

Best Practices in Hypertension Management

Ajay K. Singh, MBBS, FRCP, MBA
Nephrologist, Brigham and Women's Hospital
Senior Associate Dean for Postgraduate
Medical Education, Harvard Medical School

Ajay K. Singh Bio



- Attending Nephrologist, Brigham and Women's Hospital
- Senior Associate Dean for Postgraduate Medical Education, Harvard Medical School
- Research interests: Anemia of CKD and CKDu
- Clinical interests: managing patients with CKD

Disclosures

- **Consulting**

GSK, Bayer, Nephrology Times, Zydus,
NovoNordisk, Alexion, Vera, Chinook



Topic 1

Case 1

A 66 year old woman with **Type 2 DM w/ persistent HTN**, despite being treated with 4 medications (lisinopril 40 mg, amlodipine 10 mg, metoprolol 50 mg, and hydrochlorothiazide 50 mg). She has a past history of stage 3 CKD (eGFR 46 ml/min/1.73m²), and one hospitalization for heart failure. Asymptomatic. On exam, her BP is 164/70 mmHg, non-orthostatic, HR 54, but otherwise unremarkable. SBP in the 160s at home. Scr 1.6 mg/dL, K 4.4 mEq/L, HbA1C 7.2

- Which one of the following next steps is most appropriate?

- A.) Increase the dose of her hydrochlorothiazide to achieve better BP control
- B.) Add in an SGLT-2 inhibitor
- C.) Add in an ARB
- D.) Do nothing

Case 1

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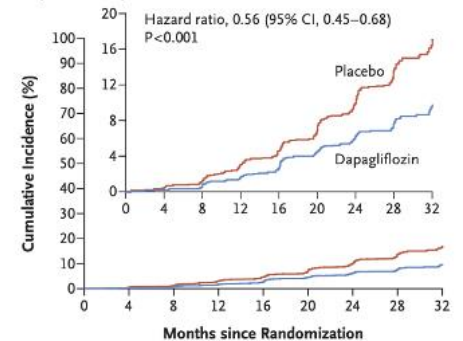
D.) Do nothing

Subgroup	Dapagliflozin <i>no. of participants/total no.</i>	Placebo	Hazard Ratio (95% CI)
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m ²	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m ²	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)

• Fewer primary outcomes in dapa (197 of 2152 participants (9.2%)) vs. placebo (312 of 2152 participants (14.5%)) (hazard ratio, 0.61; 95% CI 0.51 to 0.72; P < 0.001)

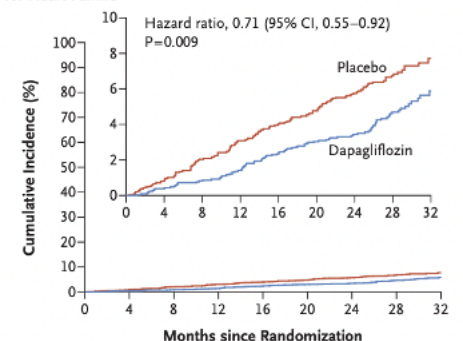
• Number needed to treat to prevent primary=19

B Renal-Specific Composite Outcome



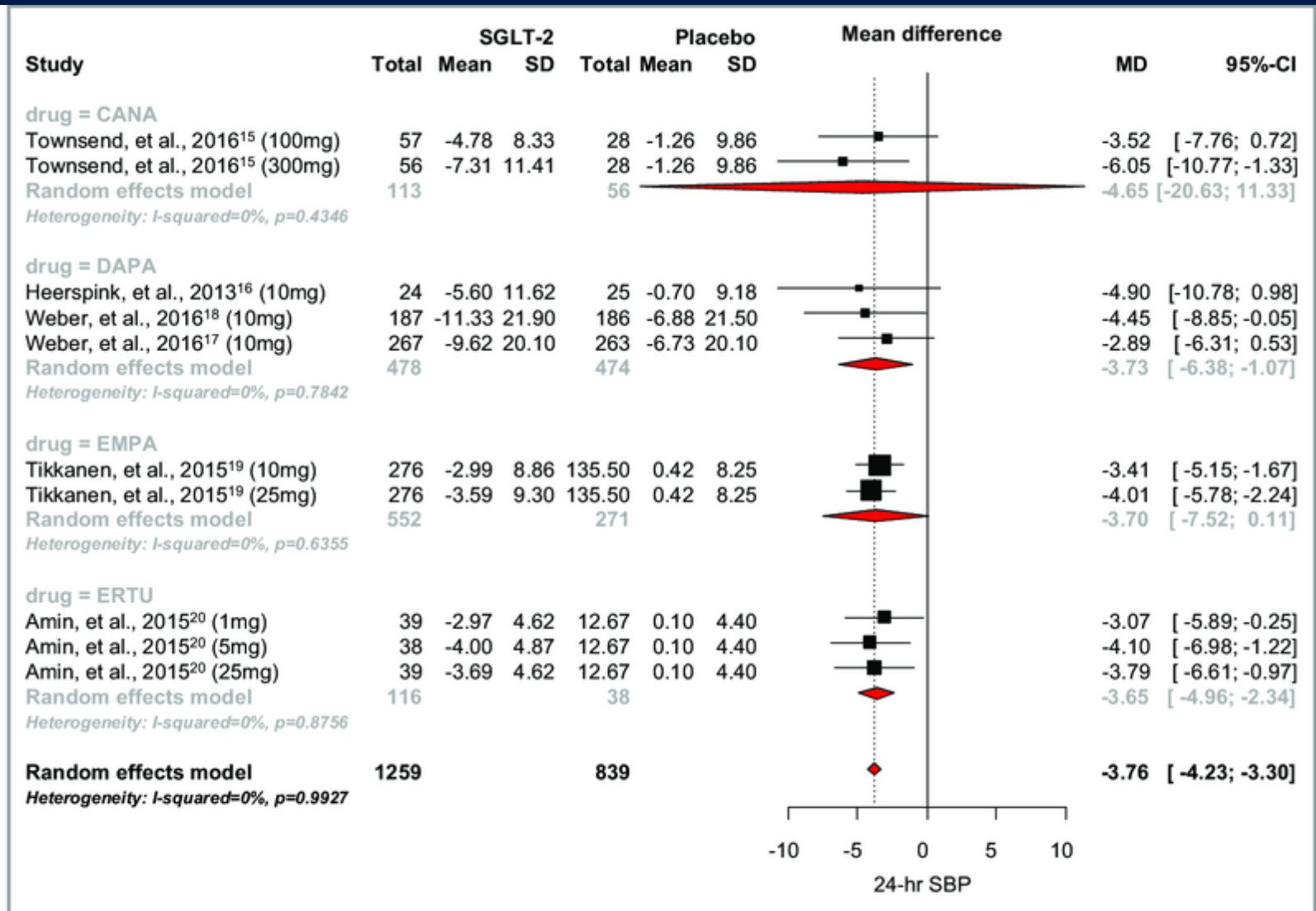
No. at Risk	0	4	8	12	16	20	24	28	32
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure



No. at Risk	0	4	8	12	16	20	24	28	32
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384

SGLT2i and BP



Reviews | August 20, 2013

Sodium–Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes

A Systematic Review and Meta-analysis

Despoina Vasilakou, MD, MSc, Thomas Karagiannis, MD, MSc, Eleni Athanasiadou, MSc, ... [See More](#) +

[Author, Article, and Disclosure Information](#)

<https://doi.org/10.7326/0003-4819-159-4-201308200-00007>

45 studies ($n = 11\,232$) of SGLT2i compared with placebo; 13 studies ($n = 5175$) with active comparators.

Compared with other agents, SGLT2 inhibitors

- **Reduced HbA1C** (mean difference vs. placebo, -0.66% [95% CI, -0.73% to -0.58%]; mean difference vs. active comparators, -0.06% [CI, -0.18% to 0.05%]).
- **Reduced body weight** (mean difference, -1.80 kg [CI, -3.50 to -0.11 kg])
- **Reduced systolic BP** (mean difference, -4.45 mm Hg [CI, -5.73 to -3.18 mm Hg]).

Home > Circulation > Vol. 143, No. 18 > Are SGLT2 Inhibitors New Hypertension Drugs?

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Are SGLT2 Inhibitors New Hypertension Drugs?

Kazuomi Kario, Keith C. Ferdinand and Wanpen Vongpatanasin

Originally published 3 May 2021 |
<https://doi.org/10.1161/CIRCULATIONAHA.121.053709> |
Circulation. 2021;143:1750–1753

This article is a commentary on the following

EVOLVING TACTICS WITH INHIBITION OF SODIUM–GLUCOSE COTRANSPORTERS | FEBRUARY 12 2015

Blood Pressure Reduction: An Added Benefit of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes

Colleen Majewski; George L. Bakris

Check for updates

Corresponding author: George L. Bakris, gbakris@gmail.com.

Diabetes Care 2015;38(3):429–430

<https://doi.org/10.2337/dc14-1596>

PubMed:25715414

Antihypertensive Agents: Mechanisms of Drug Action (Michael E. Ernst, Section Editor) |
Published: 12 February 2019

Blood Pressure Lowering and Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is): More Than Osmotic Diuresis

Hillel Sternlicht & George L. Bakris

Current Hypertension Reports 21, Article number: 12 (2019) | [Cite this article](#)

1647 Accesses | 41 Citations | 1 Altmetric | [Metrics](#)

Cardiovascular
Diabetology

BMC

Cardiovasc Diabetol. 2022; 21: 63.

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PMCID: PMC9052512

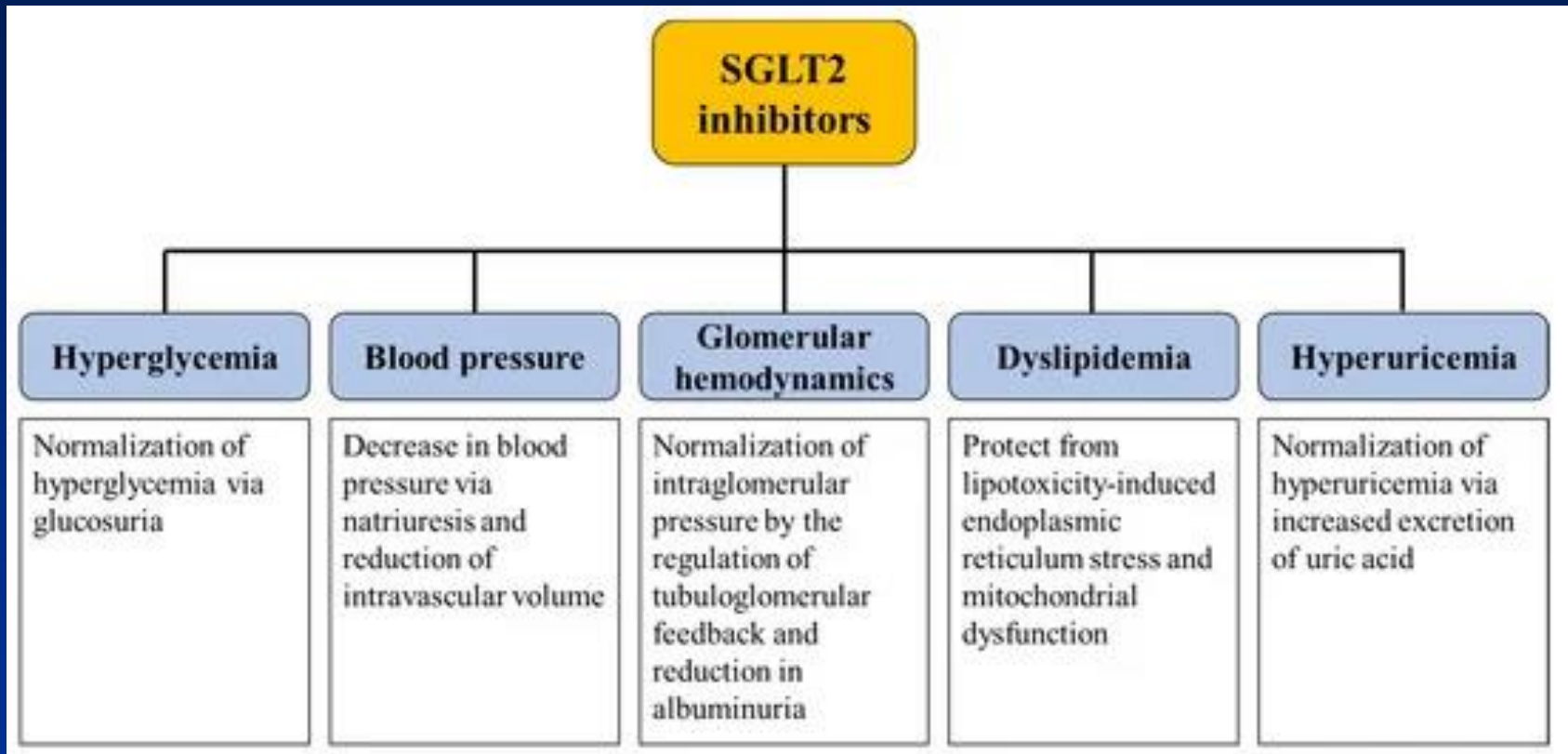
PMID: [35484607](https://pubmed.ncbi.nlm.nih.gov/35484607/)

Mechanisms underlying the blood pressure lowering effects of dapagliflozin, exenatide, and their combination in people with type 2 diabetes: a secondary analysis of a randomized trial

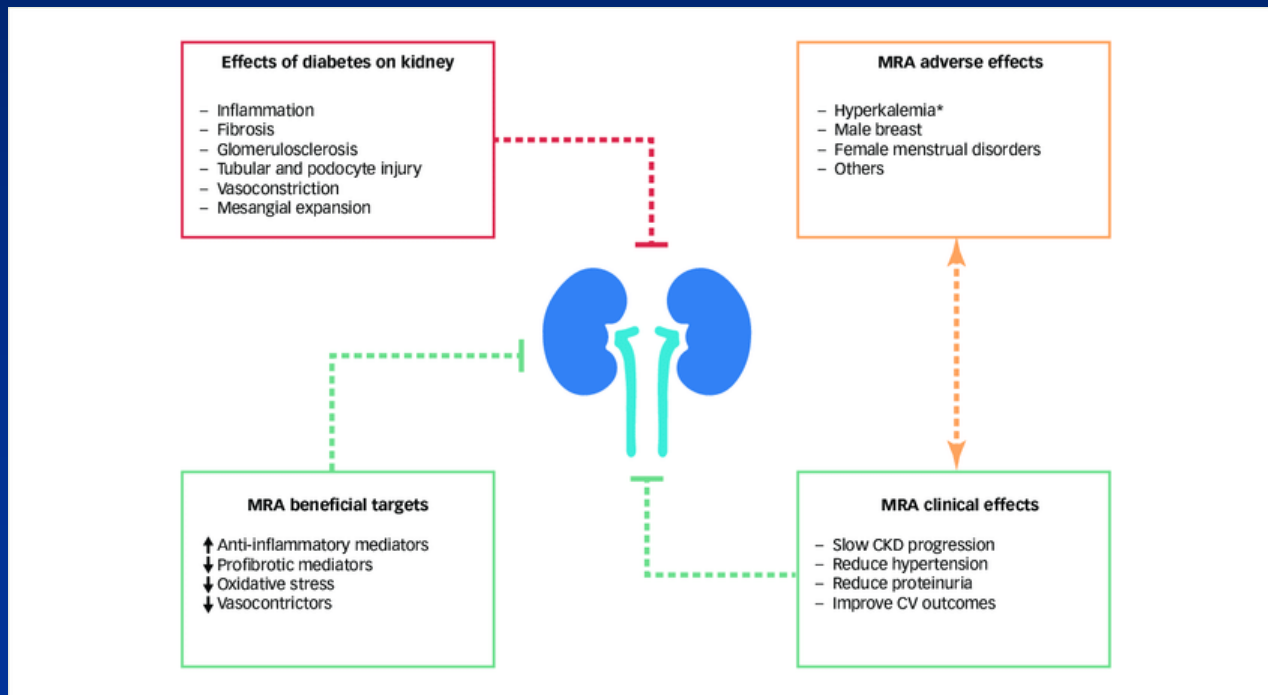
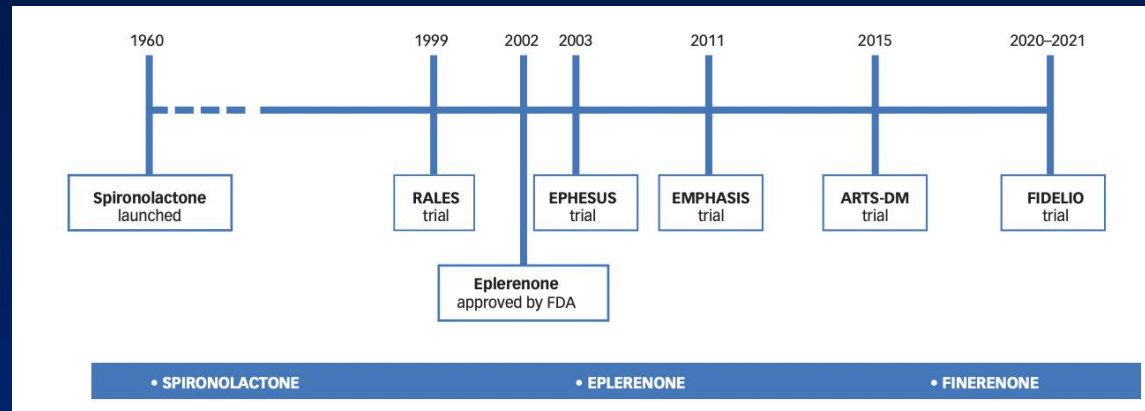
Charlotte C. van Ruiten,^{01,4} Mark M. Smits,¹ Megan D. Kok,¹ Erik H. Serné,^{1,2} Daniël H. van Raalte,¹ Mark H. H. Kramer,¹ Max Nieuwdorp,^{1,3} and Richard G. IJzerman¹

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Pleiotropic Effects of SGLT2i



Mineralocorticoid Receptor Antagonist



ARTS-DN Phase 2 Trial in CKD associated with T2D

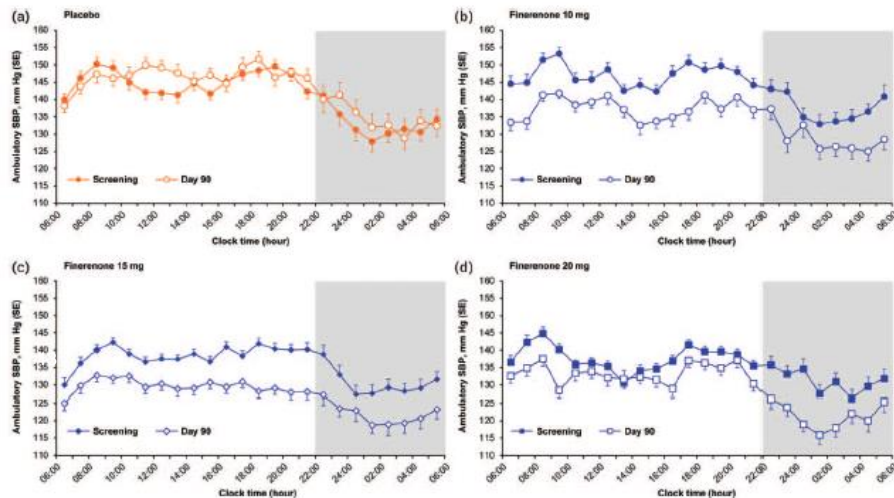
Randomized, double-blind, placebo-controlled trial¹

Patients (N=823) treated with: finerenone (1.25–20 mg) or placebo

Change from screening in 24-h, daytime, and night-time ABPM SBP in patients treated with ≥ 10 mg finerenone once daily versus placebo at Day 60 and Day 90 (n=119)

Eligible for ABPM substudy (n=240)²

LS mean change from baseline in 24-h ABPM SBP with finerenone (≥ 10 mg) versus placebo



Placebo-adjusted change in ABPM SBP Day 90

- 8.3 mmHg (–16.6 to 0.1) F-10mg (n=27)
- 11.2 mmHg (–18.8 to –3.6) F-15mg (n=34)
- 9.9mmHg (–17.7 to –2.0) F-20mg (n=31)



MPR MEDICAL
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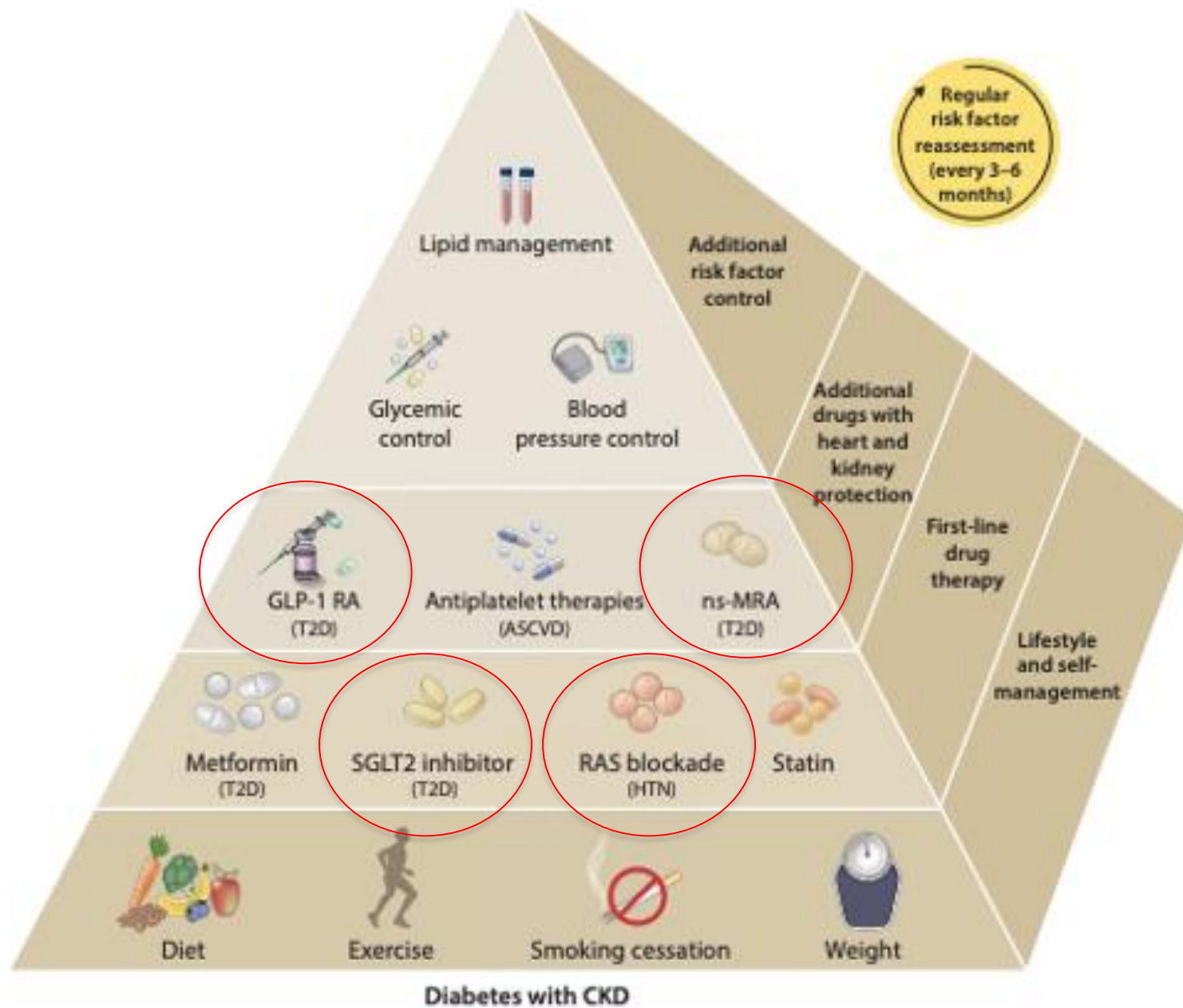
FLOW Trial: Semaglutide Reduces Risk of Kidney Disease Progression



Diana Ernst, RPh | March 5, 2024



Findings showed treatment with semaglutide 1mg reduced the risk of kidney-disease progression as well as cardiovascular and kidney death by 24% compared with placebo.





Topic 2

Case 2

You see a 58-year-old male with a history of hypertension. The patient does not have diabetes mellitus. Kidney function is normal (BUN 18, Cre 0.8 mg/dL). He is being treated with amlodipine 5 mg daily and lisinopril 20 mg daily. His systolic pressures in clinic have been in the 140-150 mm Hg range. Home blood pressures, when measured, are in the same range. Physical examination is normal. BP of 155/88 mmHg, HR 78 bpm.

Which of the following is the most appropriate next step:

- A. His BP is satisfactory
- B. His SBP can be further reduced to a target of <140 mmHg
- C. His SBP can be further reduced to a target of <120mmHg

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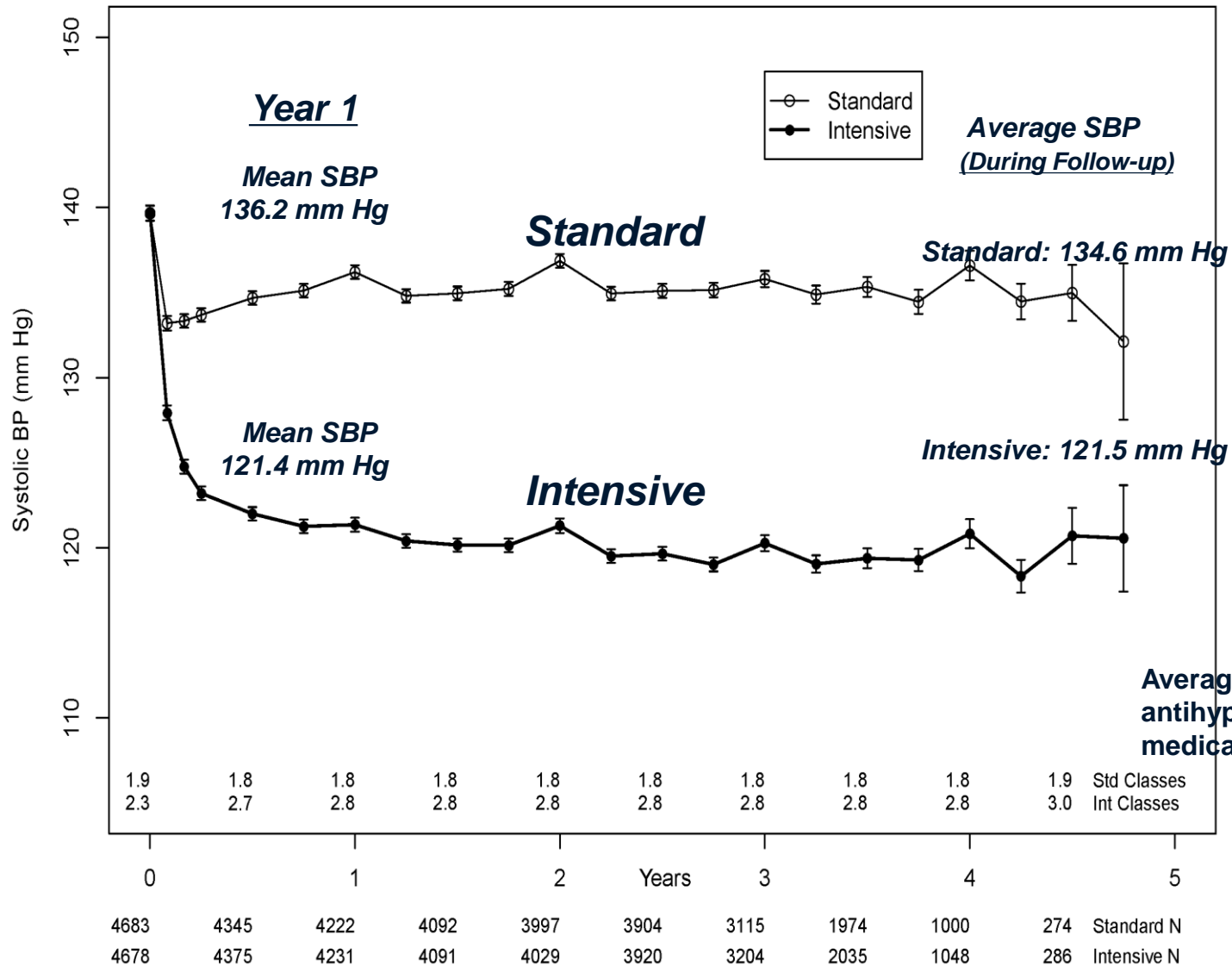
VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

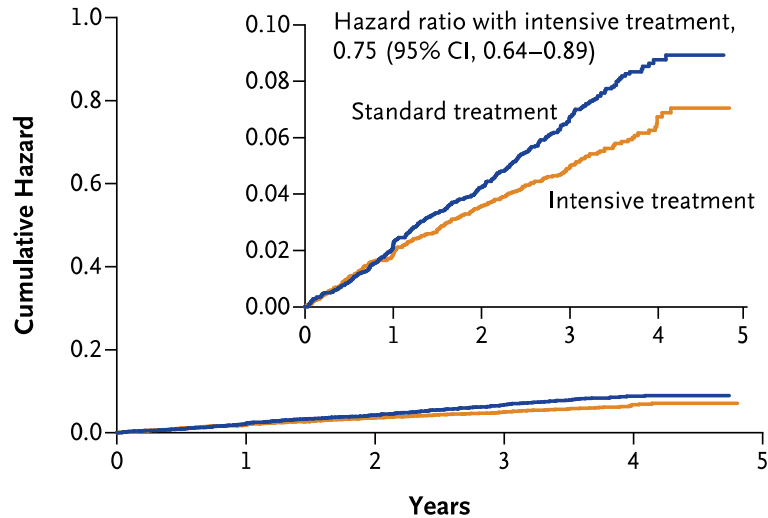
- RCT
- N=9361, mid-60s, ≈35% female, ≈30% AA, Mean 10-year Framingham CVD risk, 20%, CVD in ≈20%, mean baseline BP ≈140/78 mmHg
- Subjects with SBP_≥130 mmHg and increased cardiovascular risk, but not diabetic
- Assigned to either SBP to <120 mm Hg (intensive treatment) or SBP <140 mm Hg (standard treatment).
- Primary composite outcome: **myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.**

Figure 1: Mean Systolic BP (95% CI)



	Intensive	Standard		
	Rate, %/year	Rate, %/year	HR (95% CI)	P value
Primary Outcome	1.65	2.19	0.75 (0.64, 0.89)	<0.001
All MI	0.65	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	0.27	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	0.41	0.47	0.89 (0.63, 1.25)	0.5
All HF	0.41	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	0.25	0.43	0.57 (0.38, 0.85)	0.005

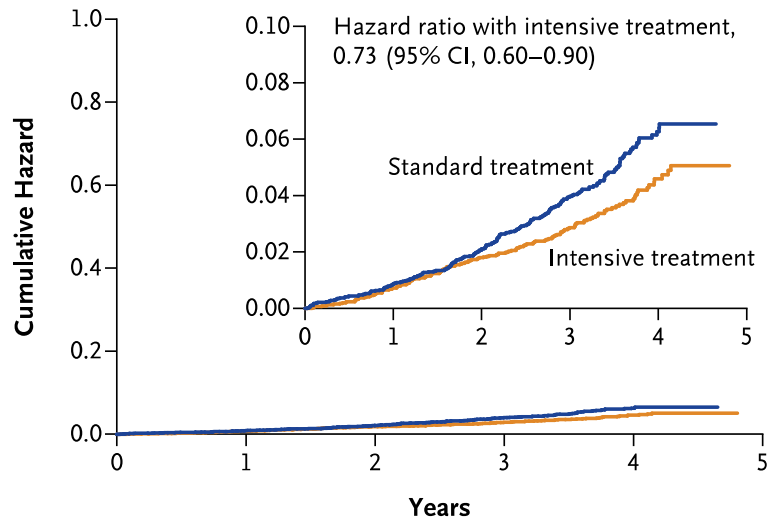
A Primary Outcome



No. at Risk

	0	1	2	3	4	5
Standard treatment	4683	4437	4228	2829	721	
Intensive treatment	4678	4436	4256	2900	779	

B Death from Any Cause

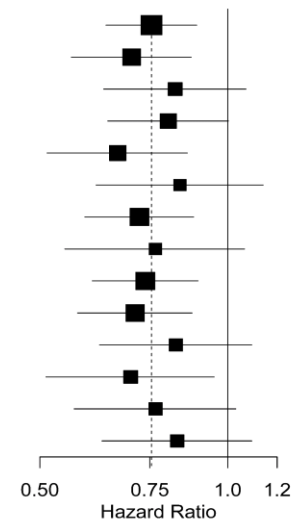


No. at Risk

	0	1	2	3	4	5
Standard treatment	4683	4528	4383	2998	789	
Intensive treatment	4678	4516	4390	3016	807	

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



SPRINT: Renal Progression during Post Intervention Observation Period

Table 2. Outcomes during the Observational Postintervention Period (through July 29, 2016).*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value†
	<i>no. of participants</i>	<i>% per year</i>	<i>no. of participants</i>	<i>% per year</i>		
All participants	(N = 4515)		(N = 4468)			
Primary outcome‡	51	2.35	57	2.70	0.87 (0.59–1.27)	0.46
Primary outcome without nonfatal heart failure	36	1.64	49	2.29	0.72 (0.46–1.10)	0.13
Secondary outcomes‡						
Myocardial infarction	13	0.58	21	0.96	0.61 (0.30–1.22)	0.16
Acute coronary syndrome	3	0.13	6	0.27	0.51 (0.11–1.94)	0.33
Stroke	10	0.44	18	0.81	0.51 (0.23–1.10)	0.09
Heart failure	32	1.42	13	0.59	2.34 (1.25–4.64)	0.007
Nonfatal heart failure	32	1.42	13	0.59	2.34 (1.25–4.64)	0.007
Death from cardiovascular causes	15	0.66	16	0.71	0.95 (0.46–1.94)	0.89
Death from any cause	53	2.31	57	2.51	0.90 (0.61–1.31)	0.57
Primary outcome or death from any cause	85	3.90	89	4.20	0.91 (0.68–1.23)	0.55
Participants with CKD at baseline	(N = 1148)		(N = 1125)			
Composite renal outcome§	1	0.16	3	0.50	0.31 (0.02–2.42)	0.27
≥50% Reduction in eGFR¶	1	0.16	1	0.17	0.79 (0.03–20.00)	0.87
Long-term dialysis	1	0.16	2	0.33	0.33 (0.03–5.82)	0.62
Kidney transplantation	0		1	0.17	0.00	0.23
Incident albuminuria	5	2.30	9	4.71	0.55 (0.16–1.67)	0.29
Participants without CKD at baseline	(N = 2887)		(N = 2967)			
≥30% Reduction in eGFR¶	10	0.64	7	0.43	1.49 (0.57–4.10)	0.42
Long-term dialysis	0		0		—	—
Kidney transplantation	0		0		—	—
Incident albuminuria	8	0.99	14	1.76	0.55 (0.22–1.30)	0.18

SPRINT: Summary and Conclusions

- Rapid and sustained difference in SBP achieved between the two treatment arms
- Incidence of primary outcome (composite of CVD events) 25% lower in Intensive compared to Standard Group and all-cause mortality reduced by 27%.
- “Number Needed to Treat” to prevent primary outcome event or death 61 and 90, respectively
- In participants with CKD at baseline, no differences in renal outcomes; without CKD at baseline, incidence of eGFR reduction \geq 30% more common in Intensive Group
- No overall difference in serious adverse events (SAEs) between treatment groups
- SAEs associated with hypotension, syncope, electrolyte abnormalities, and hospital discharge reports of acute kidney injury or acute renal failure more common in Intensive Group
- Overall, benefits of more intensive BP lowering exceeded the potential for harm

Intensive vs. Standard BP control on Probable Dementia

- **Secondary Analysis of SPRINT**

- Patients age ≥ 50 w/ HTN but no h/o stroke or diabetes
- 8563 (91.5%) completed ≥ 1 follow-up cognitive assessment
- Median follow-up of 5.11 years

- Adjudicated probable dementia

- 149 intensive group

- 176 in standard group



HR 0.83; 95% CI, 0.67-1.04

- Intensive BP control reduced risk of mild cognitive impairment (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81; 95% CI, 0.69-0.95)

- Intensive BP control reduced risk of combined rate of mild cognitive impairment or probable dementia (20.2 vs 24.1 cases per 1000 person-years; HR, 0.85; 95% CI, 0.74-0.97).

Case 2

You see a 58-year-old male with a history of hypertension. The patient does not have diabetes mellitus. Kidney function is normal (BUN 18, Cre 0.8 mg/dL). He is being treated with amlodipine 5 mg daily and lisinopril 20 mg daily. His systolic pressures in clinic have been in the 140-150 mm Hg range. Home blood pressures, when measured, are in the same range. Physical examination is normal. BP of 155/88 mmHg, HR 78 bpm.

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- C. His SBP can be further reduced to a target of <120mmHg



Topic 3

Case 3

- An 85-yr old woman is seeking a second opinion because her PCP advised her to take lisinopril-HCTZ to lower her BP. She only takes multivitamins. Her clinic and home BPs over the past 2 years have ranged from 158/60 to 180/72, consistent with isolated systolic hypertension (ISH).
- She has no diabetes, MI, or stroke, but her mother died from a stroke at age 77.
- BP is 172/65. She has no edema. Cre=0.8, UA is negative.
 - You should advise her that:
 - A. She should have 24-hour ABPM because she likely has white-coat HTN
 - B. ISH is normal with ageing and requires no therapy
 - C. Although ISH should be treated in most, there are no data pertaining to women of her age
 - D. Taking lisinopril-HCTZ may reduce her chances of dying and/or developing congestive heart failure during the next 2 years

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 - You should advise her that:
 - A. She should have 24-hour ABPM because she likely has white-coat HTN
 - B. ISH is normal with ageing and requires no therapy
 - C. Although ISH should be treated in most, there are no data pertaining to women of her age
 - D. Taking lisinopril-HCTZ may reduce her chances of dying and/or developing congestive heart failure during the next 2 years

Hypertension in the Very Elderly Trial: (HYVET)

Objective: To determine whether treatment of systolic hypertension in patients ≥ 80 years old lowers the risk of stroke

Design: Multicenter, randomized, double-blind, placebo-controlled

Patients: 3845 men and women ≥ 80 y (mean, 84 y) with sustained SBP > 160 mmHg

Treatments: Step 1: thiazide

Step 2: ACEI

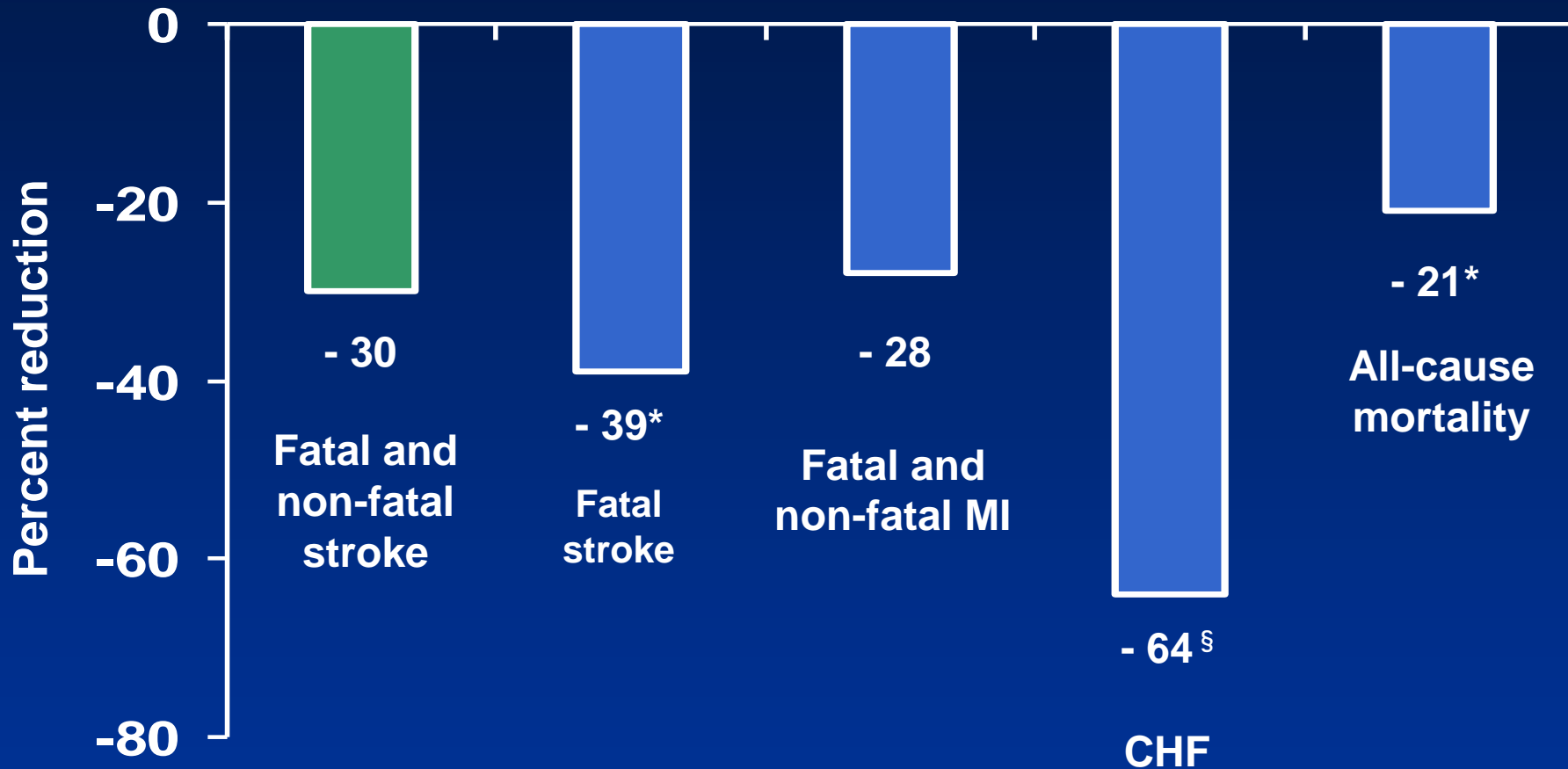
Goal: SBP < 150 mmHg

Placebo

Follow-up: 1.8 years (stopped early)

Endpoint: Fatal and non-fatal stroke

HYVET: Outcomes



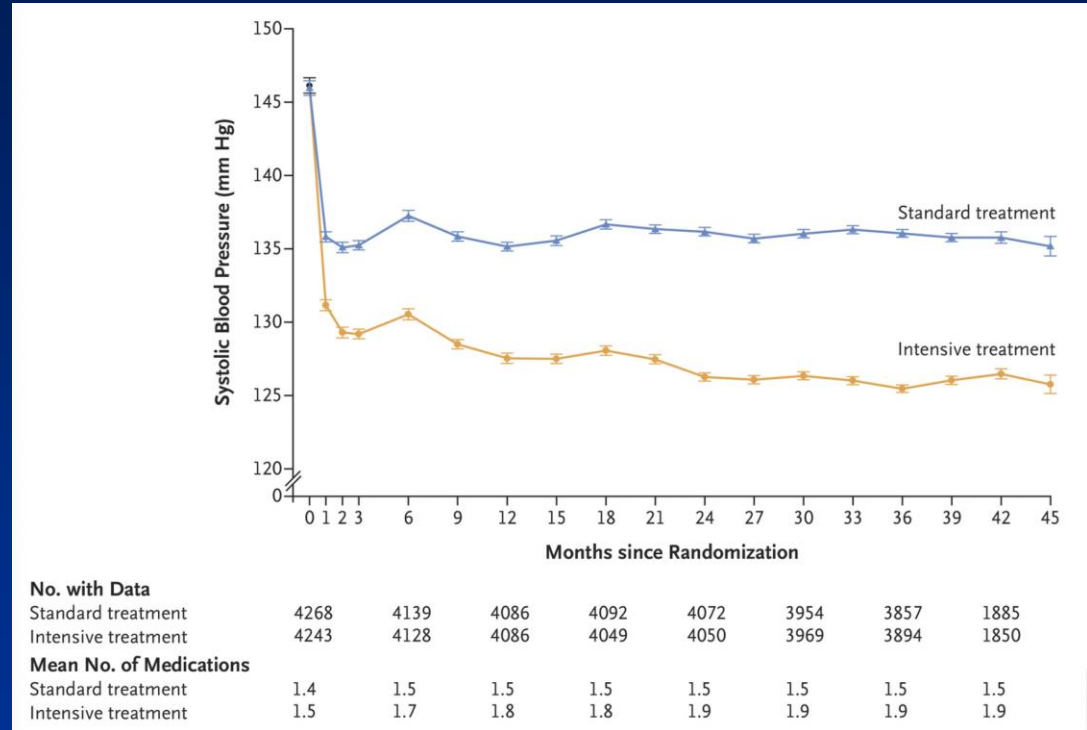
* $p < 0.05$ § $p < 0.001$

Systolic Hypertension in Oldest Adults-Whom Should We Treat?

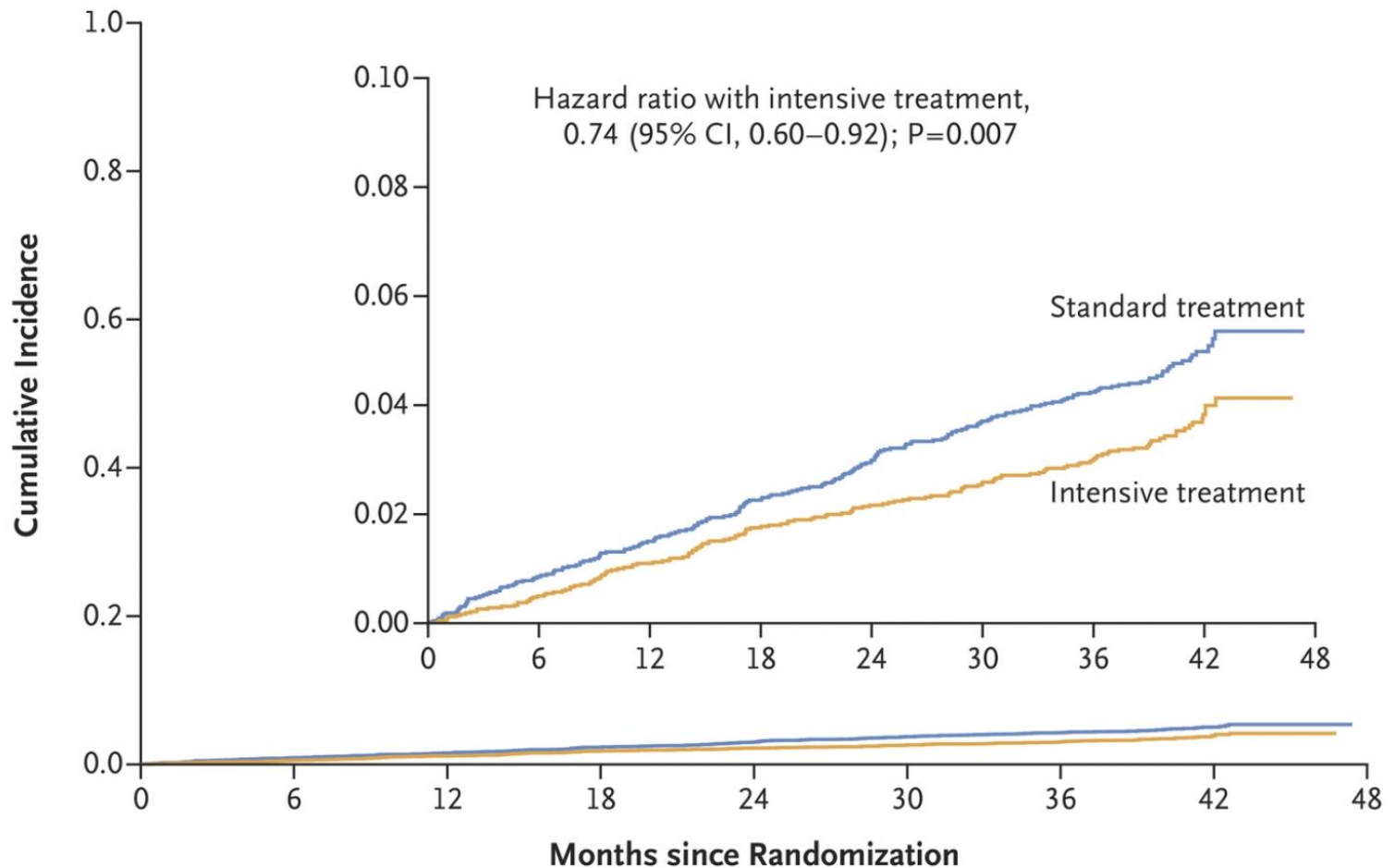
- CV benefit with treatment of high SBP may only apply to healthier older adults
- Higher baseline SBP was associated with LESS decline (physical and cognitive).
 - HYVET done on healthy adults
 - Control of BP is difficult and has many side effects
- Do frail older patients get the same benefits from BP treatment as healthy older people?
- Should all hypertensives be treated the same?

What Target in Elderly? STEP Trial

- RCT of Intensive vs. Standard BP
- N=8511; Intensive 4243, Standard 4268
- Intensive SBP 110-<130, Standard SBP 130-<150
- Primary outcome: composite of stroke, ACS (MI and hospitalization for unstable angina), acute decompensated HF, coronary revascularization, Afib or CVD death
- Median F/U 3.34 years



STEP Trial: Outcomes



No. at Risk

Standard treatment	4268	4147	4070	4000	3938	3849	3664	1200
Intensive treatment	4243	4174	4109	4039	3970	3867	3694	1234

STEP Trial: Outcomes

Table 2. Hazard Ratios for the Primary and Secondary Outcomes.*

Outcome	Intensive Treatment (N=4243)		Standard Treatment (N=4268)		Hazard Ratio (95% CI)	P Value
	<i>no. of patients (%)</i>	<i>% with event per year</i>	<i>no. of patients (%)</i>	<i>% with event per year</i>		
Primary outcome†	147 (3.5)	1.0	196 (4.6)	1.4	0.74 (0.60–0.92)	0.007
Secondary outcomes						
Components of primary outcome						
Stroke	48 (1.1)	0.3	71 (1.7)	0.5	0.67 (0.47–0.97)	—
Acute coronary syndrome	55 (1.3)	0.4	82 (1.9)	0.6	0.67 (0.47–0.94)	—
Acute decompensated heart failure	3 (0.1)	0.03	11 (0.3)	0.09	0.27 (0.08–0.98)	—
Coronary revascularization	22 (0.5)	0.1	32 (0.7)	0.2	0.69 (0.40–1.18)	—
Atrial fibrillation	24 (0.6)	0.2	25 (0.6)	0.2	0.96 (0.55–1.68)	—
Death from cardiovascular causes	18 (0.4)	0.1	25 (0.6)	0.2	0.72 (0.39–1.32)	—
Death from any cause	67 (1.6)	0.5	64 (1.5)	0.5	1.11 (0.78–1.56)	—
Major adverse cardiac events‡	100 (2.4)	0.7	138 (3.2)	1.0	0.72 (0.56–0.93)	—

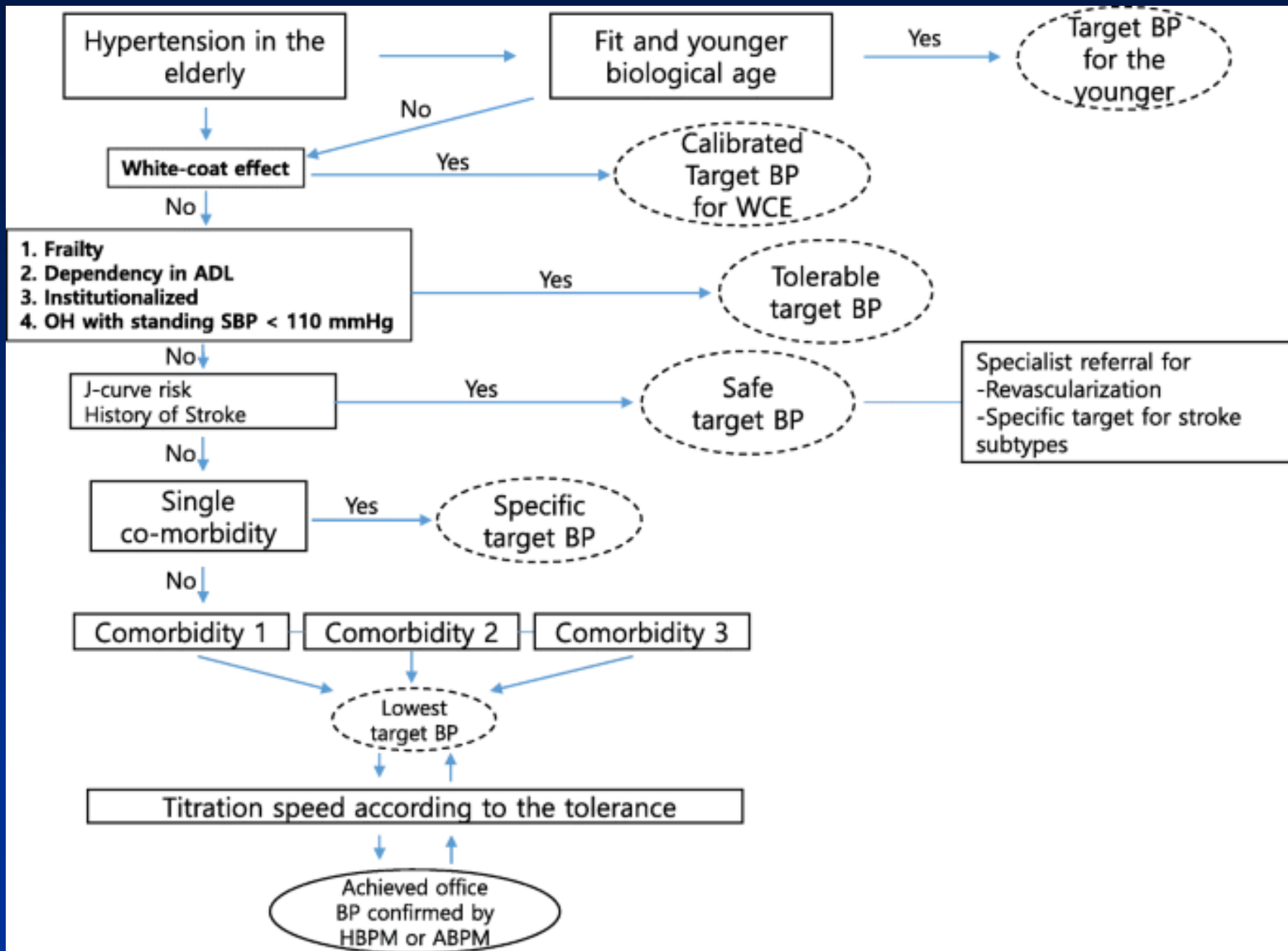
Zhang W, et al NEJM 2021; 385, 1268-1279. (Sep 30, 2021)

STEP Trial: Safety

Table 3. Safety and Renal Outcomes Related to the Blood-Pressure Intervention.*

Outcome	Intensive Treatment (N=4243)	Standard Treatment (N=4268)	Relative Risk (95% CI)	P Value
Safety outcomes — no. of patients (%)				
Adverse events				
Hypotension†	146 (3.4)	113 (2.6)	1.31 (1.02–1.68)	0.03
Dizziness‡	45 (1.1)	49 (1.1)	0.92 (0.61–1.39)	0.70
Serious adverse events				
Syncope§	6 (0.1)	2 (<0.1)	3.02 (0.61–14.97)	0.18
Fracture¶	15 (0.4)	19 (0.4)	0.79 (0.40–1.56)	0.50
Renal outcomes — no. of patients/total no. (%)				
Reduction in eGFR				
≥50% reduction in patients with chronic kidney disease at baseline	1/99 (1.0)	1/97 (1.0)	1.01 (0.06–16.09)	0.99
≥30% reduction to <60 ml/min/1.73 m ² in patients without chronic kidney disease at baseline	55/4081 (1.3)	61/4117 (1.5)	0.90 (0.63–1.30)	0.58
Elevation in serum creatinine level				
>1.5 mg/dl elevation in men	70/1953 (3.6)	70/1938 (3.6)	0.99 (0.71–1.39)	0.95
>1.3 mg/dl elevation in women	43/2227 (1.9)	48/2276 (2.1)	0.91 (0.60–1.38)	0.67
eGFR <30 ml/min/1.73 m ²	12/4243 (0.3)	13/4268 (0.3)	0.93 (0.42–2.04)	0.85

* The relative risks, 95% confidence intervals, and P values were calculated with the use of a logistic-regression model, with the standard-



Rethinking the Association of High Blood Pressure With Mortality in Elderly Adults

The Impact of Frailty

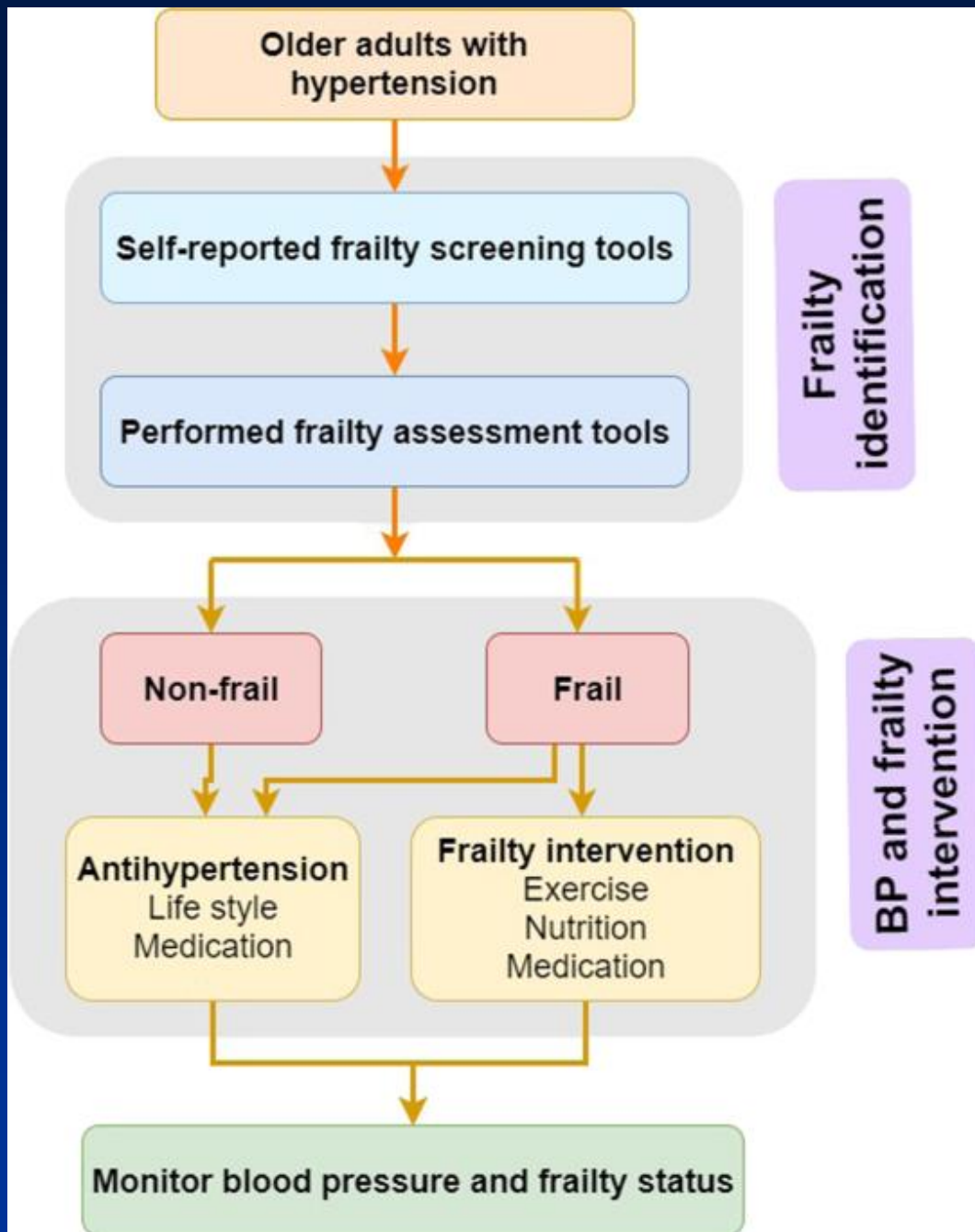
Michelle C. Odden, PhD; Carmen A. Peralta, MD, MAS; Mary N. Haan, DrPH; Kenneth E. Covinsky, MD, MPH

- Observational study done to help determine if frail or healthy status, rather than age alone, may determine who benefits from treatment for high BP (in this study $>140/90$)
- Frailty was determined by walking speed
- Slow or fast walkers determined by ability to walk 0.8 meters/second (75 feet in 30 sec)
- 2340 people mean age 74, over 7 years



Highlights

- 589 deaths from 2340 people
- Association between BP and mortality varied by walking speed
- Among faster walkers (who had fewer comorbidities), those with higher SBP (>140) had higher risk of death
- Among slower walkers, neither higher SBP or DBP was associated with death
- Among those who could not complete walk test, elevated BP strongly associated with lower risk of death
- Perhaps frail adults need higher SBP to perfuse vital organs and should be treated less aggressively



SOURCE: Liu, P., Li, Y., Zhang, Y. *et al.* Frailty and hypertension in older adults: current understanding and future perspectives. *Hypertens Res* **43**, 1352–1360 (2020). <https://doi.org/10.1038/s41440-020-0510-5>

Case 3

- An 85 yr old woman is seeking a second opinion because her PCP advised her to take lisinopril-HCTZ to lower her BP. She only takes multivitamins. Her clinic and home BPs over the past 2 years have ranged from 158/60 to 180/72, consistent with isolated systolic hypertension (ISH).
- She has no diabetes, MI, or stroke, but her mother died from a stroke at age 77.
- BP is 172/65. She has no edema. Cre=0.8, UA is negative.
 - You should advise her that:
 - A. She should have 24-hour ABPM because she likely has white-coat HTN
 - B. ISH is normal with ageing and requires no therapy
 - C. Although ISH should be treated in most, there are no data pertaining to women of her age
 - D. Taking lisinopril-HCTZ may reduce her chances of dying and/or developing congestive heart failure during the next 2 years

Key Take-Homes

- Consider SGLT2i and nsMRA for treatment of HTN
- Reducing BP to <120 systolic in non-diabetic patients; lower BP may be beneficial even among patients with “normal” BP
- Treating HTN in very elderly (>80 y) is associated with a reduced risk of fatal stroke, CHF, and death
 - Assess frailty in elderly patients w/ HTN
 - Be cautious in frail patients
- **QUESTIONS?**