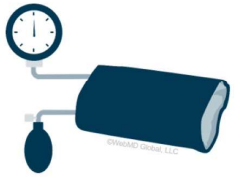
ARBs & ARBs in Single Pill Combination in Patients with CKD/ Dialysis

Prof Pham Van Bui
Univ. of Medicine Pham Ngoc Thach
Nguyen Tri Phuong Hospital
President, Society of the Nephrology-Dialysis Therapies
Invited Professor, Liege Univ. of Medicine, Belgium

High Blood Pressure and Future Risk

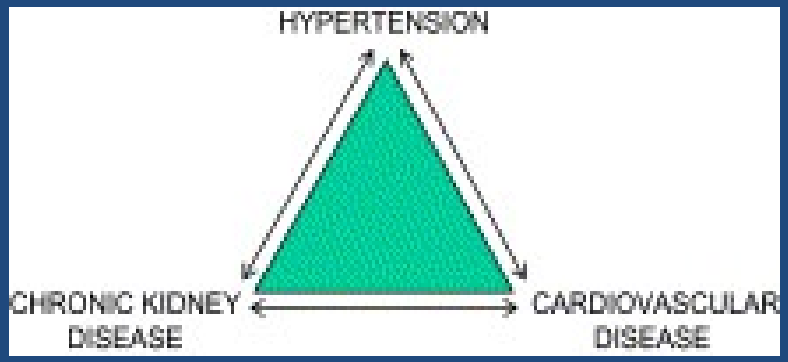


The **most important preventable cause of death globally in 2016** and is projected to remain so by 2040[a]

Contributed to **10.8 million CV deaths and 11.3 million deaths** in 2021[b]

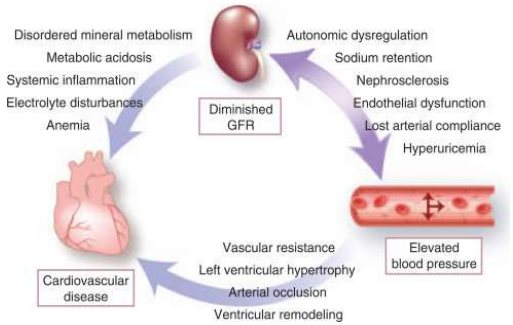
Associated with **>200 million disability life years per year** [c]

CV, cardiovascular.
a. Foreman KJ, et al. Lancet 2018;392:2052-2090; b. Vaduganathan M, et al. J Am Coll Cardiol. 2022;80:2361-2371; c. GBD 2015 Risk Factors Collaborators. Lancet. 2016;388:1659-1724.



Manuel T. Velasquez, Chapter 52 - Management of Hypertension in Chronic Kidney Disease, Editor(s): Paul L. Kimmel, Mark E. Rosenberg,Chronic Renal Disease, Academic Press, 2015,Pages 634-645, ISBN 9780124116023, https://doi.org/10.1016/B978-0-12-411602-3.00052-4.

Joint Contribution of CKD & Hypertension to Cardiac Risk.



John P Middleton et al(2010) KJ; VOLUME 77, ISSUE 9, P753-755, MAY 01, 2010)
DOI:https://doi.org/10.1038/ki.2010.19

Kidney & Primary Hypertension

Sir Richard Bright
(Guy`s Hospital Rep 1836;1:380):

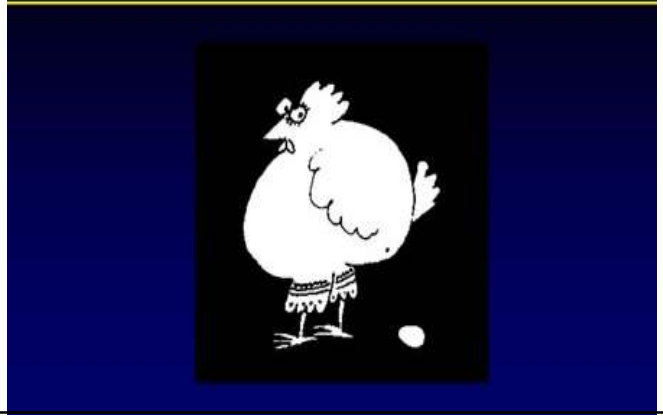
„...renal dysfunction is the primary cause of hypertension"

Kidney & Primary Hypertension

- Renal transplantation studies in rat strains suggest that hypertension "goes with the kidney".[1-3]
- Patients who received kidneys from a hypertensive donor tended to have higher blood pressures compared to patients with transplants from normotensive donors.[4]
- Individuals who had dialysis dependent renal failure as a result of hypertension despite no primary renal disease became normotensive when they received well functioning allografts from a normotensive donor.[5]

[1]Bianchi et al. Clin Scien Mol Med 1974;[2]Dahl et al.Circ Res 1974; [3]Rettig et al. Am J Phys 1990; [4]Strandgaard et al. Brit Med J 1986; [5]Curtis et al. N Engl J Med 1983

HYPERTENSION & KIDNEY



Hypertension Is a Major Risk Factor for CVD

Large cohort studies have demonstrated that high BP is an important risk factor for:

- HF
- Atrial fibrillation
- CKD
- Heart valve diseases
- Aortic syndromes
- Dementia
- Coronary heart disease
- Stroke

Munter P, et al. *JAMA*. 2020;324:1190-1200; Fuchs FD, Whelton PK. *Hypertension*. 2020;75:285-292.

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Munter P, et al. *JAMA*. 2020;324:1190-1200; Fuchs FD, Whelton PK. *Hypertension*. 2020;75:285-292.

Does nocturnal diastolic and systolic hypertension predict outcomes in CKD?

CJASN

Follow-up: 4.8 years for kidney and 5.0 years for CV events

Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE)

N=2024

24-hour ambulatory blood pressure

		CV Outcomes	Kidney Outcomes
Nocturnal **normotension** <120 / <70	N=540	Ref	Ref
Isolated nocturnal **diastolic** hypertension <120 / ≥70	N=390	HR 1.63 (0.82-3.26)	HR 1.29 (0.82-2.38)
Isolated nocturnal **systolic** hypertension ≥120 / <70	N=120	**HR 3.17** (1.61-6.23)	HR 1.29 (0.69-2.38)
Nocturnal **systolic-diastolic** hypertension ≥120 / ≥70	N=974	**HR 2.19** (1.24-3.86)	**HR 1.71** (1.17-2.49)

Conclusion: Nocturnal systolic hypertension, either alone or in combination with diastolic hypertension, is associated with higher risks for adverse outcomes in patients with CKD.

Qin Wang, Yu Wang, Jinwei Wang, et al. ***Nocturnal Systolic Hypertension and Adverse Prognosis in Patients with CKD***. CJASN doi: 10.2215/CJN.14420920. **Visual Abstract by Joel Topf, MD, FACP (2021)**

Is Ambulatory Blood Pressure monitoring valuable for risk stratifying patients with resistant hypertension and CKD?

Kidney360

1186 patients CKD

Apparent treatment resistant HTN (ATRH)

Definition: > 3 BP meds or

Office BP HTN or Ambulatory BP HTN

Composite outcome: Cardiovascular (CVS) disease, Kidney outcomes + mortality

475 Patients with ATRH by Office BP

92% ATRH confirmed by Ambulatory BP

Adjusted analyses

	ATRH	No ATRH
CVS disease	HR 1.27 (95%CI 0.59, 2.7)	Control
Kidney outcomes	HR 1.68 (95% CI 0.88, 3.21)	Control
Mortality	HR 1.27 (95% CI 0.5, 3.25)	Control

Conclusions: In this study of CKD patients, most patients with ATRH defined based on office BP had ATRH confirmed by ambulatory blood pressure monitoring. While ABPM defined apparent treatment resistant hypertension was not independently associated with clinical outcomes, it identified participants at risk for adverse clinical outcomes.

George Thomas, Jesse Felts, Carolyn S Brecklin, et al. ***Apparent Treatment Resistant Hypertension assessed by Office and Ambulatory Blood Pressure in Chronic Kidney Disease- A Report from the Chronic Renal Insufficiency Cohort Study.*** *Kidney360* doi: 10.34067/KID.0002072020. **Visual Abstract by Vicki Sandys, MBChB**

Pharmacological BP Lowering for CVD Prevention

Meta-analysis

Data for 344,716 participants from 48 randomized clinical trials

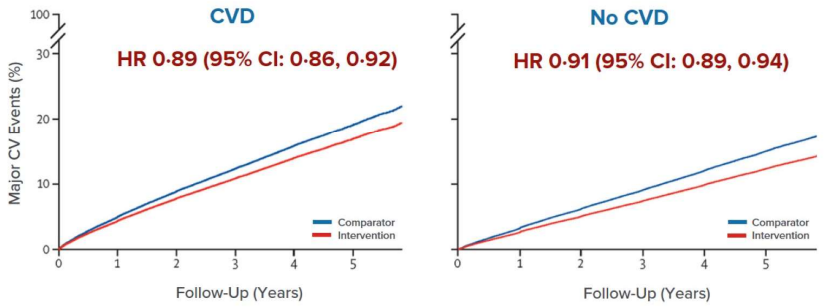
- Investigate the effects of BP-lowering treatment in participants with and without prevalent CVD across SBP categories (ranging from < 120 to ≥ 170 mm Hg)
- Pre-randomization mean SBP/DBP:
  - 146/84 mm Hg in patients with prior CVD (n = 157,728)
  - 157/89 mm Hg in patients without prior CVD (n = 186,988)

Primary outcome was a major CV event:

Composite of fatal and non-fatal stroke; fatal or non-fatal MI or ischemic heart disease; or HF causing death or requiring admission to hospital

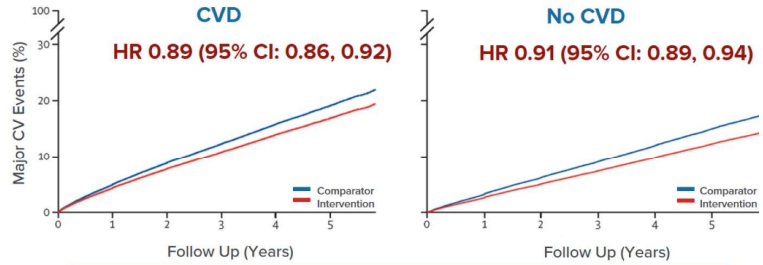
Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2021;397:1625-1636.

Rates of Major CV Events per 5 mm Hg Reduction in SBP



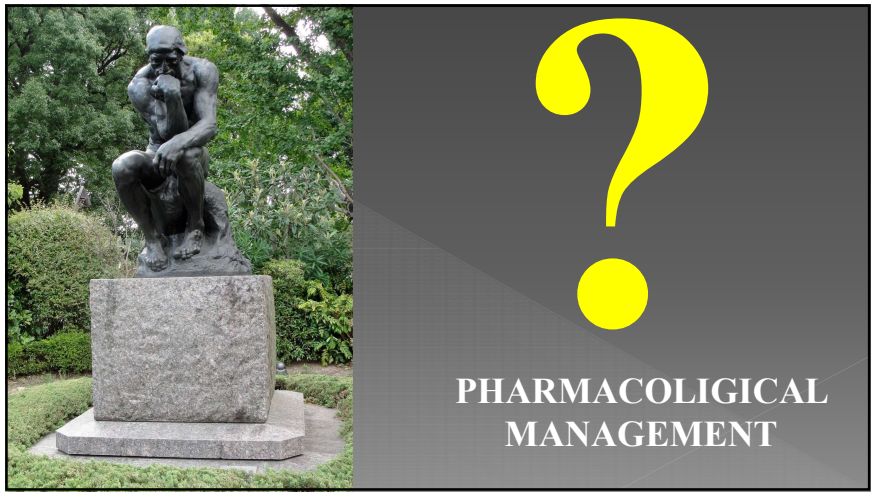
Rates of major CV events per 5 mm Hg reduction in SBP, stratified by treatment allocation and CVD status at baseline.
Major CV events were defined as a composition of fatal or nonfatal stroke, fatal or nonfatal MI or IHD, or HF causing death or requiring admission to hospital.
Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet.* 2021;397:1625-1636.

Rates of Major CV Events per 5-mm Hg Reduction in SBP

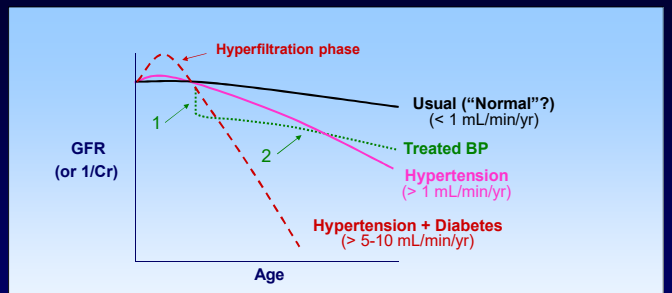


- **A 5-mm Hg reduction in OSBP equated to ~10% relative risk reduction in MACE**
  - ~13% relative risk reduction (RRR) for heart failure & stroke
  - 5% for cardiovascular death
- **Relative risk reductions were proportional to the intensity of blood pressure-lowering**
  - Baseline blood pressure and CV status did not significantly affect the outcome

MACE, major adverse cardiac event; OSBP, office systolic blood pressure.
Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2021;397:1625-1636.



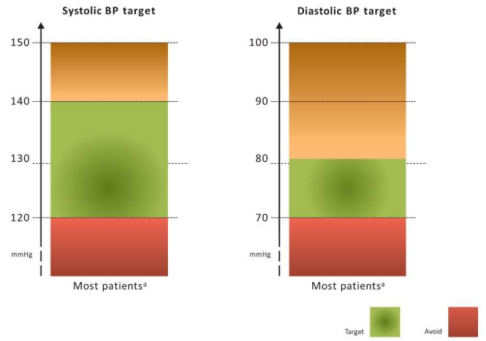
Loss of GFR with Aging and Disease



1- initial GFR drop due to acute BP decrease
2- chronic GFR stabilization with BP control

Modified from Ruilope LM and Izzo JL Jr *Hypertension Primer 4th Ed,* 2008. p261.

Office BP Targets in the General Adult Hypertensive Population
2023 ESH Guidelines

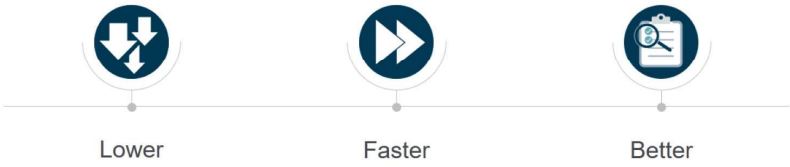


Lower BP Targets
<140/90mmHg
for all

Ideally
<130/80mmHg if
tolerated

BP, blood pressure; ESH, European Society of Hypertension.
Mancia G, et al. J Hypertens. 2023. doi: 10.1097/HJH.0000000000003480. [Epub ahead of print].

Blood Pressure Control Needs to Be …



Expert opinion.

CHAPTER
145

Best Practices in Hypertension-2017

PC Manoria, Pankaj Manoria, Piyush Manoria, SK Parashar

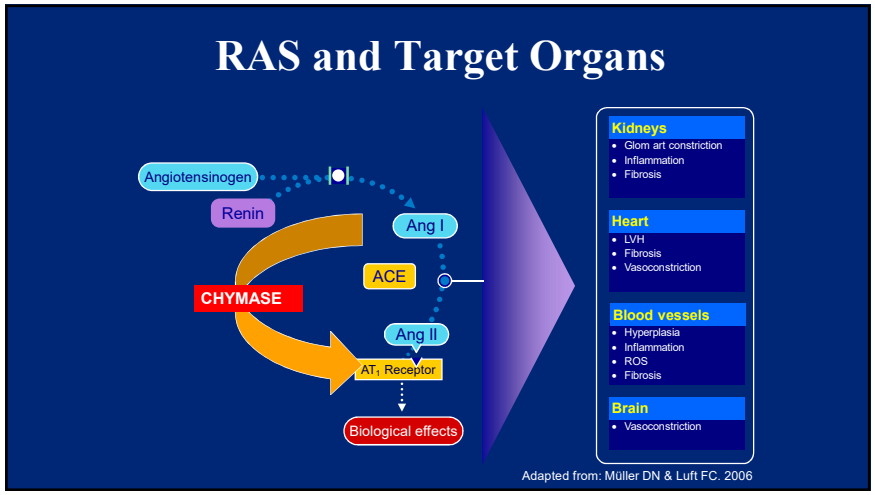
Different organs behave differently to decrease in BP:

- **Brain**: dicta:" lower is better" lower the BP, less is the incidence of stroke(ACCORD BP & INVEST)
- **Heart**:dBP< 70 - 80→↑ AMI incidence → J-shaped curved.
- **Kidney**: intraglomerular pressure(IGP) matters > BP in renal arteries:↑ IGP → proteinuria → adversely affect kidneys + CV syst → in renal hypertension, **drugs ↓ IGP like ACEI / ARBS / Cilnidipine preferred.**

Most Patients With Hypertension Will Require Drug Treatment

Most patients will require drug therapy in addition to lifestyle measures to achieve optimal BP control.

Williams B, et al. *Eur Heart J*. 2018;39:3021-3104.



- Ang II and salt are synergistic in their deleterious effects of renal autoregulation.

Saeed A et al.. *Am J Physiol Regul Integr Comp Physiol* 2010.
Inscho EW. *Hypertension* 2011
Anil K.et al. *Curr Opin Nephrol Hypertens*. 2013
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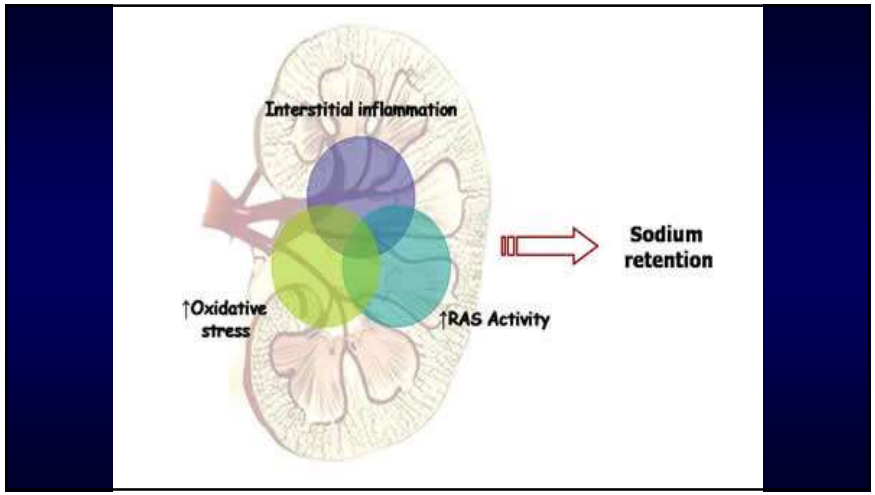

Recommendation 1.2.1. We **recommend** that **treatment with ACEi or ARB be initiated in patients with diabetes, hypertension, and albuminuria,** and that these medications **should be titrated to the highest approved dose** that is well tolerated ***(1B)*.**

- Practice Point 1.2.1. Consider **ACEi or ARB** treatment in patients with **diabetes and albuminuria, but have normal blood pressure.**
- Practice Point 1.2.2. **Monitor** for changes in **blood pressure, serum creatinine, and serum potassium within two to four weeks of initiation** or **increase in the dose** of an ACEi or ARB.
- Practice Point 1.2.3. **Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within four weeks** following initiation of treatment or an increase in dose.

KDIGO Clinical Practice Guideline on Diabetes Management in Chronic Kidney Disease 2020

How Do We Achieve Better BP Control?

Need to move to more common use of 2-drug combination therapy as initial treatment

- To improve BP-lowering efficacy for achieving BP goals
- To increase the speed to achieve BP goal
- To overcome therapeutic inertia
- To reduce variability in BP response

Slide courtesy of Williams B, MD, FRCP. Williams B, et al. Eur Heart J. 2018;39:3021-3104.

CV Risk According to Hypertension Grade/Stage
Claudette – Hypertension, T2D, and CKD

Hypertension Disease Staging	Other Risk Factors, HMOD, CVD or CKD	BP (mmHg) grading: High-Normal SBP 130 to 139 DBP 85 to 89	Grade 1 SBP 140 to 159 DBP 90 to 99	Grade 2 SBP 160 to 179 DBP 100 to 109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥ 4	Very high risk	Very high risk	Very high risk	Very high risk

	< 50 y	60-to 69 y	≥ 70 y	
	< 2.5%	< 5%	< 7.5%	Complementary risk estimation in Stage 1 with SCORE2/SCOR2-OP
	2.5 to < 7.5%	5 to < 10%	7.5 to < 15%	
	≥ 7.5%	≥ 10%	≥ 15%	

Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

Treatment Strategies in Patients With CKD
Blood Pressure Targets

2023 ESH Guidelines for the Management of Arterial Hypertension

	COR	LOE
BP should be monitored at all CKD stages **HTN is the most important risk factor for ESKD**	I	A
Immediate lifestyle interventions and drug treatment if office **BP ≥ 140/90** mm Hg	I	C
Primary goal **< 140/90** mm Hg	I	A
If tolerated **< 130/80** mm Hg	II	B
NOT < 120/70 mm Hg	III	C

COR, class of recommendation; ESKD, end-stage kidney disease; HTN, hypertension; LOE, level of evidence.
Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

Treatment Strategies in Patients With CKD
Drug Choices

2023 ESH Guidelines for the Management of Arterial Hypertension

	COR	LOE
ACE inhibitor *or* ARB at maximum-tolerated doses in moderate (UACR 30-300 mg/g) or severe albuminuria (>300 mg/g)	I	A

Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

Treatment Strategies in Patients With CKD
Drug Choices

2023 ESH Guidelines for the Management of Arterial Hypertension

	COR	LOE
ACE inhibitor *or* ARB at maximum-tolerated doses in moderate (UACR 30-300 mg/g) or severe albuminuria (>300 mg/g)	I	A
Resistant hypertension is very frequent Combination treatment **almost always recommended**	I	B

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Treatment Strategies in Patients With CKD
Drug Choices

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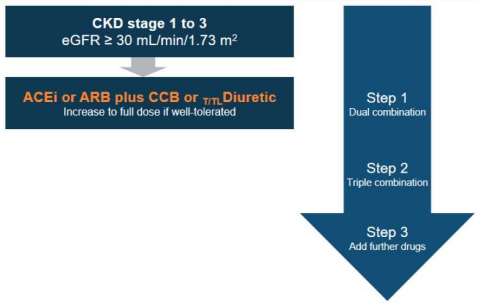
	COR	LOE
ACE inhibitor *or* ARB at maximum-tolerated doses in moderate (UACR 30-300 mg/g) or severe albuminuria (>300 mg/g)	I	A
Resistant hypertension is very frequent Combination treatment **almost always recommended**	I	B
SGLT2 inhibitors recommended for diabetic and nondiabetic CKD if eGFR ≥ 20 mL/min/1.73 m^2	I	A
Nonsteroidal MRA finerenone in T2D with albuminuria if eGFR ≥ 25 mL/min/1.73 m^2 and potassium < 5 mmol/L	I	A

MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter 2.
Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

BP-Lowering in Hypertension and CKD
ESH 2023 Guidelines

BP-Lowering in Patients With Hypertension and Chronic Kidney Disease



Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

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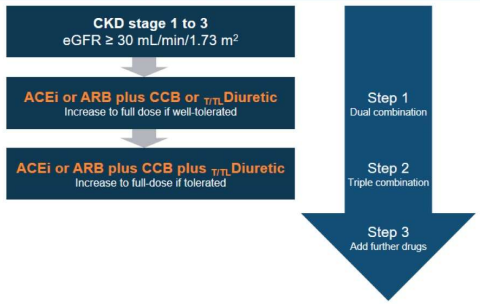

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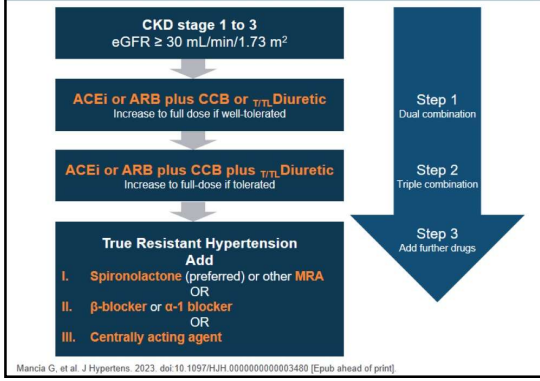

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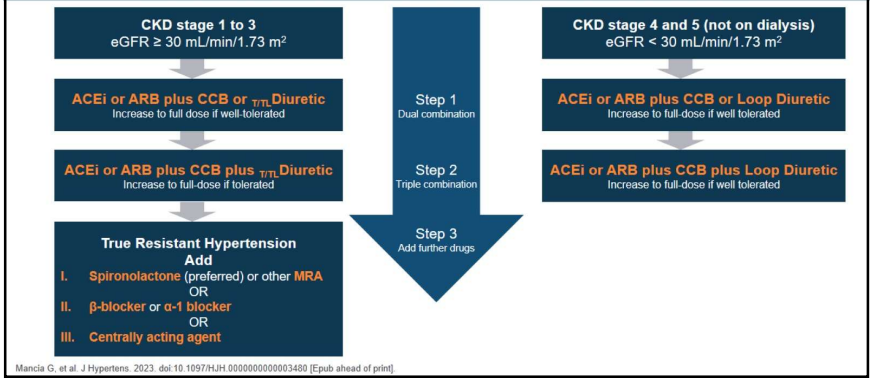

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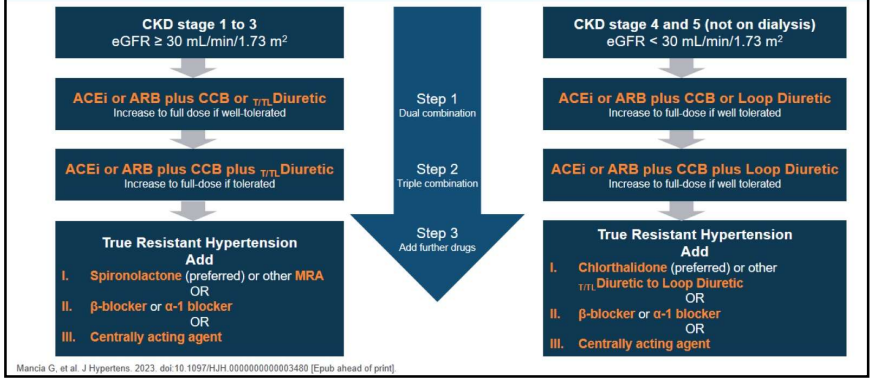

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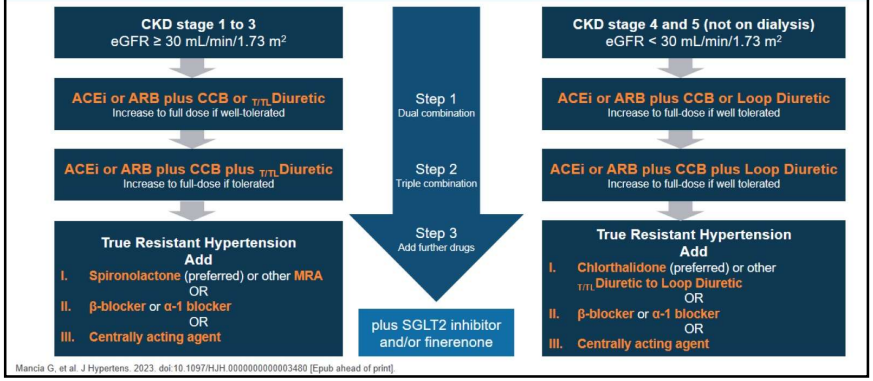
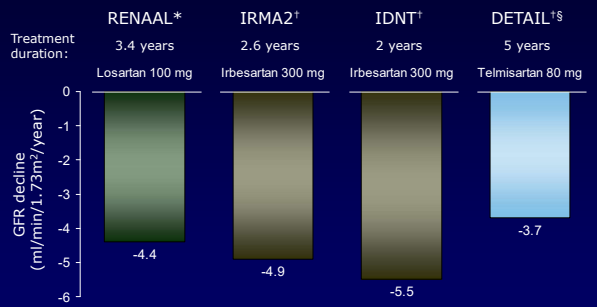


Mancia G, et al. J Hypertens. 2023. doi:10.1097/HJH.0000000000003480 [Epub ahead of print].

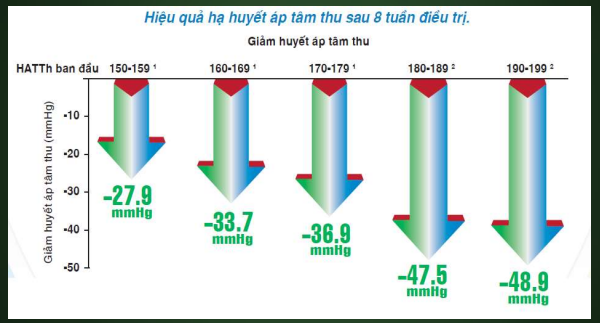
Lower Decline in GFR in patients teated by ARB



*Median; †Mean
§ Completers

Barnett A, et al.(2004). *N Engl J Med*
Barnett AH. (2005). *Acta Diabetol*

Telmisartan + Amlodipine effective at different stages of HTN



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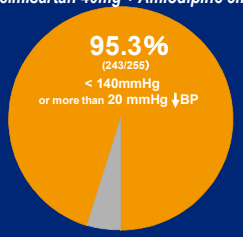
1. Littlejohn et al. J. Clin. Hyp. 2009 ; 11 : 207 - 213
2. Neutel et al. J. Clin. Hyp 2010 - in press - ASH 2010 Poster Presentation (LB-PO-10)

Combinations of Telmisartan with Other Antihypertensive Drugs Are Also Highly Effective in Reducing BP

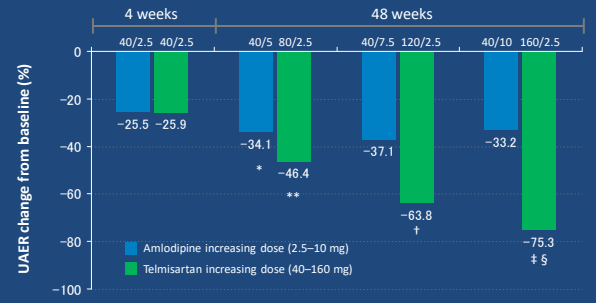
- Systolic BP Responder Rate -

Telmisartan 40mg + Amlodipine 5mg



Responder rate in 8 week long Japanese Phase III trial)

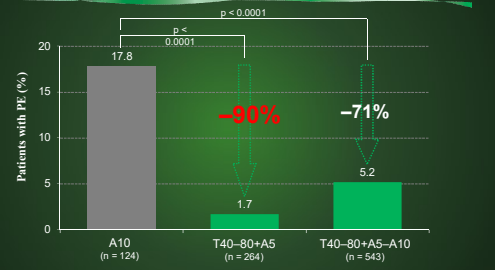
Telmisartan + Amlodipine: Reduction of Urinary Albumin Excretion



* p < 0.03; ** p < 0.01, change from baseline; † p < 0.01; ‡ p < 0.001, between treatment; § p < 0.05 vs 80/2.5
Hypertensive patients with type 2 diabetes (n = 300); microalbuminuria > 30 – < 300 mg/24 h

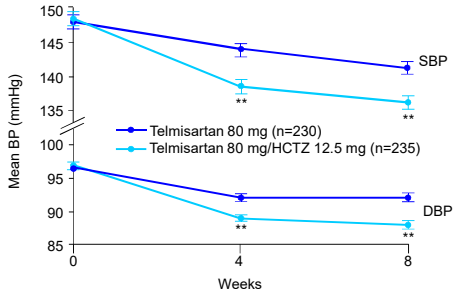
Fogari et al. *Am J Hypertens.* 2007;20:417–422.

Telmisartan + Amlodipine & Peripheral edema(PE)



Littlejohn et al. *J Clin Hypertens.* 2009;11:207–213.

Telmisartan+ HCTZ improves response
Further reductions in patients not controlled† by monotherapy

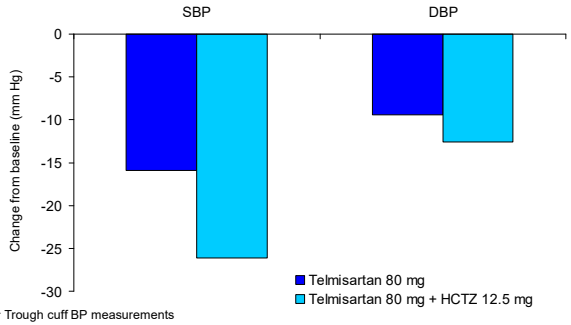


**P<0.01 versus continued telmisartan monotherapy
†DBP control (<90 mmHg after 8 weeks monotherapy)

Lacourcière et al. *J Hum Hypertens* 2001;15:763–770

Telmisartan+ HCTZ in diabetics

Additional antihypertensive power compared with monotherapy†



† Trough cuff BP measurements

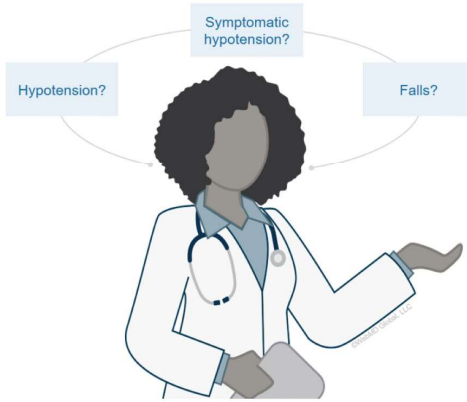
Fenton et al. *Drugs* 2003;63:2013–2026

Number of Antihypertensives and Adherence

Increased number of antihypertensive drugs prescribed associated with poor adherence

Chapman RH, et al. Drugs Aging. 2008;25:885-892; Gazmararian JA, et al. J Gen Intern Med. 2006;21:1215-1221; Ghembaza MA, et al. Curr Hypertens Rev. 2014;10:41-48; Holmes HM, et al. J Am Geriatr Soc. 2012;60:1298-1303.

Clinicians' Worries About Starting 2 or More Antihypertensive Medications at Once



Faculty opinion.

Clinicians' Worries About Starting 2 Antihypertensives at Once

- Initiating therapy with 2 drugs in a single pill does not lead to high frequency of hypotension, symptomatic hypotension, or falls
- Most patients tolerate the treatment very well and have better BP control

Faculty opinion.

Why SPCs?

Need to move to more common use of 2-drug combination therapy as initial treatment

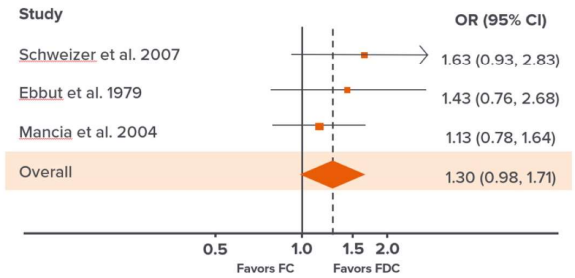
- To improve BP-lowering efficacy for achieving BP goals
- To increase the speed to achieve BP goal
- To overcome therapeutic inertia
- To reduce variability in BP response

Slide courtesy of Williams B, MD, FRCP. Williams B, et al. Eur Heart J. 2018;39:3021-3104.

Initial SPC Reduces CV Events in Hypertension *Meta-Analysis*

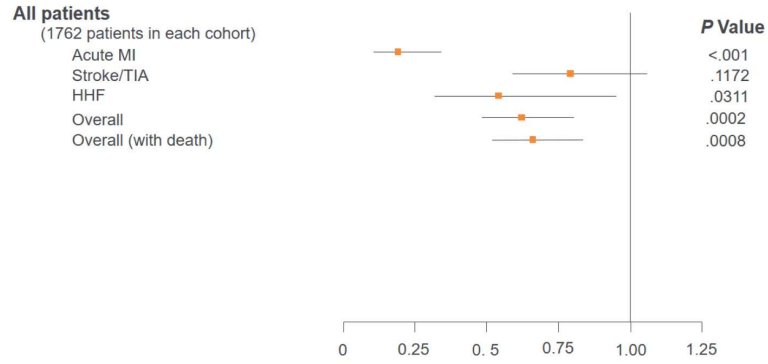
SBP and DBP Normalization Ratios

Three studies including 653 patients



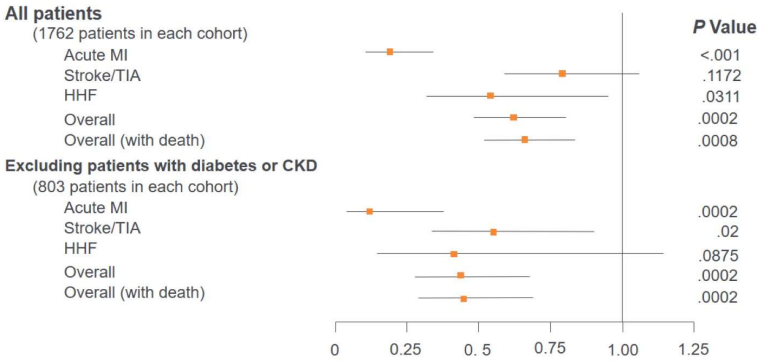
FC, free combination; FDC, fixed-dose combination.
Gupta AK, et al. Hypertension. 2010;55:399-407.

Initial SPC Reduces CV Events in Hypertension
Matched Cohorts in US Registry Data



TIA, transient ischemic attack.
Gradman AH, et al. Hypertension. 2013;61:309-318.

Initial SPC Reduces CV Events in Hypertension
Matched Cohorts in US Registry Data



TIA, transient ischemic attack.
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Initial SPC Reduces CV Events in Hypertension
Real World Data from Lombardy in Italy

Healthcare utilization database

- 44,534 residents of the region (aged 40-80 y) who started treatment with **1 antihypertensive** drug (n = 37,078) **or a 2-drug FDC** (n = 7456) in 2010
- Followed for 1 year after treatment initiation to compare the **risk for hospitalization for CVD** associated with the 2 treatment strategies

FDC, fixed dose combination.
Rea F, et al. Eur Heart J. 2018;39:3654-3661.

Initial SPC Reduces CV Events in Hypertension
Real World Data

Effect of Starting Antihypertensive Treatment With FDCs vs Monotherapy on the 1-y Risk for CV Outcomes

Outcome	HR (95% CI)	*P* Value
Any CV event	0.85 (0.74, 0.97)	.02
Ischemic heart disease	0.73 (0.56, 0.95)	.02
Cerebrovascular disease	0.83 (0.61, 1.14)	.26
Heart failure	0.9 (0.54, 1.51)	.69
Atrial fibrillation	0.63 (0.42, 0.94)	.02

Database of the Lombardy Region (Italy)

- 44,534 residents
- Started on monotherapy (n = 37,078) or an FDC (n = 7456)
- Evaluation of the risk for CV events
- FDCs were associated with more effective CV protection

Rea F, et al. Eur Heart J. 2018;39:3654-3661.

CONCLUSIONS

Single Pill Combination vs Free Equivalent Combination
The Evidence

- Better adherence
- Better persistence with therapy
- Better BP control
- Better target achievement
- Patients' preference

Expert opinion.

Combination Approach Simplifies Treatment Decisions

- Combination approach combining a RAS blocker with a CCB or a diuretic, for most patients, makes it much simpler to follow the guidelines
- Clear, simple algorithms in the latest guidelines
- Start with a single pill in most patients
  - Monotherapy for just a few patients

Faculty opinion.

Summary

Need to move to more common use of 2-drug combination therapy as initial treatment

- To improve BP-lowering efficacy for achieving BP goals
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Slide courtesy of Williams B, MD, FRCP. Williams B, et al. Eur Heart J. 2018;39:3021-3104.


Thank you for
your attention