Hypertension in Special Populations

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Disclosure

Consultant: Eli Lilly; Medtronic; Novo Nordisk; ReCor; UpToDate (Hypertension Section)

Research Grant: Ablative Solutions; ReCor

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LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to treat:

- **The Pregnant Patient with Hypertension**
- **The Patient with Chronic Kidney Disease and Hypertension**
- **The Older Patient with Hypertension**

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The Pregnant Patient with Hypertension

"Hypertensive disorders in pregnancy (HDP), remain the leading cause of adverse maternal, fetal, and neonatal outcomes. Epidemiological factors, comorbidities, assisted reproduction techniques, placental disorders, and genetic predisposition determine the burden of the disease."

Management of hypertensive disorders in pregnancy: a Position Statement of the European Society of Hypertension Working Group 'Hypertension in Women'

Thomopoulos, Costas; Hitij, Jana Brguljan; De Backer, Tine; Gkaliagkousi, Eugenia; Kreutz, Reinhold; Lopez-Sublet, Marilucy; Marketou, Maria; Mihailidou, Anastasia S.; Olszanecka, Agnieszka; Pechère-Bertschi, Antoinette; Pérez, Mariana Paula; Persu, Alexandre; Piani, Federica; Socrates, Thenral; Stolarz-Skrzypek, Katarzyna; Cífková, Renata Less

Journal of Hypertension. 42(7):1109-1132, July 2024.

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6 Hypertensive Disorders of Pregnancy: A Spectrum of Peri-partum Conditions That Include:

- **Chronic Hypertension-hypertension that either starts before pregnancy, before 20 weeks gestation, or persists longer than 6-12 weeks postpartum.**
- **Gestational hypertension-first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage and resolves within 12 weeks of delivery.**
- **Pre-eclampsia without severe features-new onset hypertension with proteinuria (> 300 mg protein/ 24 hours) w/o severe features after 20 weeks gestation.**
- **Pre-eclampsia with severe features (HEELP)-In addition to hypertension, there must be either Headache-not responsive to Tylenol, Elevated LFTs [2x nl] or Elevated creatinine or proteinuria, Epigastric pain-unexplained, pulmonary Edema, or Low Platelets (thrombocytopenia < 100,000).**
- **Superimposed pre-eclampsia on chronic hypertension**
- **Eclampsia-presence of seizures in a patient with pre-eclampsia.**

Powe CE, et al. *Circ* 2011; 123:2856-2869.

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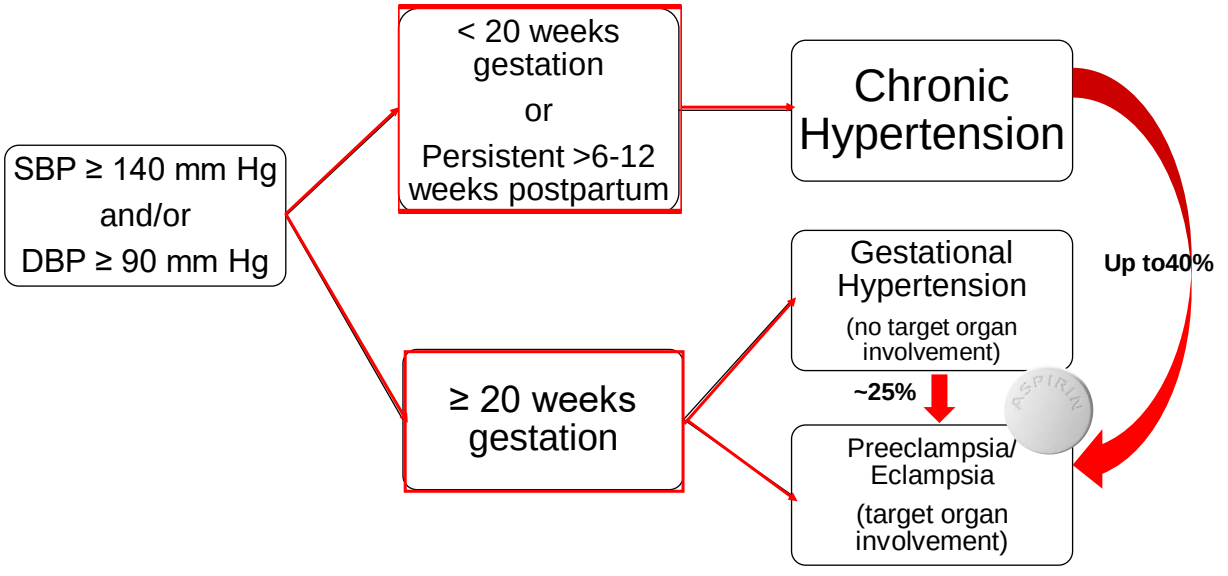
Hypertensive Conditions in Pregnancy



ACOG Practice Bulletin Nos. 202 and 203. Jan 2019; USPSTF. October 2014

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Question?

Which Antihypertensive Agents Should and Should Not be Used to Treat Hypertension During Pregnancy?

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Pregnancy

COR	LOE	Recommendations for Treatment of Hypertension in Pregnancy
I	C-LD	Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy.
III: Harm	C-LD	Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.

Adapted from 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

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Oral Antihypertensive Therapy

Labetalol 100-200mg BID, increase Q2-3d; max 2400 mg/24h
Nifedipine ER 30-60mg QD, increase Q7-14d; max 120 mg/24h
Methyldopa 250 mg BID-TID, increase Q2d; max 3000 mg/24h

Hydralazine* 10mg QID, increase Q2-5d; max 200 mg/24h

Thiazide diuretics-Hctz 12.5-50 mg daily, second or 3rd line agent

CONTRAINDICATED: ACEI/ARB, Renin Inhibitors, MRAs

**Hydralazine should not be used in isolation due to reflex tachycardia*

ACOG Practice Bulletin Nos. 202 and 203. Obstet Gynecol. 133 (1): e26-e50. January 2019

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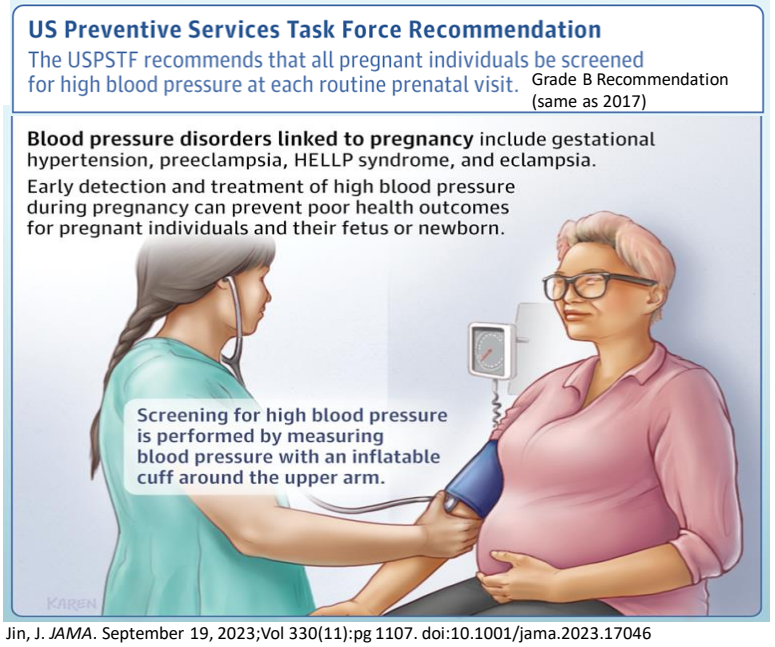
Screening for Hypertensive Disorders of Pregnancy:



GRADE B
Moderate certainty that the net benefit is moderate to substantial.

Jin, J. *JAMA*. September 19, 2023;Vol 330(11):pg 1107. doi:10.1001/jama.2023.17046
Bello, N.A. et al. Accuracy of BP Measurement Devices in Pregnancy. Hypertension. 2018;71:326-335.

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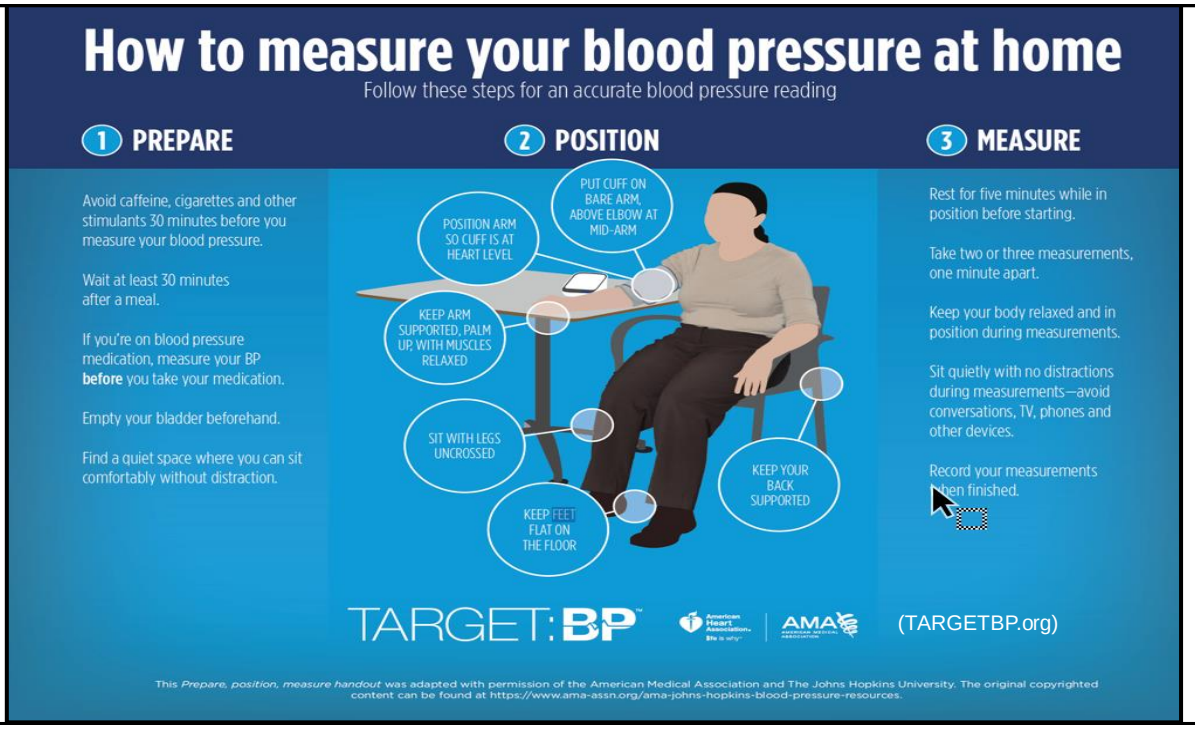

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Risk Factors That Increase the Risk of a Pregnancy Being Complicated by Preeclampsia

Risk factor	Mean RR (95% CI)
Antiphospholipid syndrome	9.72 (4.34–21.75)
Previous preeclampsia	7.19 (5.85–8.83)
Insulin-dependent diabetes	3.56 (2.54–4.99)
Multiple pregnancy	2.93 (2.04–4.21)
Nulliparity	2.91 (1.28–6.61)
Family history of preeclampsia	2.90 (1.70–4.93)
Obesity	2.47 (1.66–3.67)
Age >40 years	1.96 (1.34–2.87)
Preexisting hypertension	1.38 (1.01–1.87)

Abbreviations: CI, confidence interval; RR, relative risk.

English, F.A. et al. *Integr. Blood Pressure Control* 2015; 8: 7–12.

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Question?

Which BP Target Should You Aim For While Treating Hypertension During Pregnancy?

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ACOG Treatment Initiation & BP Goals Up to 2021

	Severe Chronic HTN*	Gestational HTN	Preeclampsia
Start	SBP ≥ 160 mm Hg DBP ≥ 105 mm Hg	SBP ≥ 160 mm Hg DBP ≥ 110 mm Hg	
Target?	SBP 120-160 mm Hg DBP 80-110 mm Hg	NO DATA	

* In the setting of co-morbidities or renal dysfunction, treating to a lower threshold may be appropriate

- **Weight loss and extremely low sodium diets (<100 mEq/day) are not recommended for BP management in pregnancy**
- **Moderate exercise can be continued**

ACOG Practice Bulletin Nos. 202 and 203. Obstet Gynecol, 133 (1): e26-e50, January 2019

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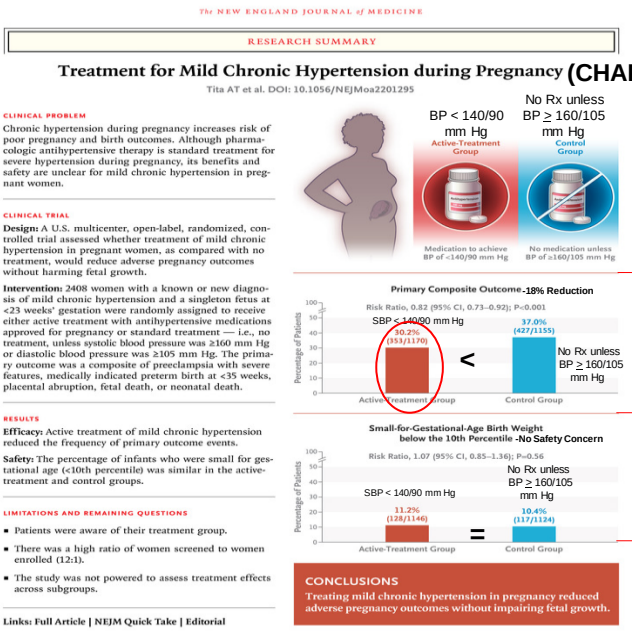

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Treatment for Mild Chronic Hypertension during Pregnancy (CHAP)

Tita AT et al. DOI: 10.1056/NEJMoa2201295

CLINICAL PROBLEM

Chronic hypertension during pregnancy increases risk of poor pregnancy and birth outcomes. Although pharmacologic antihypertensive therapy is standard treatment for severe hypertension during pregnancy, its benefits and safety are unclear for mild chronic hypertension in pregnant women.

CLINICAL TRIAL

Design: A U.S. multicenter, open-label, randomized, controlled trial assessed whether treatment of mild chronic hypertension in pregnant women, as compared with no treatment, would reduce adverse pregnancy outcomes without harming fetal growth.

Intervention: 2408 women with a known or new diagnosis of mild chronic hypertension and a singleton fetus at <23 weeks' gestation were randomly assigned to receive either active treatment with antihypertensive medications approved for pregnancy or standard treatment — i.e., no treatment, unless systolic blood pressure was ≥160 mm Hg or diastolic blood pressure was ≥105 mm Hg. The primary outcome was a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks, placental abruption, fetal death, or neonatal death.

RESULTS

Efficacy: Active treatment of mild chronic hypertension reduced the frequency of primary outcome events.

Safety: The percentage of infants who were small for gestational age (<10th percentile) was similar in the active-treatment and control groups.

LIMITATIONS AND REMAINING QUESTIONS

- Patients were aware of their treatment group.
- There was a high ratio of women screened to women enrolled (12:1).
- The study was not powered to assess treatment effects across subgroups.

Links: Full Article | NEJM Quick Take | Editorial

N=2408 pregnant women with known or new dx of mild chronic htn and singleton fetus , < 23 weeks gestation

Primary Composite outcome: Pre-eclampsia, Preterm birth at < 35 weeks gestation, Placental abruption, and Fetal or Neonatal death at < 28 days. [RR 0.82 (0.74-0.92) p<0.001]

Safety outcome: Small for Gestational Age [RR 1.07 (0.85-1.36) p=0.56]]

Treating mild chronic hypertension to < 140/90 reduced adverse pregnancy outcomes w/o impairing fetal growth

Tita, A et al. CHAP Trial. *N Engl J Med* May 12, 2022; 386:1781-1792

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Society of Maternal-Fetal Medicine (SMFM) Statement 2022 Antihypertensive Therapy for Mild Chronic Hypertension in Pregnancy

Key Recommendations-Rx Goals <u>in Pregnancy</u>:

- In conclusion, the CHAP trial provides evidence that treating mild chronic hypertension in pregnancy reduces the risk for maternal and peri-natal morbidity without increasing the risk for SGA infants or other neonatal morbidities compared with no treatment unless hypertension becomes severe.

- **Based on the available evidence, SMFM recommends treatment of mild chronic hypertension in pregnancy with antihypertensive therapy to a goal BP of < 140/90 mm Hg.**

Society of Maternal-Fetal Medicine Publication Committee. *August 2022.*

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Question?

Should Aspirin be Used for Prophylaxis in All Pregnant Patients to Prevent Pre-Eclampsia?

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When to Use Aspirin in Pregnancy: Clinical Risk Assessment for Pre-Eclampsia ACOG Task Force Final Recommendation Statement

Risk Level	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

§Moderate-risk factors vary in their association with increased risk of preeclampsia.

Modified from LeFevre, ML. U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014;161:819–26.

Table 1. ACOG Committee Opinion. 2018 (Reaffirmed 2023); No 743 Vol 132: e44-e52.

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When to Use Aspirin in Pregnancy: ACOG Task Force Final Recommendation Statement

Low-Dose Aspirin Use During Pregnancy

ABSTRACT: Low-dose aspirin has been used during pregnancy, most commonly to prevent or delay the onset of preeclampsia. The American College of Obstetricians and Gynecologists issued the *Hypertension in Pregnancy Task Force Report* recommending daily low-dose aspirin beginning in the late first trimester for women with a history of early-onset preeclampsia and preterm delivery at less than 34 0/7 weeks of gestation, or for women with more than one prior pregnancy complicated by preeclampsia. The U.S. Preventive Services Task Force published a similar guideline, although the list of indications for low-dose aspirin use was more expansive. Daily low-dose aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal, or fetal complications, or both, related to use. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the U.S. Preventive Services Task Force guideline criteria for prevention of preeclampsia. Low-dose aspirin (81 mg/day) prophylaxis is recommended in women at high risk of preeclampsia and should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery. Low-dose aspirin prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia. Women at risk of preeclampsia are defined based on the presence of one or more high-risk factors (history of preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than one of several moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index greater than 30, family history of pre-eclampsia, sociodemographic characteristics, and personal history factors). In the absence of high risk factors for preeclampsia, current evidence does not support the use of prophylactic low-dose aspirin for the prevention of early pregnancy loss, fetal growth restriction, stillbirth, or preterm birth.

ACOG Committee Opinion. 2018 (Reaffirmed 2023); No 743 Vol 132: e44-e52.

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Adverse Pregnancy Outcomes Lead to Future Cardiometabolic Disorders and Increased Long-Term Mortality in Women

Adjusted Hazard Ratios (HRs) for All-Cause Mortality Associated With Adverse Pregnancy Outcomes by Time Since Delivery

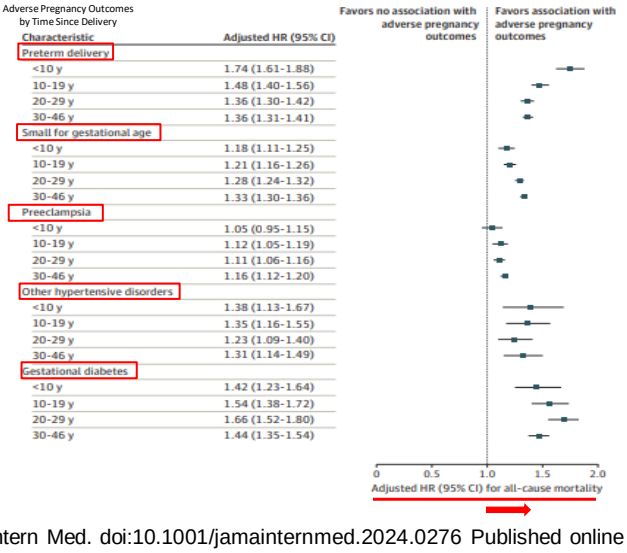

Fig 1. Crump C. et al. JAMA Intern Med. doi:10.1001/jamainternmed.2024.0276 Published online April 15, 2024.

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Summary on Hypertension in Pregnancy

1. **Pre-eclampsia complicates 2 to 4% of all pregnancies and accounts for about 46,000 maternal deaths and 500,000 fetal or newborn deaths each year.**
2. **Risk of Pre-eclampsia can be reduced:**
   - **in low-calcium intake populations by suggesting 500 mg/day of supplemental calcium in the second half of pregnancy.**
   - **in woman at high risk for preeclampsia by offering aspirin (≥ 81 mg/day) before 16 weeks gestation.**
   - **in low-risk nulliparous women by inducing labor during the 39th week gestation.**
3. **Oral labetalol, nifedipine, or methyldopa is usually recommended for BP control.**
4. **The recently published Chronic Hypertension and Pregnancy (CHAP) trial (involving 2408 women) showed that blood pressure control (to <140/90 mm Hg and most commonly with oral labetalol) was associated with a reduction in a composite adverse outcome (of preeclampsia with severe features, medically indicated pre-term birth at < 35 weeks' gestation, placental abruption, or fetal or neonatal death), with no significant increase in babies with birth weight below the 10th percentile for gestational age, (ie; < 140/90 mm Hg was effective and safe).**
5. **Antihypertensive agents and magnesium sulfate can help control the systemic manifestations of pre-eclampsia, which is usually resolved by delivery of the placenta.**

Magee L. et al. N Engl J Med 2022;386:1817-1832, May 12, 2022.

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The Patient with CKD and Hypertension

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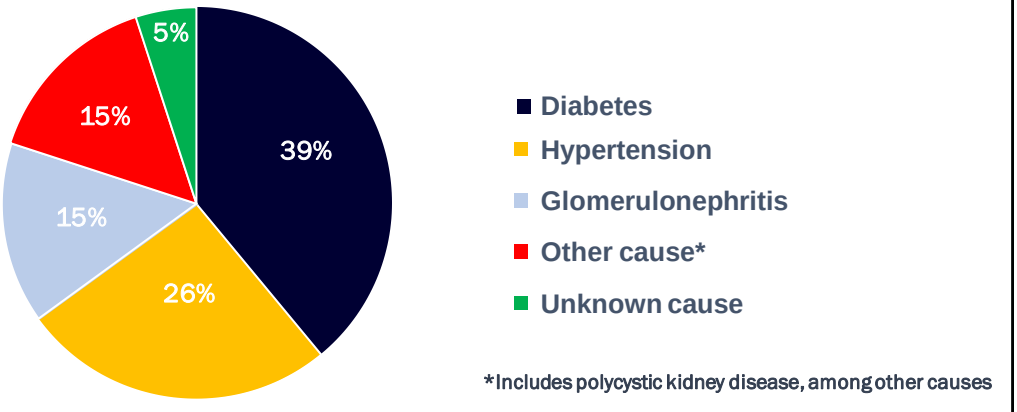
MOST COMMON CAUSES OF CKD IN THE US

N=785,883 (All Ages, 2018)



*Includes polycystic kidney disease, among other causes

CDC. Accessed 10/10/22. https://www.cdc.gov/kidneydisease/publications-resources/annual-report/ckd-risk-prevention.html

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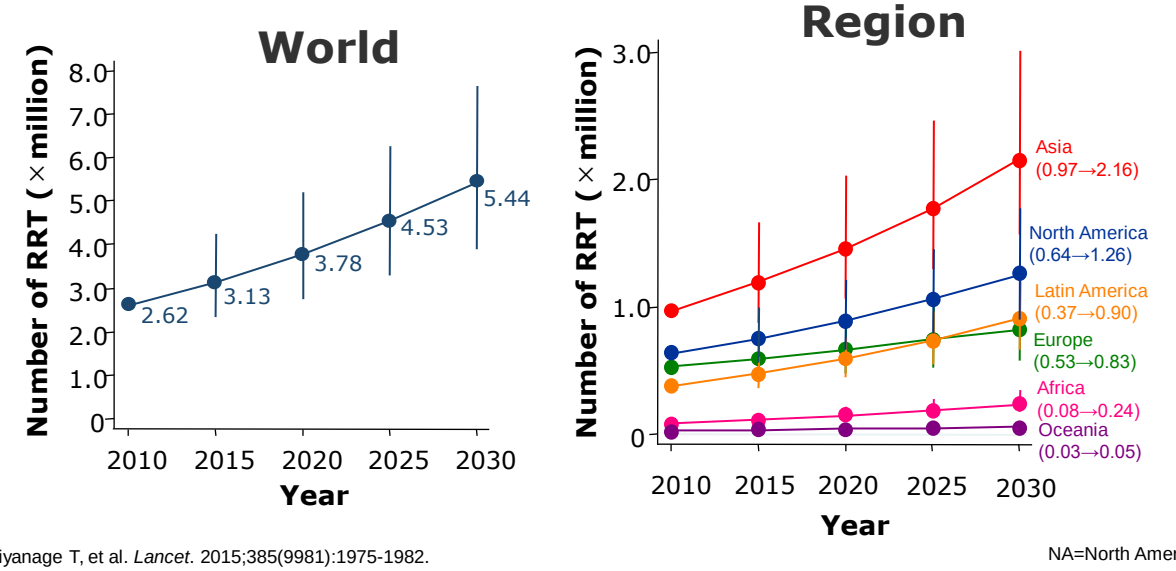
Number of People Receiving Renal Replacement Therapy Is Projected to Double in the World and NA



Liyanage T, et al. *Lancet*. 2015;385(9981):1975-1982.

NA=North America

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Definition of CKD

- CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, with implications for health
  - Abnormalities include:
    - Kidney Damage (albuminuria, urine sediment abnormalities (RBC's, WBC,s, casts), electrolyte or other abnormalities due to tubular disorders, abnormalities detected by histology (biopsy), structural abnormalities (detected by imaging-ultrasound, CT), history of transplant)
    - Decreased GFR (<60 ml/min/1.73m2)

Kidney International Supplements (2013) **3,** 4; doi:10.1038/kisup.2012.76

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Screening and Diagnosis: KDIGO 2022

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

de Boer Ih et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027. doi: 10.2337/dci22-0027. Epub ahead of print. PMID: 36189689.

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CKD: Importance of Proteinuria

Independent of eGFR, proteinuria is associated with :

- Increased all cause mortality
- Increased CV events and CV mortality
- Progression of CKD
- ESRD

Hemmelgarn, *JAMA*, 2010

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Monitoring Disease Progression in Chronic Kidney Disease: Synopsis of the 2020 KDIGO Clinical Practice Guideline

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Increasing CV & CKD Risk

Numbers indicate guide to the frequency of monitoring (# of times per year)

Increasing CV and CKD Risk

- Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression

Navaneethan SD et al. Synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med* 2020 Nov 10; [e-pub]. (https://doi.org/1o.7326/M20-5938)

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When to Refer to a Nephrologist

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			REFER
	G2	Mildly decreased	60–89			REFER
	G3a	Mildly to moderately decreased	45–59			REFER
	G3b	Moderately to severely decreased	30–44		REFER	REFER
	G4	Severely decreased	15–29	REFER	REFER	REFER
	G5	Kidney failure	<15	REFER	REFER	REFER

KDIGO Diabetes Guidelines-Kidney Int Suppl 2023

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Drugs Used to Treat Hypertension (<130/80) in CKD

- ACEi or ARB

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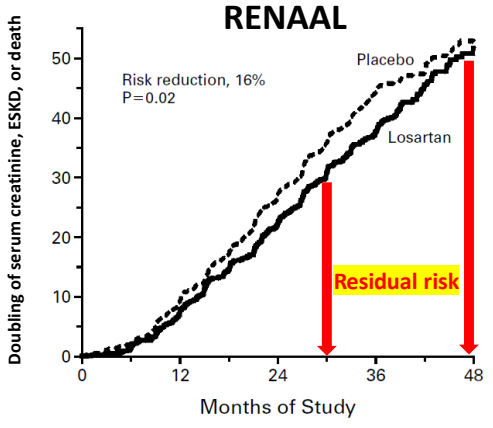
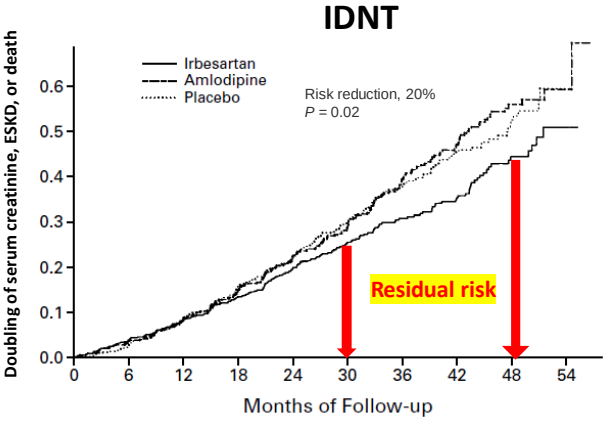
Angiotensin Receptor Blockade in Type 2 Diabetes and CKD with Heavy Proteinuria



2.5 and 4-year absolute residual risks:
~30% and ~45%

Brenner B *et al. N Engl J Med* **2001**;345:861–869



2.5 and 4-year absolute residual risks:
~25% and ~40%

Lewis EJ *et al. N Eng J Med*. **2001**;345:851-860

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Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Fan Fan Hou, M.D., Ph.D., Xun Zhang, M.D., Guo Hua Zhang, M.D., Ph.D., Di Xie, M.D., Ping Yan Chen, M.D., Wei Ru Zhang, M.D., Ph.D., Jian Ping Jiang, M.D., Min Liang, M.D., Ph.D., Guo Bao Wang, M.D., Zheng Rong Liu, M.D. and Ren Wen Geng, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med Volume 354;2:131-140 January 12, 2006

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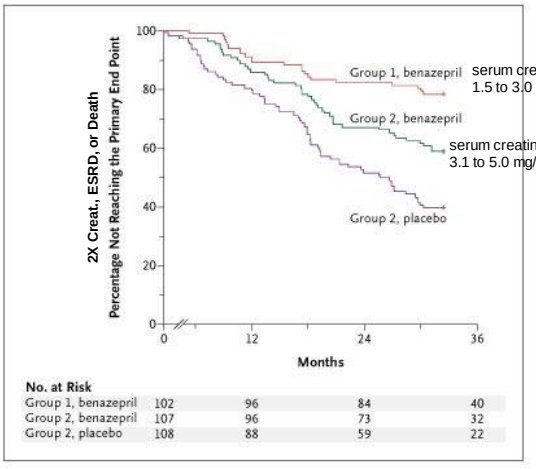
Kaplan-Meier Estimates of the Percentage of Patients Not Reaching the Primary Composite End Point of a Doubling of the Serum Creatinine Level, ESRD, or Death



Hou, F. et al. N Engl J Med 2006;354:131-140

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Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Study Conclusions

- Angiotensin-converting-enzyme (ACE) inhibitors provide renal protection in patients with mild-to-moderate renal insufficiency, slowing progression.
- The results of this randomized, double-blind study indicate that benazepril, an ACE inhibitor, confers substantial renal benefits in patients without diabetes who have advanced renal insufficiency.

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Drugs Used to Treat Hypertension (<130/80) in CKD

- ACEi or ARB
- Thiazide Diuretics (Chlorthalidone pref down to eGFR mean 23)

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Why Add Chlorthalidone?

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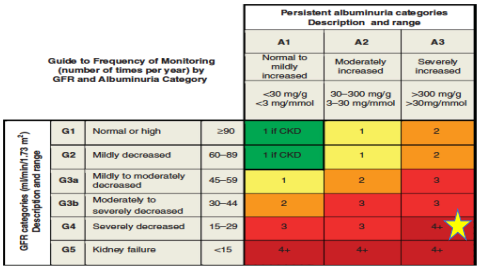
CLICK Trial:
ChLorthalidone for Hypertension In Advanced Chronic Kidney Disease

- **160 Hypertensive Pts**
- **Median Age 66**
- **Female 22%**
- **Stage 4 CKD**
- **eGFR 23 cc/min**
- **Alb/Cr=840 mg/g Cr**
- **DM +HTN=85%**
- **Mean BP 140/68 mm Hg**
- **All on RAS blocker**
- **Mean # of antihypertensives 3.4**
- **Chlorthalidone 12.5 mg every 4 weeks to 50 mg at 12 weeks vs placebo**
- **Average dose of chlorthalidone was 25 mg at 12 weeks**
- **60% on loop diuretics**
- **More hypokalemia, hyperuricemia, and hyperglycemia on chlorthalidone**



Agarwal R, et al. *N Engl J Med 2021;* DOI:10.1056/NEJMoa2110730. Nov 5, 2021

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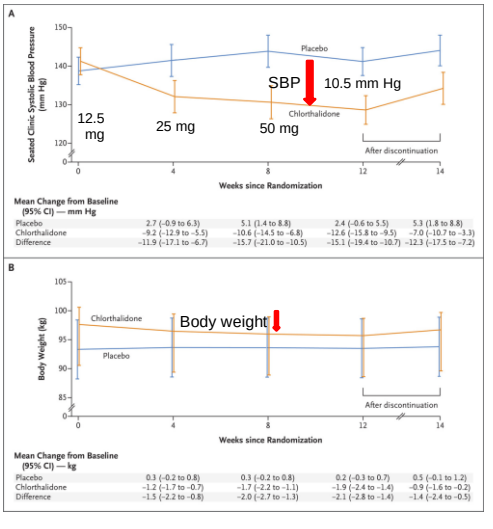
Systolic Blood Pressure (A) and Body Weight (B) in the Trial Groups in CLICK.



R Agarwal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2110730

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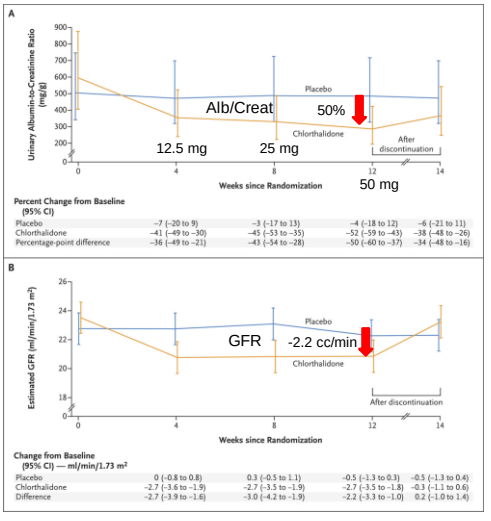
Changes in Urinary Albumin-to-Creatinine Ratio and Estimated GFR in the Trial Groups over the Trial Period in CLICK.



R Agarwal et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2110730

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Adverse Events but Not Serious Adverse Events Occurred During the Treatment Period

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Table 3. Adverse Events and Serious Adverse Events That Occurred during the Treatment Period.

Event	Chlorthalidone (N=81)		Placebo (N=79)	
	no. of patients with event (%)	no. of events	no. of patients with event (%)	no. of events
Adverse events				
Total	74 (91)	330	68 (86)	219
Infection	6 (7)	6	10 (13)	10
Cardiovascular event	2 (2)	2	3 (4)	3
Other	42 (52)	57	39 (49)	64
Event of interest	69 (85)	265	56 (71)	142
Hypokalemia	8 (10)	10	0	0
Hypomagnesemia	19 (23)	35	13 (16)	26
Hyponatremia	9 (11)	12	6 (8)	6
Hypocalcemia	1 (1)	1	1 (1)	3
Hypercalcemia	2 (2)	3	2 (3)	3
Hyperglycemia	13 (16)	18	4 (5)	5
Hyperuricemia	16 (20)	32	7 (9)	9
Hyperkalemia	5 (6)	5	7 (9)	8
Hypernatremia	0	0	1 (1)	1
Acute gout	2 (2)	2	3 (4)	3
Syncope	2 (2)	2	1 (1)	1
Orthostatic hypotension*	8 (10)	12	5 (6)	8
Dizziness†	20 (25)	33	13 (16)	24
Asymptomatic orthostatic hypotension‡	21 (26)	39	18 (23)	33
Acute kidney injury	33 (41)	61	10 (13)	12
Serious adverse events§				
Infection	2 (2)	3	1 (1)	1
Cardiovascular event	3 (4)	3	5 (6)	7
Renal event	1 (1)	1	1 (1)	1
Event of interest	3 (4)	4	0	0
Other	3 (4)	3	5 (6)	6
Total	8 (10)	14	11 (14)	15

* Orthostatic hypotension was defined as a decrease in the standing systolic blood pressure greater than 20 mm Hg, accompanied by a feeling of dizziness or light-headedness.
† Dizziness was recorded when the patient felt dizzy when standing from a seated position but did not have a decrease in the systolic blood pressure greater than 20 mm Hg.
‡ Asymptomatic orthostatic hypotension was defined as a decrease in the standing systolic blood pressure greater than 20 mm Hg that was not accompanied by a feeling of dizziness or light-headedness.
§ Some patients had multiple serious adverse events. The four events of interest that occurred among the three patients in the chlorthalidone group were orthostatic hypotension, acute kidney injury, hyperglycemia, and hypokalemia.

R Agarwal et al. *N Engl J Med Dec 30* 2021; 385:2507-2519

40

Drugs Used to Treat Hypertension (<130/80) in CKD

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- Thiazide Diuretics (Chlorthalidone pref down to eGFR mean 23)
- Loop Diuretics (only when necessary for continued volume overload, edema, or very low eGFR cc/min/1.73m)

41

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- SGLT2 inhibitors (Diabetic or Non-Diabetic, eGFR > 20 cc/min, any degree of albuminuria)-some BP reduction

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SGLT2i Effect on Kidney Outcomes

***EMPA-KIDNEY population
eGFR≥ 20 to < 45 ml/min/1.73 m²
eGFR≥ 45 to < 90 ml/min/1.73 m²
and UACR≥ 200 mg/g
Average eGFR 38cc/min/1.73/m²

**DAPA-CKD population
eGFR >25 to< 75 ml/ min/1.73 m²
and UACR >200 mg/g
14% had eGFR < 30 cc/min
Average eGFR 43 cc/min/1.73 m²

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
G1	Normal or high	≥90		1 if CKD	1	2
G2	Mildly decreased	60–89		1 if CKD	1	2
G3a	Mildly to moderately decreased	45–59		1	2	3
G3b	Moderately to severely decreased	30–44		2	3	3
G4	Severely decreased	15–29		3	3	4+
G5	Kidney failure	<15		4+	4+	4+

Numbers indicate guide to the frequency of monitoring (# of times per year)

*ClinicalTrials.gov. NCT03036150-DAPA-CKD-2/3 had diabetic nephropathy
**ClinicalTrials.gov. NCT03594110– -EMPA-Kidney-20% did not have albuminuria

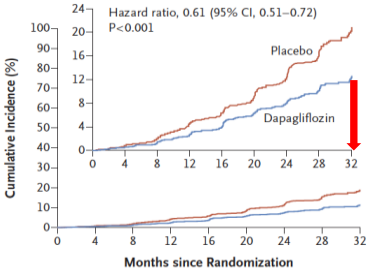
43

SGLT2 Inhibitors on Top of RAS Inhibition for CKD

All SGLT2 inhibitor trials in CKD were stopped early based on clear evidence of benefit – A first in Nephrology

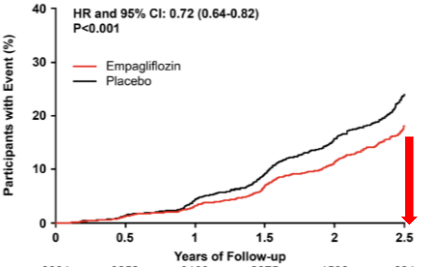
Primary outcomes: Substantial eGFR decline (40%, 50%, 57%), kidney failure, or death due to kidney or cardiovascular causes

Residual risk



DAPA-CKD
Adults with or without type 2 diabetes, eGFR ≥25 mL/min/1.73 m2, UACR >200 mg/g (n=2906).

Heerspink HJL *et al. N Engl J Med.* 2020;383(15):1436-1446

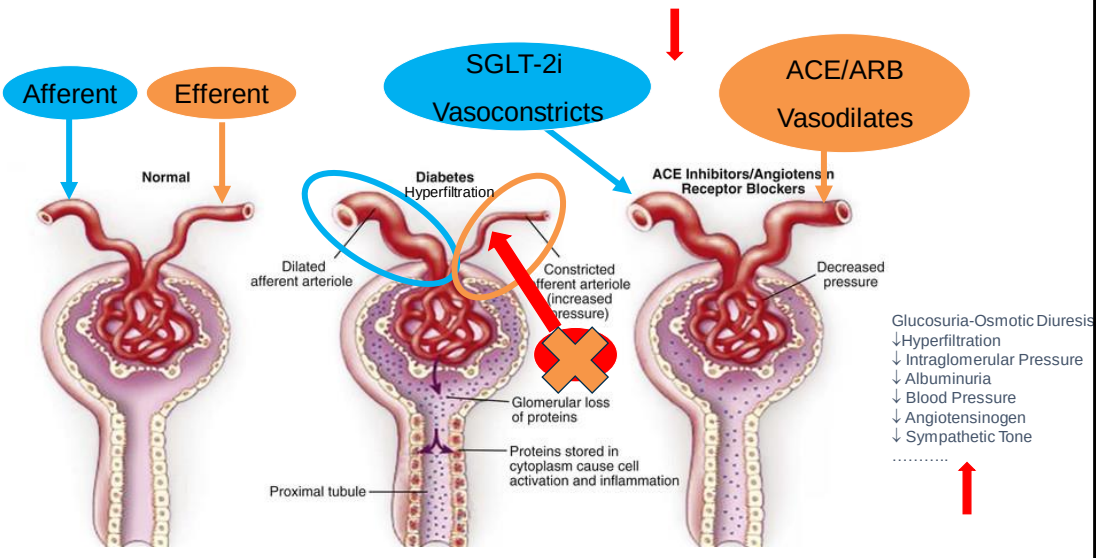


EMPA-KIDNEY
Adults with or without type 2 diabetes, eGFR ≥45 to <90 mL/min/1.73 m² and UACR ≥200 mg/g or ≥20 to <45 mL/min/1.73 m² irrespective of albuminuria (N=6609).

Herrington W *et al.* for the EMPA-KIDNEY Collaborative Group. *N Engl J Med.* 2023;388:117-127

44

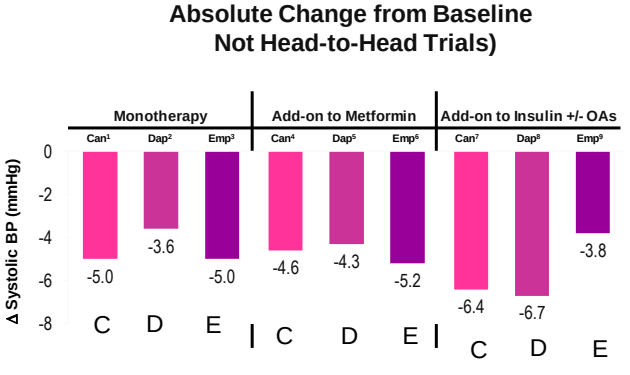
SGLT2 Inhibitors + ACE/ARB Provides Glomerular-Tubular Balance



Wolf G. Pathogenesis of DM. Abdominal Key. 2016

45

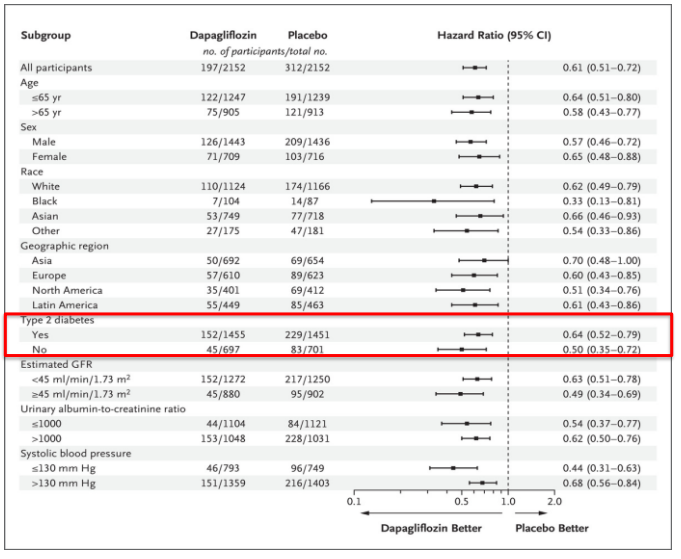
Additive BP Changes with SGLT2 Inhibitors



1.Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382.-Canagliflozin
2.Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224.-Dapagliflozin
3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219-Empagliflozin.
4. Cefalu WT, et al. *Lancet*. 2013;382:941-950.- Canagliflozin
5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022 .-Dapagliflozin.
6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659-Empagliflozin.
7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473.-Canagliflozin
8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415 .-Dapagliflozin.
9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823-Empagliflozin.

46

DAPA-CKD
Primary Outcome According to Prespecified Subgroups at Baseline



HJ Heerspink et al. N Engl J Med 2020;383:1436-1446.

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EMPA-KIDNEY
Primary Outcome in Key Pre-specified Subgroups
(N=6609)

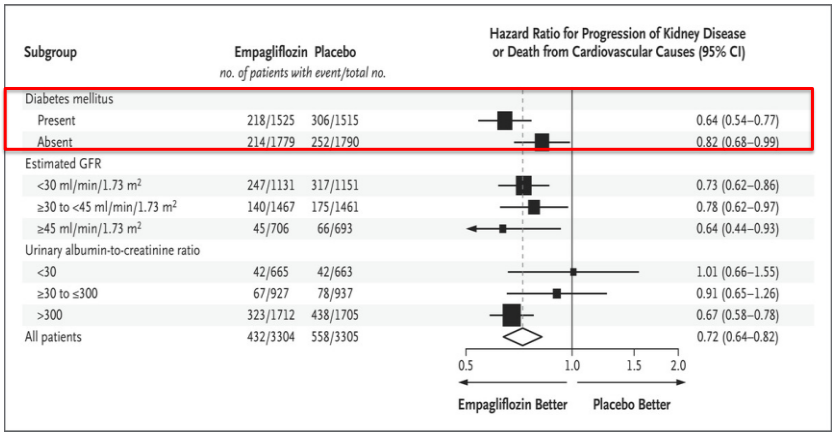

Figure 2. The EMPA-KIDNEY Collaborative Group N Engl J Med Volume 388(2):117-127 January 12, 2023

48

Empa-Kidney: Change from Baseline in the Estimated GFR.

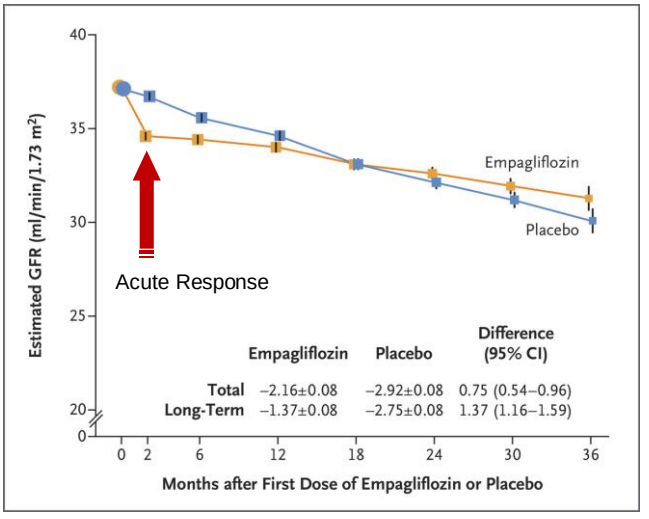

Figure 3. The EMPA-KIDNEY Collaborative Group N Engl J Med Volume 388(2):117-127 January 12, 2023

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Effects of Empagliflozin on Progression of Chronic Kidney Disease: A Pre-specified Secondary Analysis from the EMPA-KIDNEY Trial

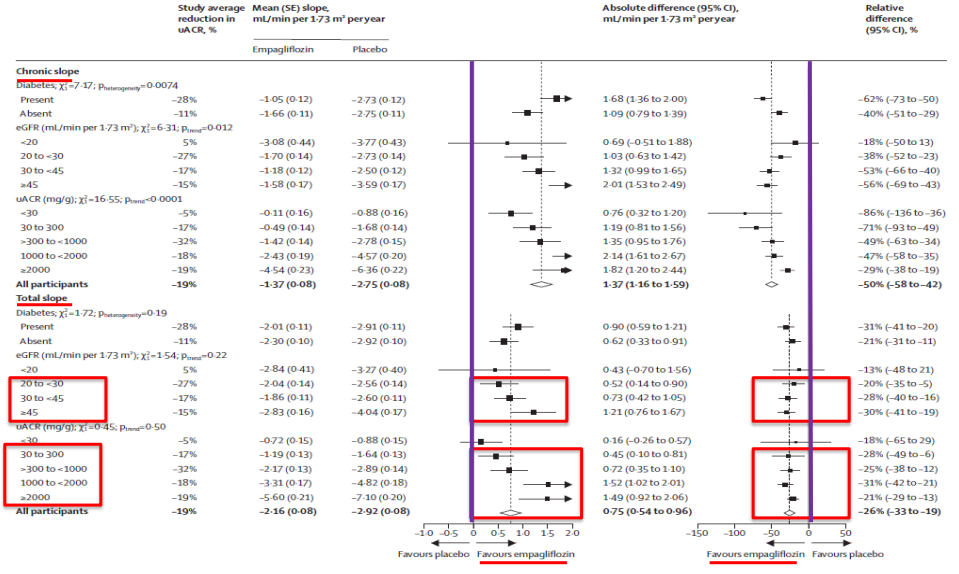

Fig 2. The Empa-Kidney Collaborative Group. *The Lancet Diabetes & Endocrinology* Jan 2024 Vol 12 Issue 1:Pages 39-50. DOI: (10.1016/S2213-8587(23)00321-2)

50

Conclusion of Empa-Kidney (Editorial)

- Empagliflozin is nephroprotective independent of the etiology of the primary kidney disease, the baseline eGFR, and the degree of albuminuria.

Zoccali C. and Mallamaci F. Editorial *The Lancet Diabetes & Endocrinology* Jan 2024 Vol 12 Issue 1:Pages 5-7.

51

Label Change April 2021 Dapagliflozin - Farxiga®

- **To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.**

- **These outcomes are independent of the patient having diabetes, and the recommended dose is 10 mg once daily.**

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Label Change Sept 2023 Empagliflozin - Jardiance®

- To reduce the risk of <u>sustained eGFR decline, end-stage kidney disease</u>, cardiovascular death, and first and recurrent hospitalizations in adults with chronic kidney disease.
- These outcomes are <u>independent</u> of the patient having diabetes, and the recommended dose is 10 mg once daily.

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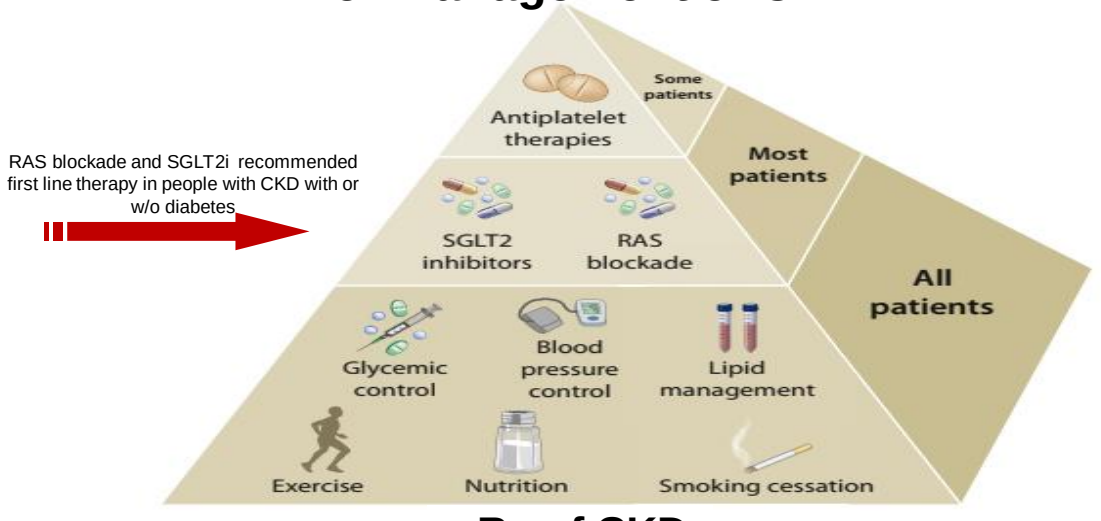
KDIGO 2022 Clinical Practice Guideline for Management of CKD



Rx of CKD

Executive summary: de Boer IH *et al*, *Kidney Int* 2022

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Drugs Used to Treat Hypertension (<130/80) in CKD

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- Mineralocorticoid Receptor Antagonists

  -Spironolactone and Eplerenone for CKD when eGFR > 30cc/min and K+ ≤ 4.5

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Role of Mineralocorticoid Receptor Antagonists (MRA's) in CKD and Hypertension

56

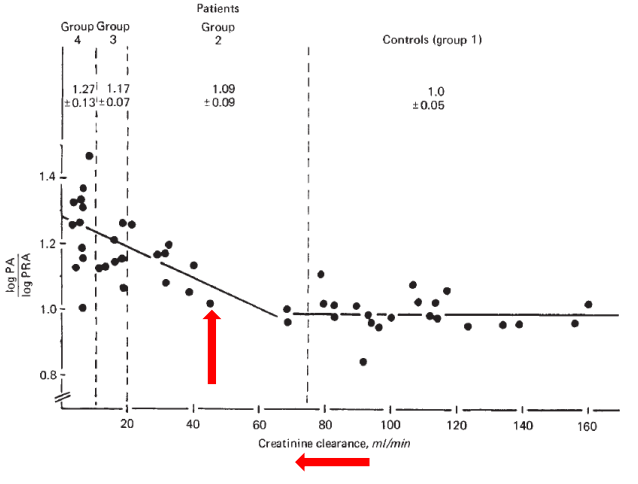
Diuretics Used to Treat Hypertension

		BA (%)	$T_{½}$ (hours)	DOA (hours)
Thiazide and Thiazide-like Diuretics	Hydrochlorothiazide	65 – 75	3.0 – 10.0	6 – 12
	Chlorothiazide	30 – 50	15.0 – 25.0	6 – 12
	Chlorthalidone	65	24.0 – 55.0	24 – 72
	Bendroflumethiazide	90	2.5 – 5.0	18 – 24
	Indapamide	90	6.0 – 15.0	24 – 36
	Metolazone	65	14	12 – 24
Loop Diuretics	Bumetanide	80 – 90	0.3 – 1.5	4-6
	Furosemide	10 – 100	0.3 – 3.4	6-8
	Torsemide	80 – 100	3.0 – 4.0	6-8
Potassium-Sparing Diuretics	Amiloride	15-20	17.0 – 26.0	24
	Triamterene	83 (55)*	3.0 (3.0)*	7-9
	Spironolactone	>90	1.5 – 15.0†	48-72
	Eplerenone	69	2.2 – 9.4	Give bid above 50 mg

*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h.
BA = bioavailability; T½ = half-life; DOA = duration of action: NA = unknown.
Reprinted from Brater DC. In: *Principles of Pharmacology: Based Concepts and Clinical Applications*. 1995:657-672, with permission from Springer Science and Business Media; Delyani JA, et al. *Cardiovasc Drug Rev*. 2001;19:185-200; Rosenberg J, et al. *Cardiovasc Drug Ther*. 2005;19:301-306; Sica DA. *Congest Heart Fail*. 2003;9:100-105.

57

Plasma Aldosterone Rises as GFR Falls



Hené RJ et al, Kidney Int. 1982 Jan;21(1):98-101.

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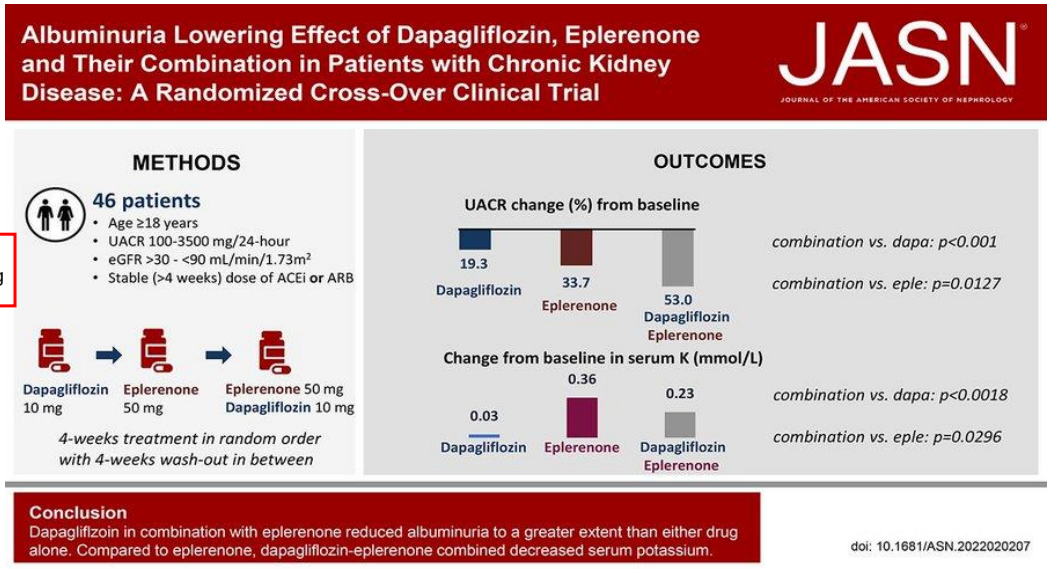
SGLT2 Inhibitor + MRA in CKD

Mean eGFR 58.1
Median UACR 401 mg/g



Provenzano M. et al. JASN August 2022, 33 (8) 1569-1580: DOI: https://doi.org/10.1681/ASN.2022020207

59

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- CCBs for BP control only

60

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  -Spironolactone and Eplerenone for CKD when eGFR > 30cc/min and K+ ≤ 4.5
- CCBs for BP control only
- Currently Finerenone and Semaglutide only for DKD

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4
PILARS of STRENGTH

CKD

HF

ASCVD

Adapted from Bakris GL

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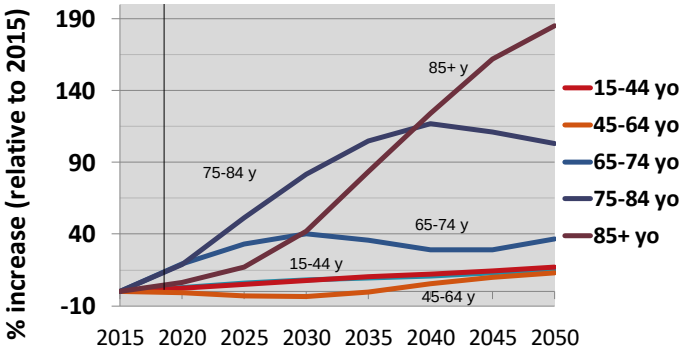
Hypertension in the Older Patient

63

Projected Percent Growth in US Population by Age, 2015 to 2050 "Greying of America"



Source: US Census Bureau, Table 12 Projections of Population by Age 2015 to 2050

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HTN Prevalence Based on New Thresholds and NHANES 2011-2014

	SBP/DBP ≥130/80 mmHg or self-reported antihypertensive medication		SBP/DBP ≥140/90 mmHg or self-reported antihypertensive medication	
Overall, crude	**46%**		**32%**	
	Men (n=4,717)	Women (n=4,906)	Men (n=4,717)	Women (n=4,906)
Overall, age-sex adjusted	48%	43%	31%	32%
Age group, years				
20-44	30%	19%	11%	10%
45-54	50%	44%	33%	27%
55-64	70%	63%	53%	52%
65-74	77%	75%	64%	63%
75+	79%	85%	71%	78%
Race/ethnicity				
Non-Hispanic White	47%	41%	31%	30%
Non-Hispanic Black	59%	56%	42%	46%
Non-Hispanic Asian	45%	36%	29%	27%
Hispanic	44%	42%	27%	32%

Muntner PO, et al. Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. *Circ* 2018; 137: 109-118.Table 7
2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

65

Age-Related Issues

COR	LOE	Recommendations for Treatment of Hypertension in Older Persons
I	A	Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for non-institutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher.
IIa	C-EO	For older adults (≥65 years of age) with hypertension and a high burden of co-morbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

Whelton PK, Carey RM et al. 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension 2018; 71:e13-e115.

66

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Target SBP → **Intensive Group < 120 mm Hg; Standard Group < 140 mm Hg.**

N Engl J Med 2015;373:2103-16.

67

SPRINT: Major Inclusion Criteria

- **At least 50 years old with no upper age exclusion**
- **Systolic Blood Pressure (SBP)**
  - **SBP: 130 – 180 mm Hg on 0 (up to 180 mm Hg) up to 4 (not > 150 mm Hg) medications**
- **Risk (one or more of the following 4 high-risk groups)**

1) Clinical or Subclinical CVD (not stroke)-20%
2) Chronic Kidney Disease (CKD), defined as eGFR 20–59 ml/min/1.73m^2 -28%
3) Age ≥ 75 years-28%
4) Framingham Risk Score for 10-year CVD risk ≥ 15%- 22%

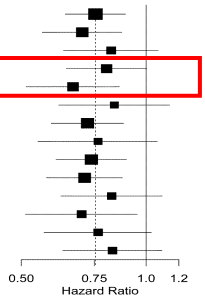
SPRINT Research Group, NEJM 2015; 373:2103-2116.

68

Primary Outcome Experience in the 6 Pre-specified Subgroups of Interest*

Subgroup	HR	P*
Overall	0.75 (0.64,0.89)	
No Prior CKD	0.70 (0.56,0.87)	0.36
Prior CKD	0.82 (0.63,1.07)	
Age < 75	0.80 (0.64,1.00)	0.32
Age ≥ 75	0.67 (0.51,0.86)	
Female	0.84 (0.62,1.14)	0.45
Male	0.72 (0.59,0.88)	
African–American	0.77 (0.55,1.06)	0.83
Non African–American	0.74 (0.61,0.90)	
No Prior CVD	0.71 (0.57,0.88)	0.39
Prior CVD	0.83 (0.62,1.09)	
SBP ≤ 132	0.70 (0.51,0.95)	0.77
132 < SBP < 145	0.77 (0.57,1.03)	
SBP ≥ 145	0.83 (0.63,1.09)	

*Unadjusted for multiplicity



*Treatment by subgroup interaction

SPRINT Research Group. *N Engl J Med*. 2015;373:2103-2116.

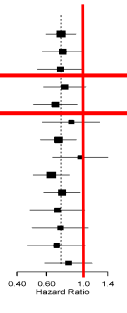
69

All Cause Mortality Experience in the Six Pre-specified Subgroups of Interest

Figure 4: All–Cause Mortality

Subgroup	Intensive	Standard	HR	Int P
Overall	155/4678 (3.31)	210/4683 (4.48)	0.73 (0.60,0.90)	
No Prior CKD	85/3348 (2.54)	115/3367 (3.42)	0.75 (0.57,1.00)	0.76
Prior CKD	70/1330 (5.28)	95/1316 (7.22)	0.73 (0.53,1.00)	
Age < 75	82/3361 (2.44)	104/3364 (3.09)	0.77 (0.58,1.03)	0.58
Age ≥ 75	73/1317 (5.54)	106/1319 (8.04)	0.68 (0.50,0.92)	
Female	46/1684 (2.73)	54/1648 (3.28)	0.85 (0.57,1.26)	0.49
Male	109/2994 (3.64)	156/3035 (5.14)	0.71 (0.55,0.91)	*
African–American	53/1454 (3.65)	55/1493 (3.68)	0.95 (0.65,1.40)	0.06
Non African–American	102/3224 (3.16)	155/3190 (4.86)	0.64 (0.50,0.82)	
No Prior CVD	106/3738 (2.84)	140/3746 (3.74)	0.75 (0.58,0.96)	0.78
Prior CVD	49/940 (5.21)	70/937 (7.47)	0.70 (0.48,1.02)	
SBP ≤ 132	46/1583 (2.91)	64/1553 (4.12)	0.73 (0.49,1.07)	0.70
132 < SBP < 145	41/1489 (2.75)	63/1549 (4.07)	0.69 (0.46,1.03)	
SBP ≥ 145	68/1606 (4.23)	83/1581 (5.25)	0.81 (0.59,1.13)	

*p=0.34, after Hommel adjustment for multiple comparisons



SPRINT Research Group. *N Engl J Med*. 2015;373:2103-2116.

SPRINT

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SPRINT
Major Exclusion Criteria

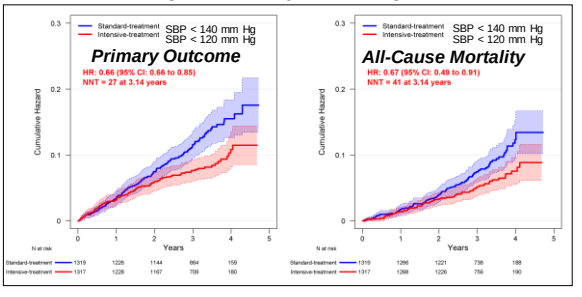
- Stroke (SPS3)
- Diabetes (ACCORD)
- Congestive heart failure (symptoms or EF < 35%)
- Proteinuria >1g/d
- CKD with eGFR < 20 mL/min/1.73m^2 (MDRD)
- Adherence flags anywhere in the chart
- Non-Ambulatory
- Living in a Nursing Home

SPRINT Research Group, NEJM 2015; 373:2103-2116.

71

SPRINT Primary Outcome and All-Cause Mortality

Participants ≥75 years: Kaplan-Meier Survival



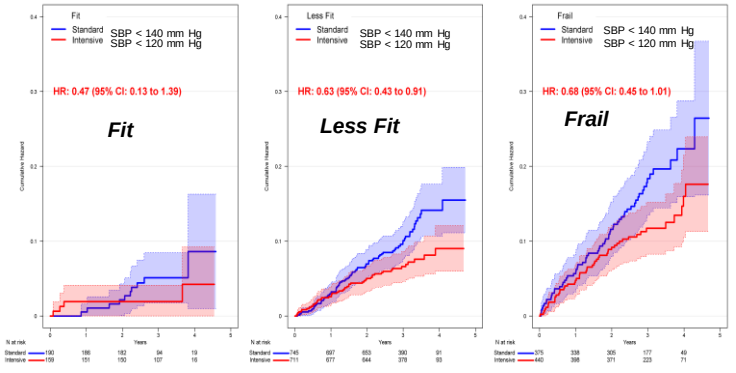
Primary outcome includes non-fatal myocardial infarction (MI), acute coronary syndrome not resulting in MI, non-fatal stroke, non-fatal acute decompensated heart failure, and CVD death.

Williamson et al. *JAMA*.2016;315:2673-2682.

72

SPRINT Primary Outcome by Frailty Status

Participants ≥75 years: Kaplan-Meier Survival Curves



Williamson et al. *JAMA*.2016;315:2673-2682.

73

SPRINT-MIND:
Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group: Intensive SBP < 120 mm Hg N=4278 — No. With Outcome/Person-Years	Intensive — Cases per 1000 Person-Years	Standard SBP < 140 mm Hg N=4285 — No. With Outcome/Person-Years	Standard — Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	P Value
Primary outcome: Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Secondary outcome: Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Secondary outcome: Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Treatment lasted a median of 3 years, and patients were followed for cognitive outcomes over a total of 5 years.

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SPECIAL POPULATIONS

In Terms of Benefit on Cognitive Function in the Older Patient, the Concept of "Pack-Years" of HTN is important.
It is more important to begin Controlling BP Earlier in Life, Than to Believe You Can Reverse Changes in Vascular and White Matter Disease After 60 Years of Age

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Key Clinical Points on Hypertension Management in Older Adults

1. As the global population ages, clinicians will see significantly more older adults with hypertension.
2. The benefits of intensive antihypertensive therapy outweighs the risks in older adults with good cognitive function and absent moderate and severe frailty.
3. Hypertension in older adults is a woman's health equity issue as women live longer than men and hypertension prevalence increases more and BP control falls more as women age.
4. Comprehensive assessment of cognitive and physical function is important in determining BP treatment intensity and treatment goals should be a shared decision in older adults with hypertension.
5. In healthy older adults with hypertension, both sodium reduction and weight reduction are successful lifestyle interventions for improved BP control.
6. The adage "start low and go slow" contributes to clinical inertia in managing BP among older adults. Monthly reviews with Rx intensification to control BP is appropriate absent any mitigating factors such as orthostatic hypotension and frailty.

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Summary of Hypertension-Special Populations

1. All pregnant patients should have their BP < 140/90 mm Hg.
2. In pregnant patients, labetalol, Nifedipine ER, and methyldopa are preferred.
3. Pregnant Patients with Hypertensive Complications of Pregnancy have a n increased lifetime risk for CV Disease and need appropriate lifetime f/up.
4. Define CKD by 3 months of persistently reduced eGFR < 60 cc/min and/or clinical proteinuria. Treat with RAS blockers, chlorthalidone, SGLT2 inhibitors, and MRAs as permitted by eGFR and serum K+ for improved outcome and BP control.
5. The older patient should be controlled earlier in life to a BP < 130/80 mm Hg but as patients get older, clinical judgement, individual circumstances, and co-morbidities should be taken into account as to the best BP for that patient.