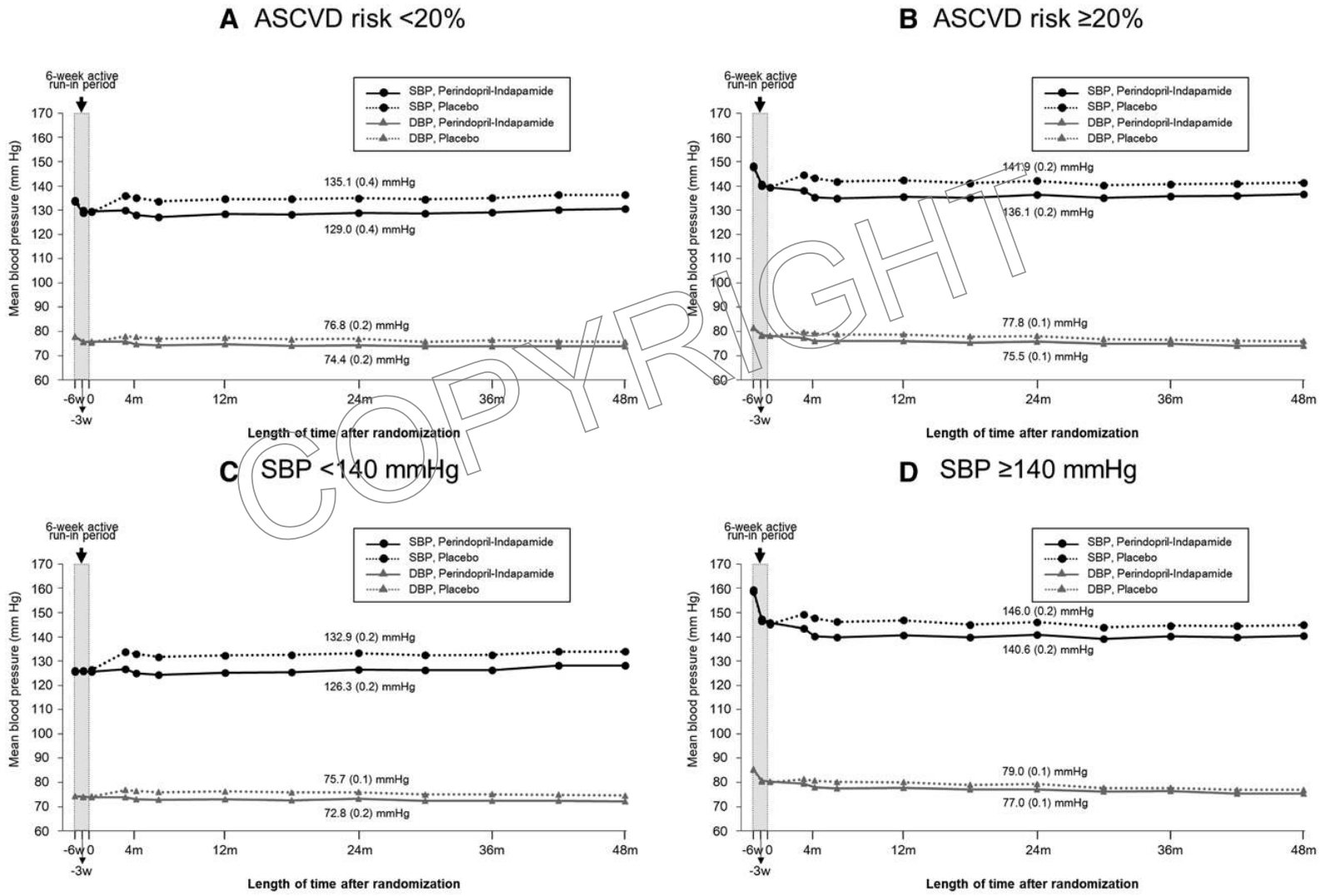
Clinical end point	Patients with aggregate end points		Absolute risk (events per 1000 patient years)		P value	Relative risk for tight control (95% CI)
	Tight control (n=758)	Less tight control (n=390)	Tight control	Less tight control		
Any diabetes related end point	259	170	50.9	67.4	0.0046	0.76 (0.62 to 0.92)
Deaths related to diabetes	82	62	13.7	20.3	0.019	0.68 (0.49 to 0.94)
All cause mortality	134	83	22.4	27.2	0.17	0.82 (0.63 to 1.08)
Myocardial infarction	107	69	18.6	23.5	0.13	0.79 (0.59 to 1.07)
Stroke	38	34	6.5	11.6	0.013	0.56 (0.35 to 0.89)
Peripheral vascular disease	8	8	1.4	2.7	0.17	0.51 (0.19 to 1.37)
Microvascular disease	68	54	12.0	19.2	0.0092	0.63 (0.44 to 0.89)

Turner et al., UKPDS BMJ VOLUME 317, 1998

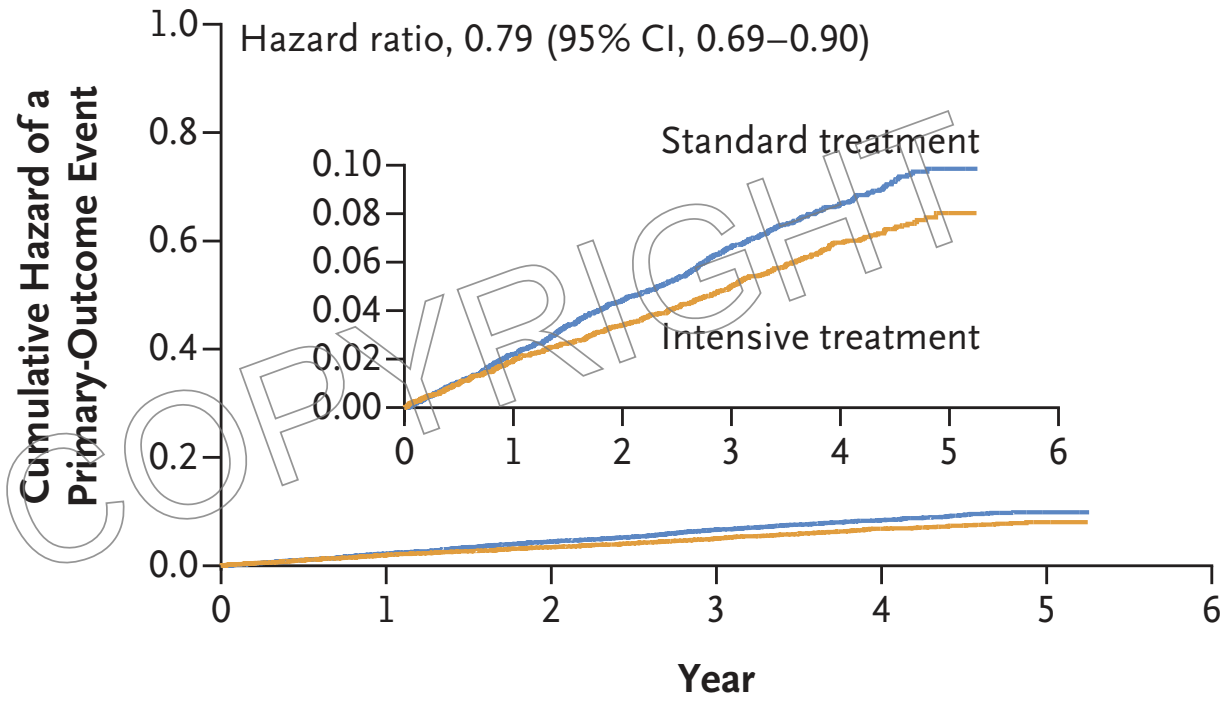


Only non-fatal stroke

ACCORD N Engl J Med 2010;362:1575-85. Cushman et al.



Rahman et al. : ADVANCE Hypertension.2019;73:1291-1299. DOI: 10.1161/HYPERTENSIONAHA.118.12414



No. at Risk

Standard treatment	6407	6087	5814	4626	3674	132
Intensive treatment	6414	6092	5871	4692	3738	112

Broad Group: Bi et al., N Engl J Med 2025;392:1155-67. DOI: 10.1056/NEJMoa2412006

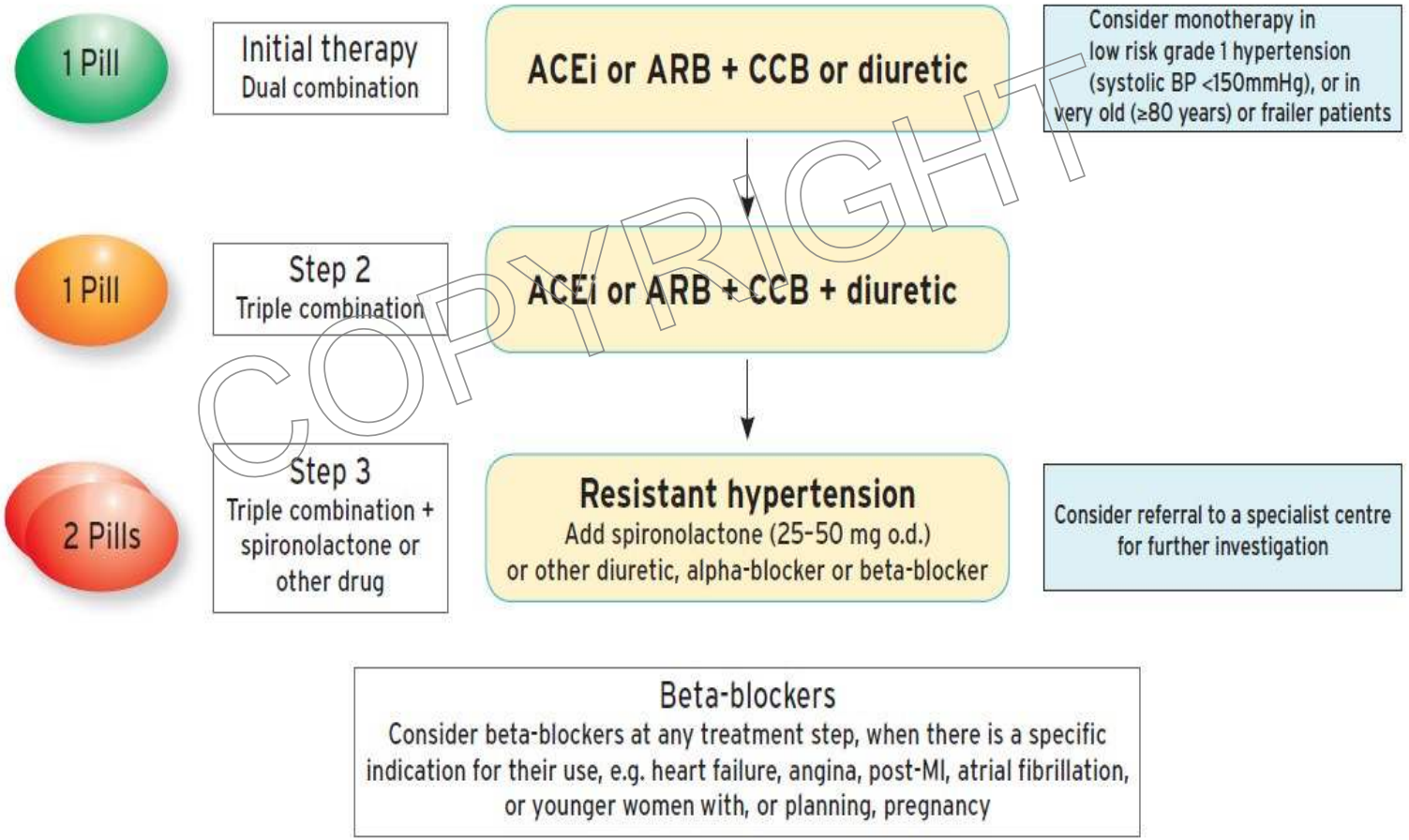
Comparison of trials

	UKPDS	ACCORD BP	ADVANCE*	BROAD
Published	1998	2010	2019	2025
Target	150/85 vs 180/105	<140 vs <120	Placebo vs per/ind	<140 vs <120
Population	English/ Irish	US & Canada	Australia, Asia, EU, North America	China
Outcomes	DM mortality	MACE	Difference in outcomes based on baseline BP	MACE
CV Risk		high	high	high
BP achieved	144/82 vs 154/87	134/71 vs 119/65	135/77 vs 129/74	133 vs 122
Findings	24% comparative reduction	No significant benefit for MACE but lower stroke rate	BP lowering decreased CV risk	Lower MACE led by stroke and death by any cause, lower albuminuria

* Comparing <20% ASCVD risk

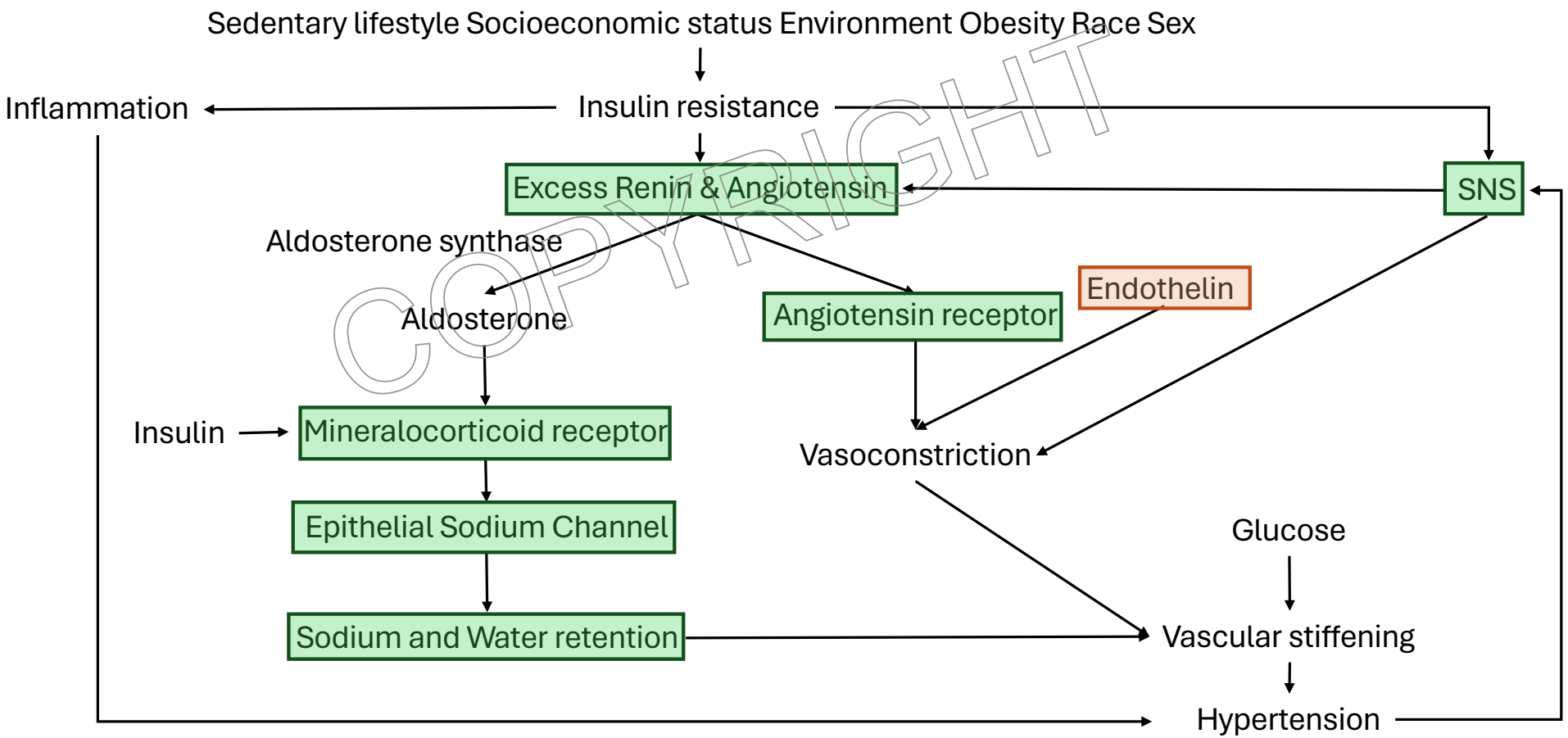
In the intensive arm there were more people with hypotension, hyperkalaemia and rise in creatinine

Treatment Options



Williams B et al. European Heart Journal. 2018;39:3021–3104

Current treatment options targeting pathophysiology



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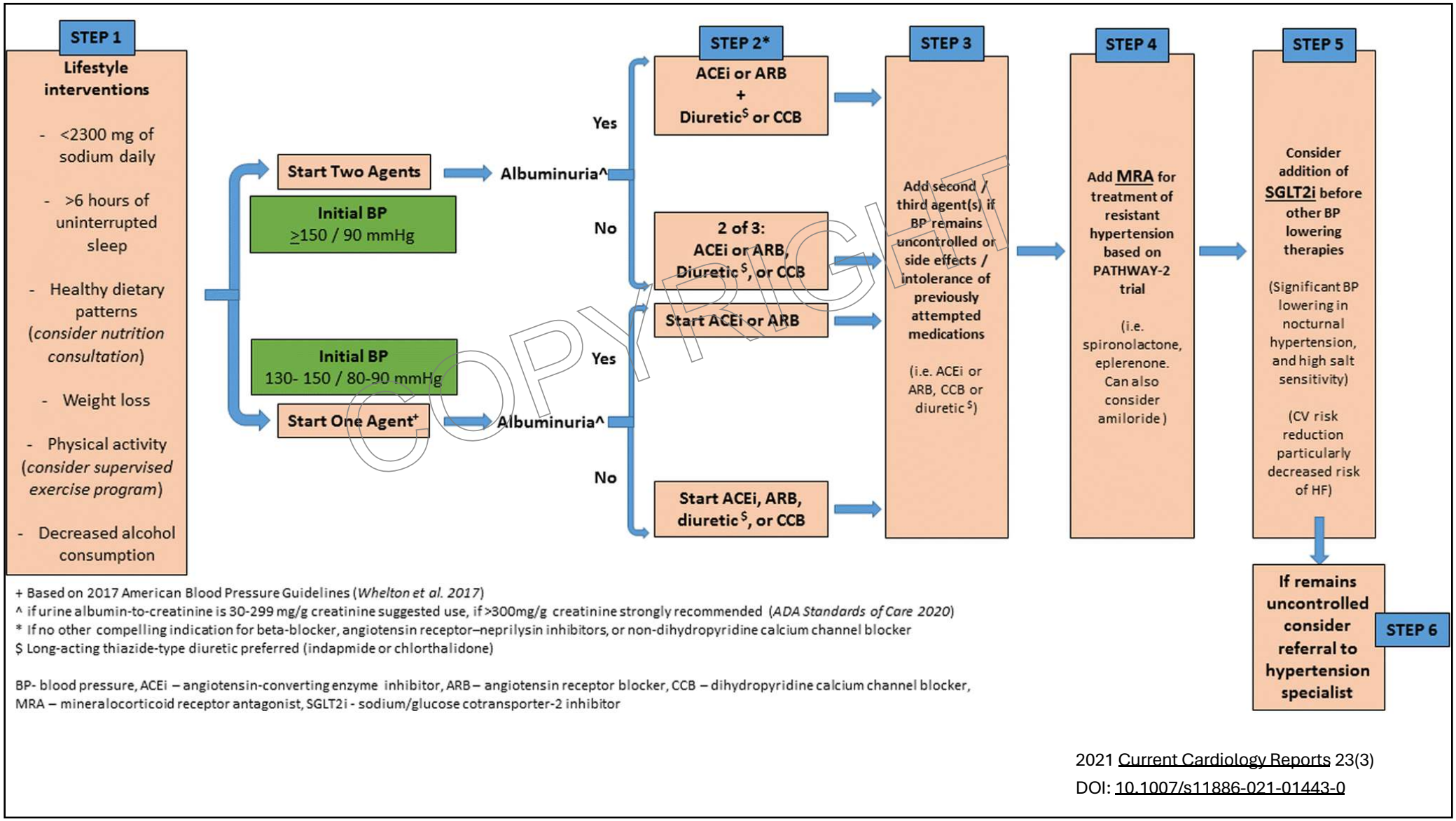
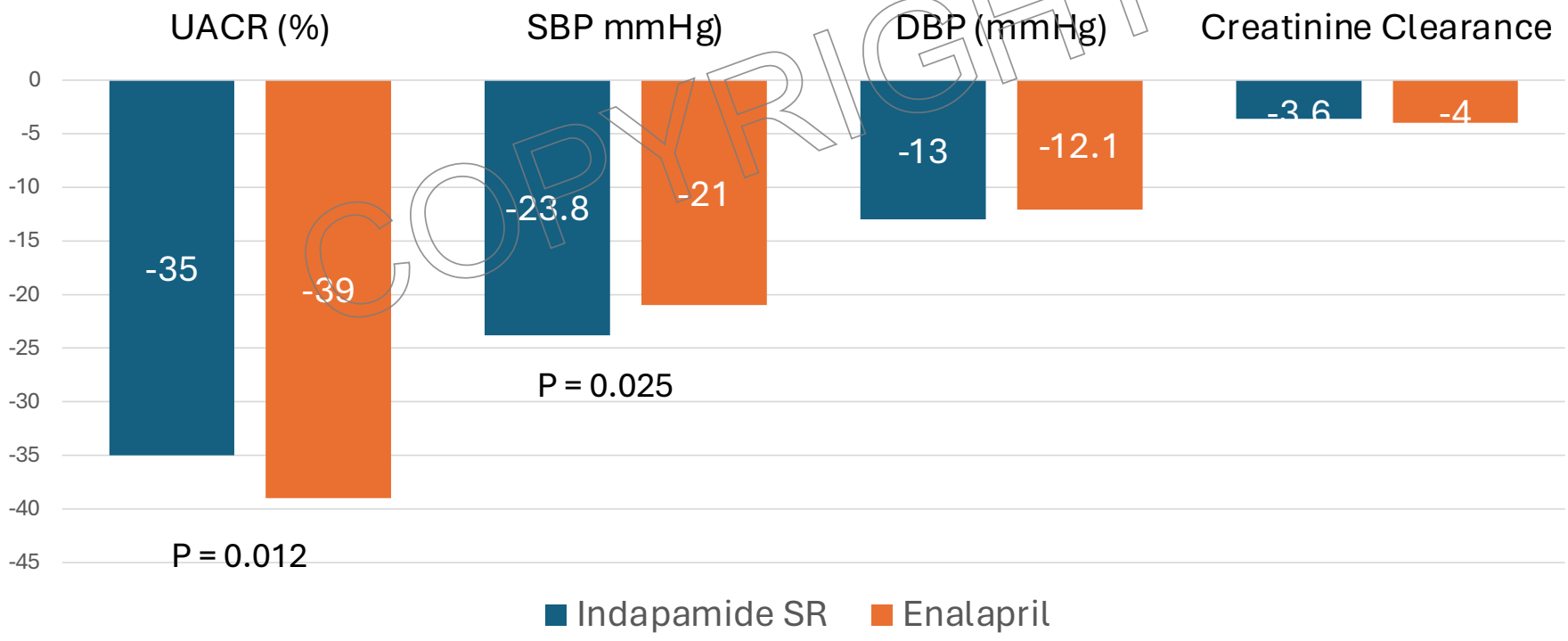


+ Based on 2017 American Blood Pressure Guidelines (*Whelton et al. 2017*)
^ if urine albumin-to-creatinine is 30-299 mg/g creatinine suggested use, if >300mg/g creatinine strongly recommended (*ADA Standards of Care 2020*)
* If no other compelling indication for beta-blocker, angiotensin receptor–neprilysin inhibitors, or non-dihydropyridine calcium channel blocker
$ Long-acting thiazide-type diuretic preferred (indapmide or chlorthalidone)

BP- blood pressure, ACEi – angiotensin-converting enzyme inhibitor, ARB– angiotensin receptor blocker, CCB – dihydropyridine calcium channel blocker, MRA – mineralocorticoid receptor antagonist, SGLT2i - sodium/glucose cotransporter-2 inhibitor

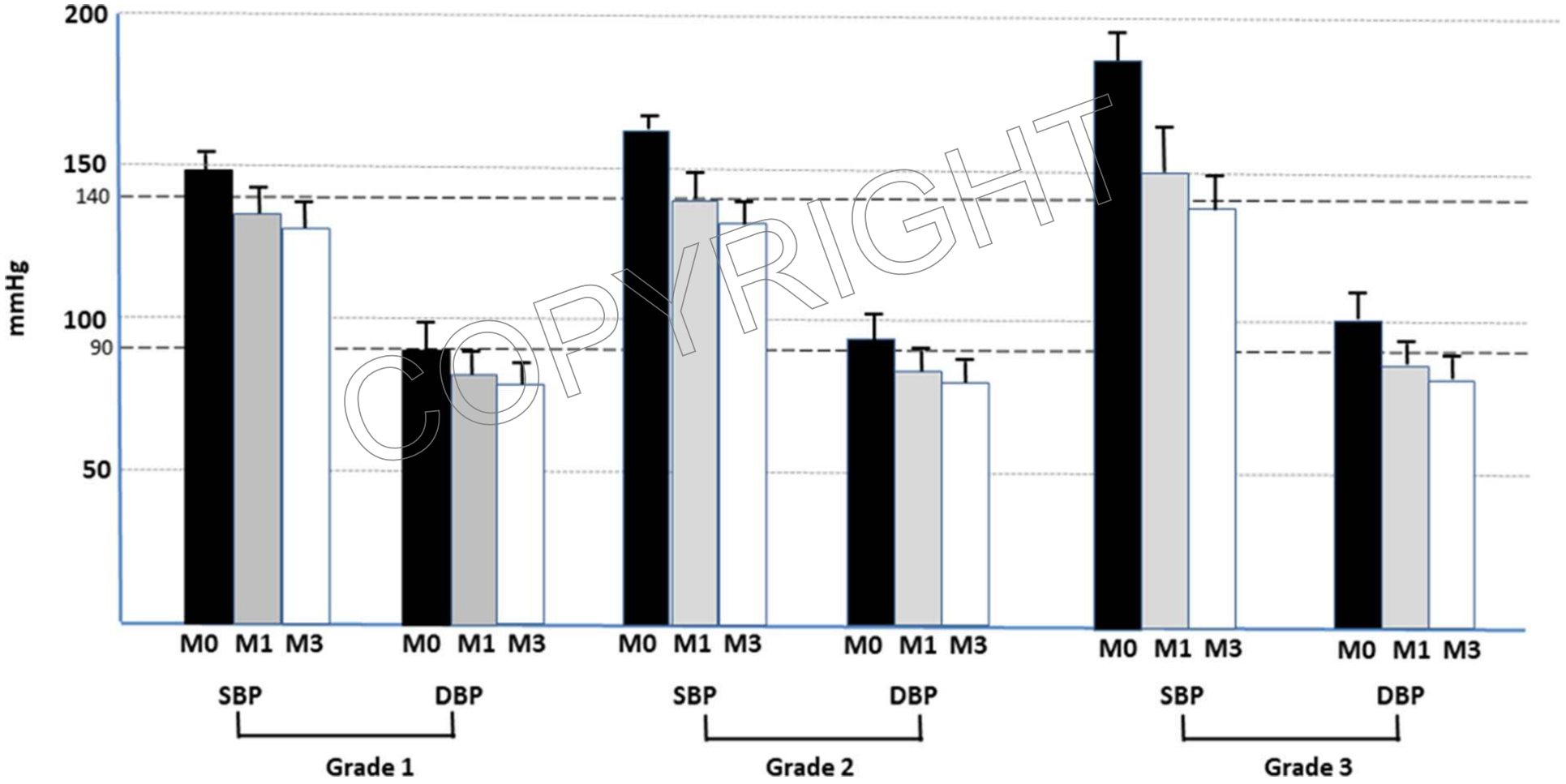
2021 Current Cardiology Reports 23(3)
DOI: 10.1007/s11886-021-01443-0

Diabetes Mellitus



Marre *et al.*, 2004 J Hypertens 22:1613

Perindopril/ Indapamide combination on blood pressure in people with DM ± Obesity ± Metabolic Syndrome

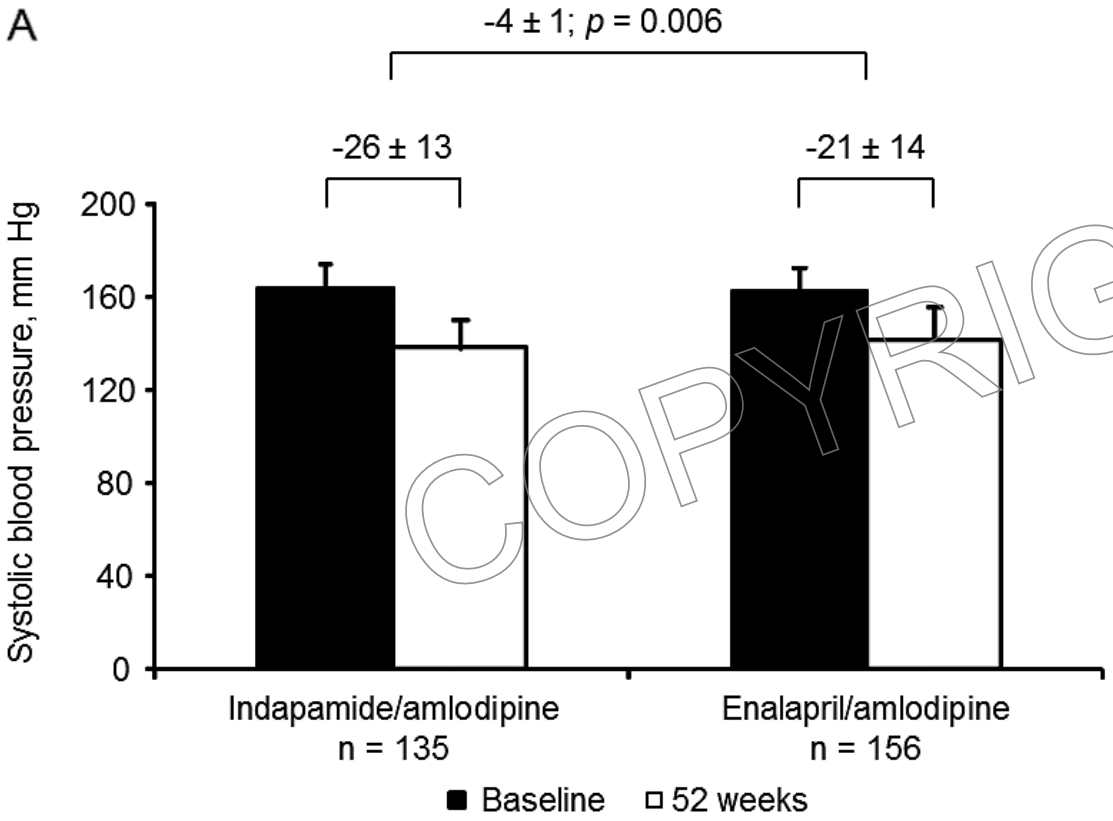


Farsang et al., Adv Ther (2021) 38:1776–1790 https://doi.org/10.1007/s12325-021-01619-8

Table 3 Blood pressure control rates at 3 months in the patient subgroups according to baseline SBP severity and overall

BP control at 3 months	Mild HT (%) (grade I)	Moderate HT (%) (grade II)	Severe HT (%) (grade III)	Overall (%)
Diabetes subgroup	72	54	42	60
Obese subgroup	78	65	49	68
MetS subgroup	76	64	49	66
Whole cohort	80	67	53	70

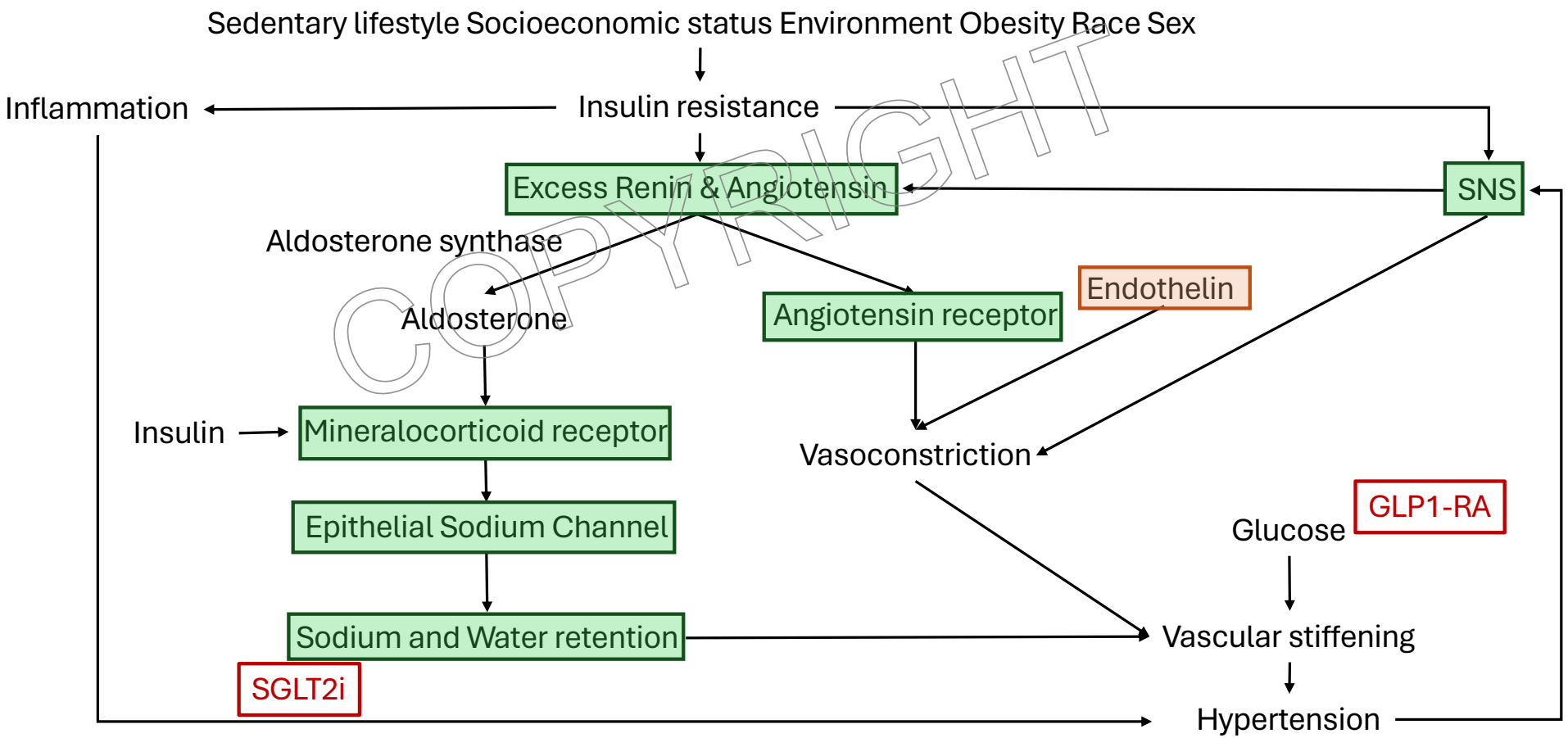
BP blood pressure, *HT* hypertension, *MetS* metabolic syndrome



Age 60 years
France
39.3% > 65 years
Diabetes and microalbuminuria
Decrease in proteinuria:
40.3% vs 44.4% (NS)
Generally well tolerated

Hanon *et al.*, 2015 Am J Hypertens. 28(8)

Potential treatment options targeting pathophysiology

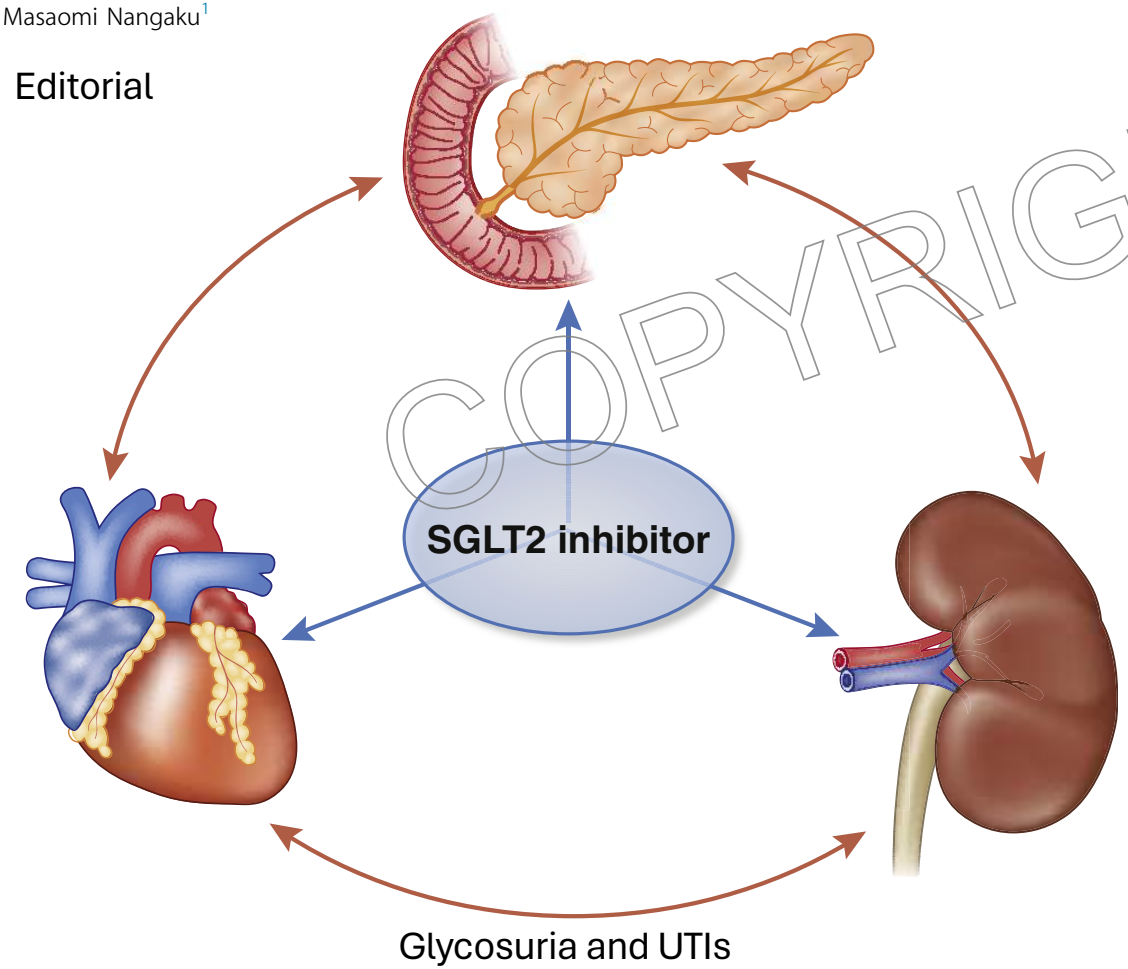


Hypertension. 2021;78:1197–1205. DOI: 10.1161/HYPERTENSIONAHA.121.17981

More reasons to use SGLT2 inhibitors: EMPEROR-reduced and DAPA-CKD

Masaomi Nangaku[1]

Editorial

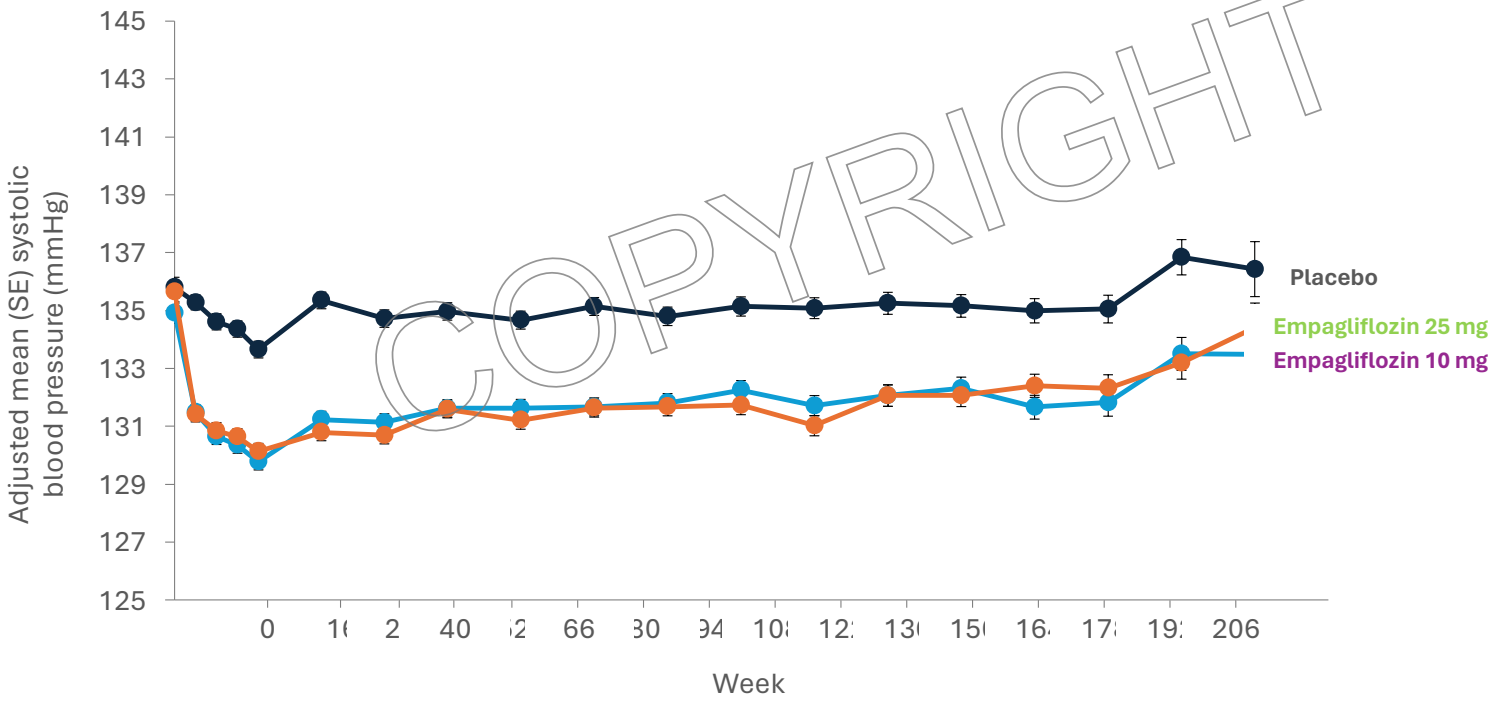


Independent of DM
Improvement of hard CV outcomes
In pts with heart failure
But not much improvement if eGFR <60

Slower decline in eGFR
Less combined renal outcome

Protection of the kidney
Glycaemic control
Amelioration of glomerular hyperfiltration
Improvement of oxidative stress
Preservation of renal capillaries
Improvement of renal hypoxia

Systolic blood pressure and SGLT2i



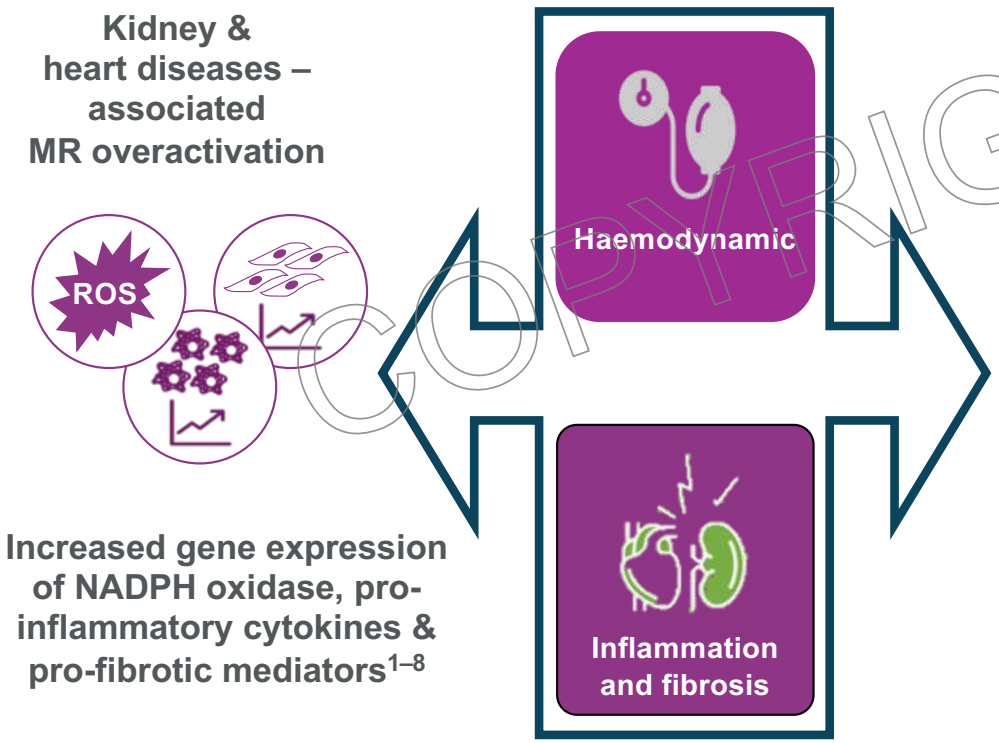
Placebo	322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

Blood pressure lowering from SGLT2i

	Systolic Blood Pressure	Diastolic Blood Pressure
Empagliflozin 25 mg/d	−4.78 mmHg	−1.90 mmHg
Canagliflozin	−3.93 mmHg	−1.39 mmHg
Dapagliflozin	−2.70 mmHg	−0.70 mmHg
Exenatide	−1.57 mmHg	+0.25 mmHg
Liraglutide	−1.20 mmHg	+0.60 mmHg
Dulaglutide	−1.70 mmHg	+0.12 mmHg
Semaglutide	−2.60 mmHg	+0.14 mmHg

Przezak, A.; Bielka, W.; Pawlik, A. Int. J. Mol. Sci. 2022, 23,6500. https://doi.org/10.3390/ijms23126500

MR and kidney and CV damage



Kidney damage[3,7]
- Glomerular damage
- Proteinuria
- Tubular injury
- Reduced renal blood flow
- Kidney injury

Vascular damage[1,6]
- Vascular remodelling
- Endothelial dysfunction
- Increased vascular stiffness

Heart damage[1,3]
- Myocardial hypertrophy
- Ventricular remodelling/fibrosis
- Reduced coronary blood flow
- Ischaemia/infarction
- Myocardial injury

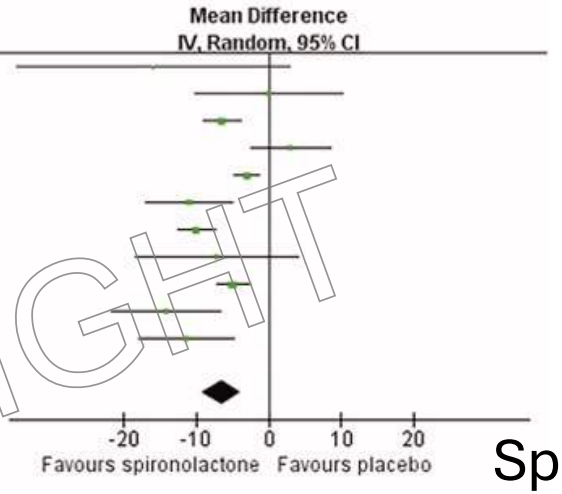
CV, cardiovascular; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species

1. Buonafine M, *et al. Am J Hypertens* 2018;31:1165–1174; 2. Kolkhof P, *et al. Handb Exp Pharmacol* 2017;243:271–305; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 4. Gomez-Sanchez E & Gomez-Sanchez CE. *Compr Physiol* 2014;4:965–994; 5. Brown NJ. *Nat Rev Nephrol* 2013;9:459–469; 6. Biwer LA, *et al. Am J Hypertens* 2019;32:123–134; 7. Barrera-Chimal J, *et al. Kidney Int* 2019;96:302–319; 8. van de Heijden CDCC, *et al. Cardiovasc Res* 2018;114:944–953

(A) **Systolic blood pressure**

Study or Subgroup	Spironolactone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
J. Davies2005	137	21	10	153	22	10	1.7%	-16.00 [-34.85, 2.85]
J.I.Davies2004	128	27	42	128	20	42	4.7%	0.00 [-10.16, 10.16]
Kanchan V2016	120.25	4.24	20	126.7	3.9	20	13.8%	-6.45 [-8.97, -3.93]
Kosmala W2011	140	14	40	137	11	39	9.3%	3.00 [-2.54, 8.54]
Nielsen SE2012	138	3	21	141	3	21	14.7%	-3.00 [-4.81, -1.19]
Oxlund CS2013	133	15.6	61	144	17.5	58	8.7%	-11.00 [-16.97, -5.03]
Rossing K2005	132	4	20	142	4	20	13.8%	-10.00 [-12.48, -7.52]
Saklayen MG2008	141.6	16.54	24	148.82	22.68	24	4.1%	-7.22 [-18.45, 4.01]
Schjoedt KJ2005	131	4	20	136	3	20	14.2%	-5.00 [-7.19, -2.81]
Swaminathan K2008	135.5	16.4	38	149.7	16.7	38	7.0%	-14.20 [-21.64, -6.76]
van den Meiracker AH2006	137.1	12.55	24	148.4	11.48	28	8.0%	-11.30 [-17.88, -4.72]
Total (95% CI)			320			320	100.0%	**-6.57 [-9.21, -3.93]**

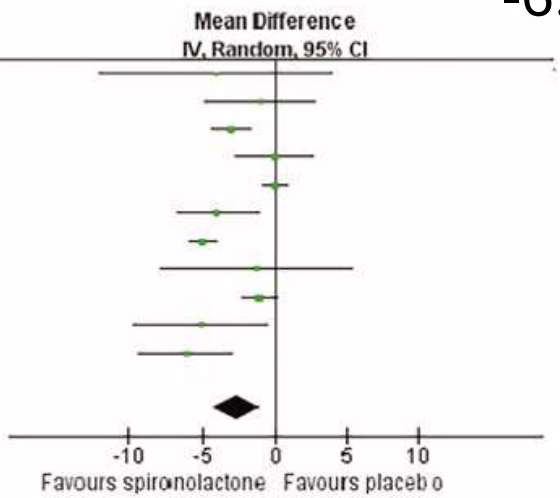
Heterogeneity: Tau² = 11.55; Chi² = 43.50, df = 10 (P < 0.00001); I² = 77%
Test for overall effect: Z = 4.87 (P < 0.00001)



(B) **Diastolic blood pressure**

Study or Subgroup	Spironolactone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
J. Davies2005	75	7	10	79	11	10	3.1%	-4.00 [-12.08, 4.08]
J.I.Davies2004	71	9	42	72	9	42	7.6%	-1.00 [-4.85, 2.85]
Kanchan V2016	81.05	2.06	20	84.05	2.54	20	12.2%	-3.00 [-4.43, -1.57]
Kosmala W2011	80	6	40	80	6	39	9.9%	0.00 [-2.65, 2.65]
Nielsen SE2012	71	1	21	71	2	21	12.9%	0.00 [-0.96, 0.96]
Oxlund CS2013	73	8	61	77	7.6	58	9.6%	-4.00 [-6.80, -1.20]
Rossing K2005	71	2	20	76	1	20	12.8%	-5.00 [-5.98, -4.02]
Saklayen MG2008	76.68	11.74	24	77.91	11.32	24	4.2%	-1.23 [-7.75, 5.29]
Schjoedt KJ2005	71	2	20	72	2	20	12.5%	-1.00 [-2.24, 0.24]
Swaminathan K2008	75.5	9.5	38	80.6	10.8	38	6.5%	-5.10 [-9.67, -0.53]
van den Meiracker AH2006	76.6	6.16	24	82.7	5.54	28	8.8%	-6.10 [-9.31, -2.89]
Total (95% CI)			320			320	100.0%	**-2.63 [-4.25, -1.02]**

Heterogeneity: Tau² = 5.06; Chi² = 68.37, df = 10 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.19 (P = 0.001)

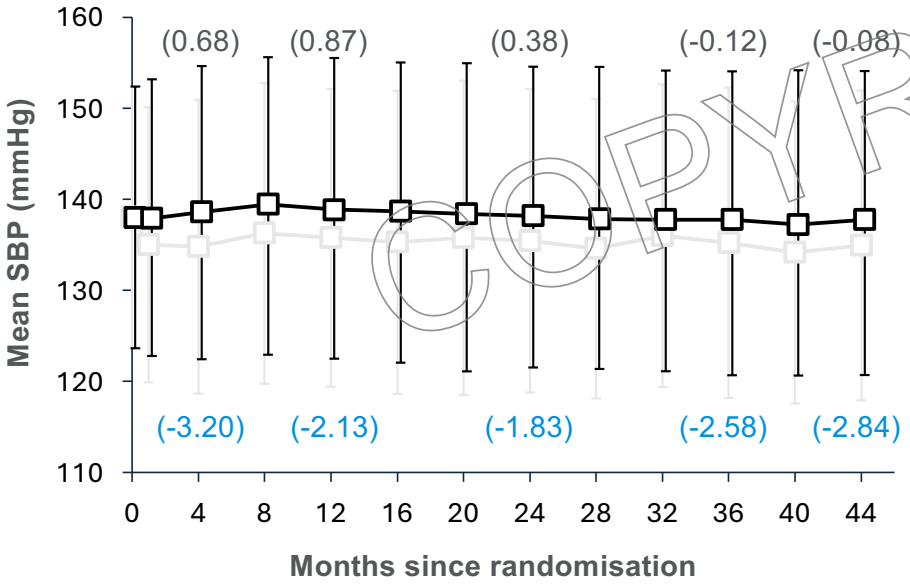


Spironolactone
-6.57/2.63 mmHg

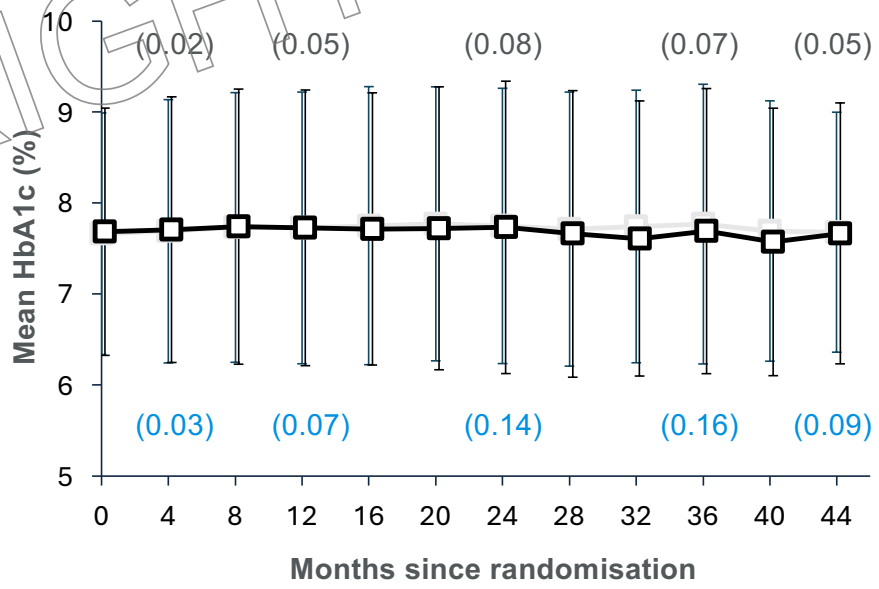
Lin et al., *Blood Pressure*, *30*(3), 145–153.
https://doi.org/10.1080/08037051.2021.1880881

Finerenone & blood pressure and blood glucose

Change in SBP over time



Change in HbA1c over time

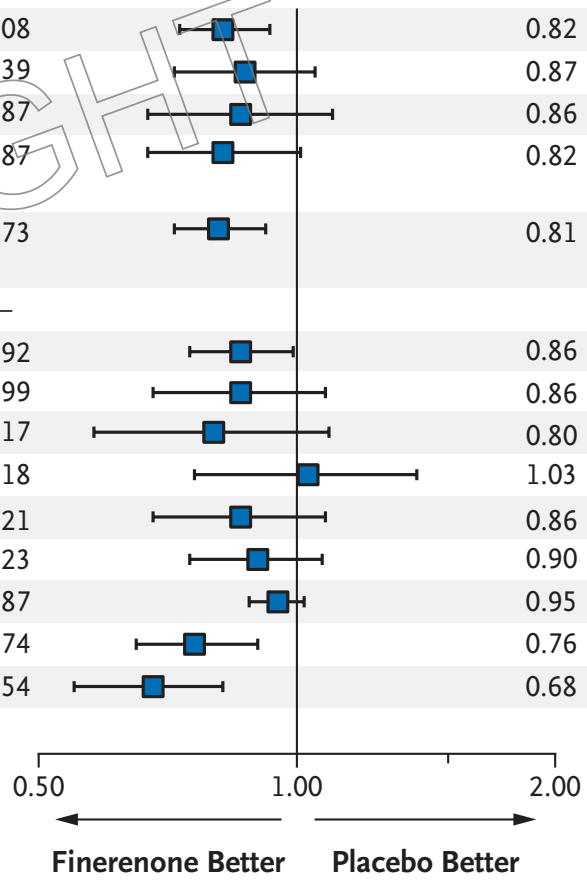


Placebo Finerenone

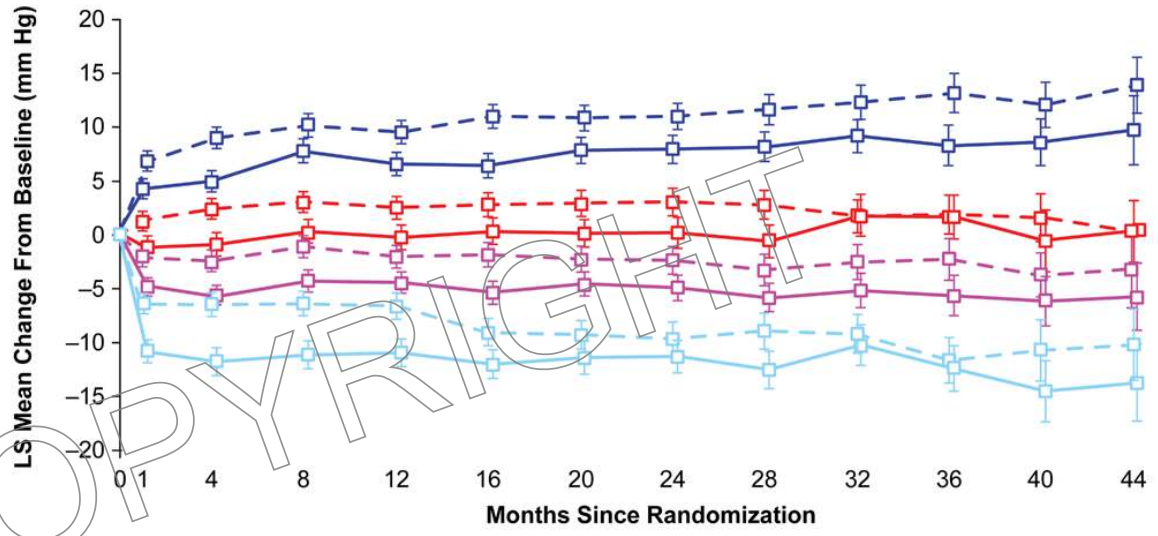
HbA1c, glycated haemoglobin; SBP, systolic blood pressure

Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

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)	—

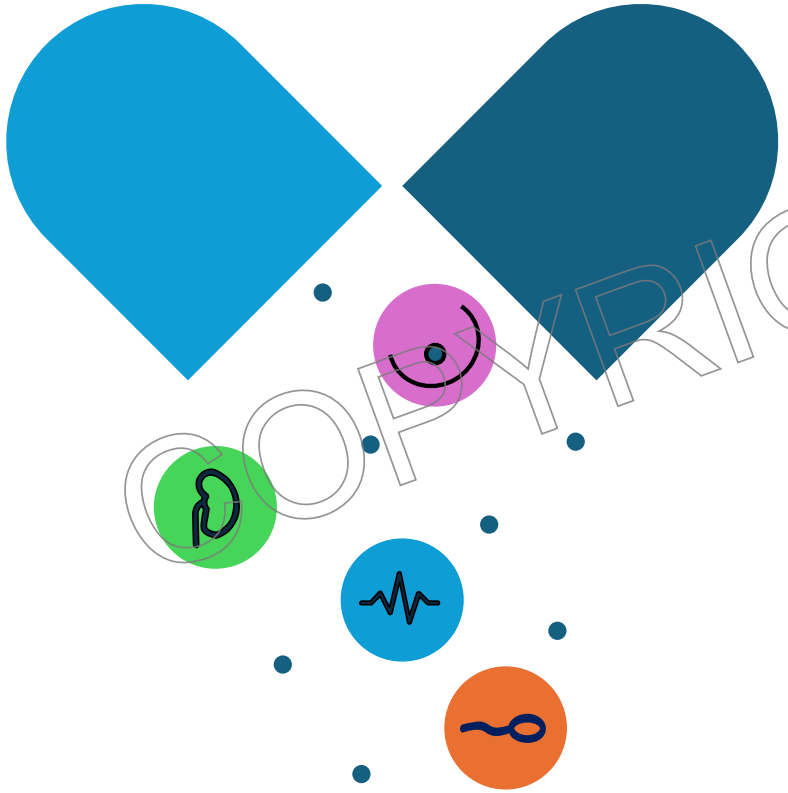


But when the BP was higher …



Overall LS Mean Difference: −3.14 (95% CI −4.30 to −1.99)							
LS Mean Change From Baseline (mm Hg)							
SBP Q1 (≤128.7 mm Hg)	Finerenone	4.30	4.99	6.61	7.95	8.31	9.72
	Placebo	6.88	9.01	9.56	11.01	13.18	13.92
Overall LS Mean Difference: −2.03 (95% CI −3.14 to −0.93)							
LS Mean Change From Baseline (mm Hg)							
SBP Q2 (>128.7 to ≤138.3 mm Hg)	Finerenone	−1.13	−0.85	−0.22	0.22	1.65	0.50
	Placebo	1.31	2.43	2.55	3.07	1.89	0.38
Overall LS Mean Difference: −2.74 (95% CI −3.85 to −1.64)							
LS Mean Change From Baseline (mm Hg)							
SBP Q3 (>138.3 to ≤148.0 mm Hg)	Finerenone	−4.80	−5.63	−4.40	−4.88	−5.62	−5.71
	Placebo	−2.11	−2.40	−2.00	−2.34	−2.25	−3.18
Overall LS Mean Difference: −2.65 (95% CI −4.01 to −1.28)							
LS Mean Change From Baseline (mm Hg)							
SBP Q4 (>148.0 mm Hg)	Finerenone	−10.79	−11.76	−10.94	−11.28	−12.38	−13.69
	Placebo	−6.89	−6.44	−6.61	−9.63	−11.63	−10.20

Ruilope et al., *Hypertension*. 2022;79:2685–2695. DOI: 10.1161/ HYPERTENSIONAHA.122.19744



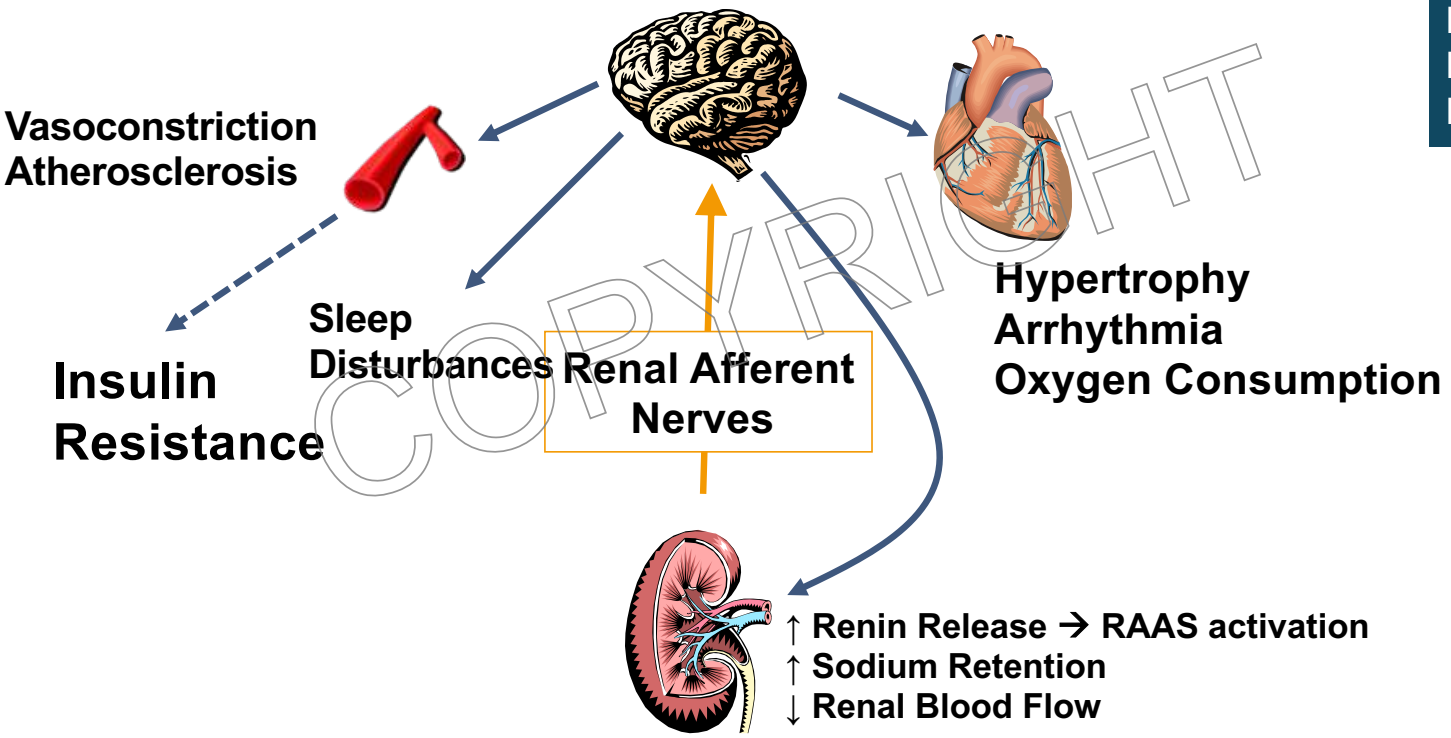
The downside of mineralocorticoid antagonists

- Impotence
- eGFR decline -2.38ml/min/m^2
- Hyperkalaemia
- Gynaecomastia

Agarwal et al., 2021 European Heart Journal 42; 152-161

Renal Denervation

Reasons to Denervate
Persistent RHT
Poor adherence
Patient preference
Deteriorating HMOD
Extensive side effects



Renal Sympathetic Afferent Nerves:
Kidney as Origin of Central Sympathetic Drive

Schmeider JH 2021 Jan 39(1), 162

Summary