Hypertension In Elderly: Pathophysiology And Treatment Strategy

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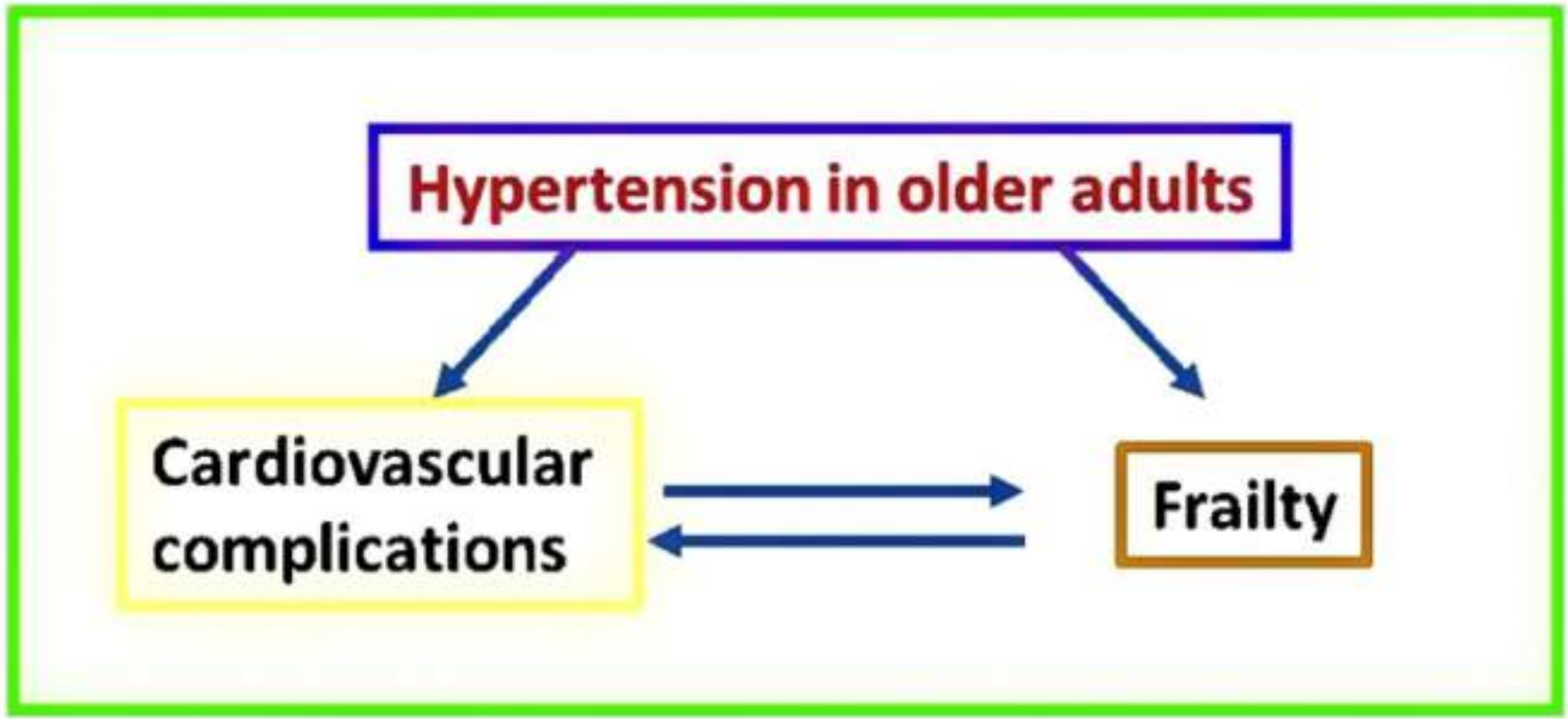
Introduction:

- Hypertension is frequently found in patients aged 65 or older
- It represents a risk factor for various cardiovascular diseases :
  - heart failure
  - atrial fibrillation
  - stroke
  - kidney diseases
  - dementia
- Hypertension in the elderly is associated with an accelerated decline in health status and frailty
- Frailty is defined as a condition of increased vulnerability to stressors leading to a reduced ability to combat potential acute negative events and reduced ability to maintain homeostasis. Frailty can lead to an increased risk of adverse health outcomes
- Hypertension and frailty are closely interconnected. Hypertension may lead to frailty and may produce frailty and disability through cardiovascular complications.

Figure 1. Inter-relationship between hypertension, cardiovascular complication and frailty.



Hypertension and frailty are closely interconnected. Hypertension may lead to frailty and may produce frailty and disability through cardiovascular complications.

Evidence:

- Hypertension increases with age, with its prevalence increasing from 27% in patients aged younger than 60 years to 74% in those aged older than 80 years.
- There is strong evidence of the benefits of treating hypertension in the elderly. Recent data demonstrates CVD benefits in treating hypertension in older adults.
  - UK Prospective Diabetes Study (UKPDS)
  - The Systolic HTN in the Elderly Program (SHEP)
  - SPRINT
  - The Systolic HTN in Europe trial (Syst-Eur)
  - Medical Research Council Working Party
  - The HTN in the Very Elderly Trial (HYVET)

Pathophysiology:

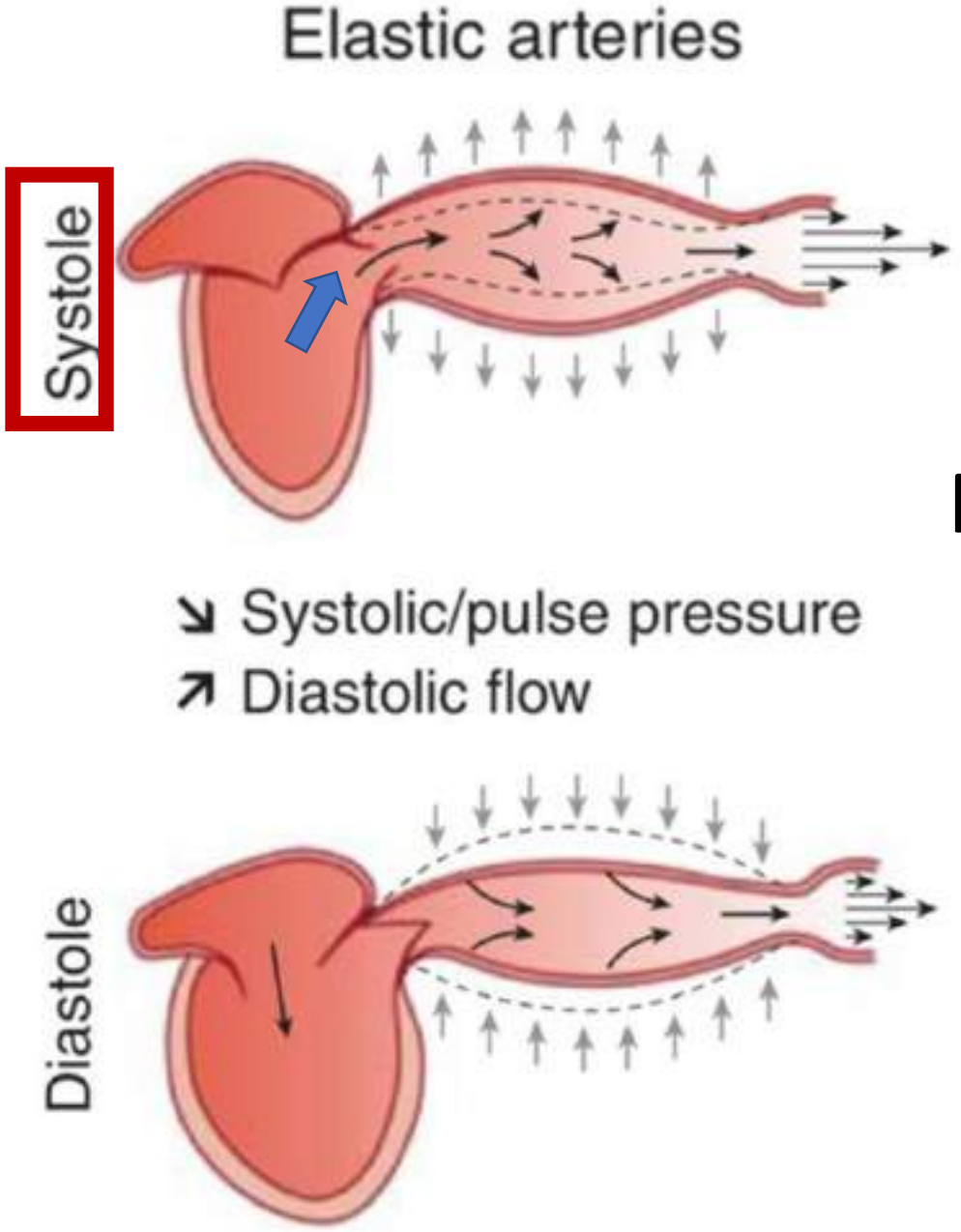
- There are specific underlying mechanisms of HTN in older persons:
  - mechanical hemodynamic changes
  - arterial stiffness
  - neuro- hormonal and autonomic dysregulation
  - the aging kidney

Pathophysiology:

- Over time, the arteries stiffen, with fracturing of the elastic lamellae and intimal hyperplasia is seen in the aorta.
- The stiffened arteries have decreased capacitance, and limited recoil, with subsequent difficulty to accommodate volume changes throughout the cardiac cycle.
- Both systolic BP (SBP) and diastolic BP (DBP) increase with age, however, after the age of 60 years, the central arterial stiffness predominates, and as a consequence, SBP continues to rise while the DBP declines thereafter.
- This results in isolated systolic HTN and a widened pulse pressure

Pathophysiology:

- Furthermore, there are hemodynamic mechanical changes that alter wave reflection causing a reduction in the aortic elasticity, as well as loss of recoil during diastole.
- There is also increase in pulse pressure and pulse-wave velocity.
- The change in arterial structure causes an increase in the reflected pressure waves added to the forward pressure waves in the ascending aorta that further augments the central SBP.

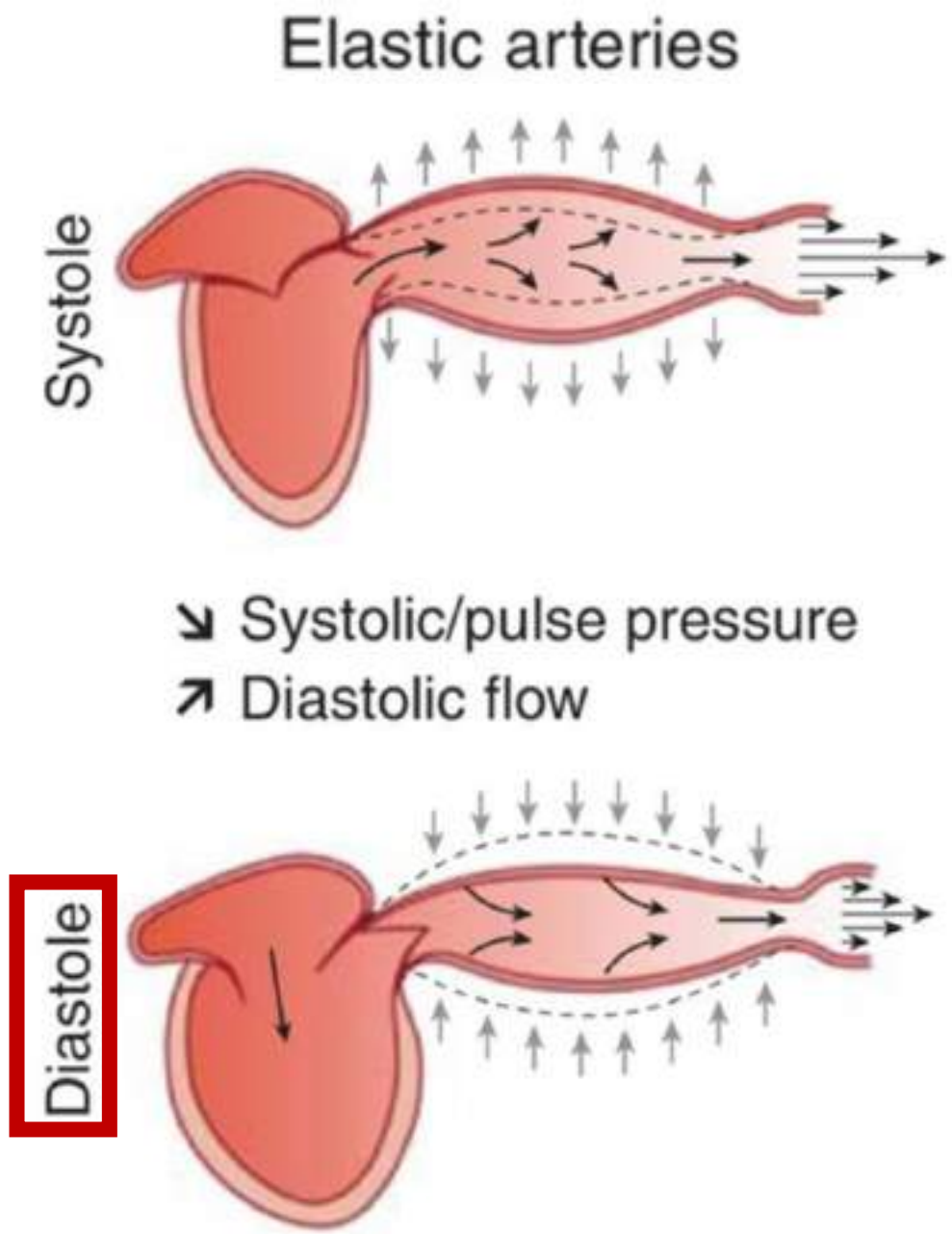


↑ Low pressure
to stretch
elastic aorta.

Part of the heart energy
in distension of arterial
wall.

Energy “stored”
in vessel walls during
systole, recoils aorta
during diastole.

Briet M. et al. Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int. (2012) 82:388–400. doi: 10.1038/ki.2012.131



Squeezes accumulated blood forward into the peripheral tissues:
= sustains diastolic flow.

S. Laurent et al. Arterial Stiffness and Hypertension in the Elderly. Frontiers in Cardiovascular Medicine. doi:10.3389/fcvm.2020.544302
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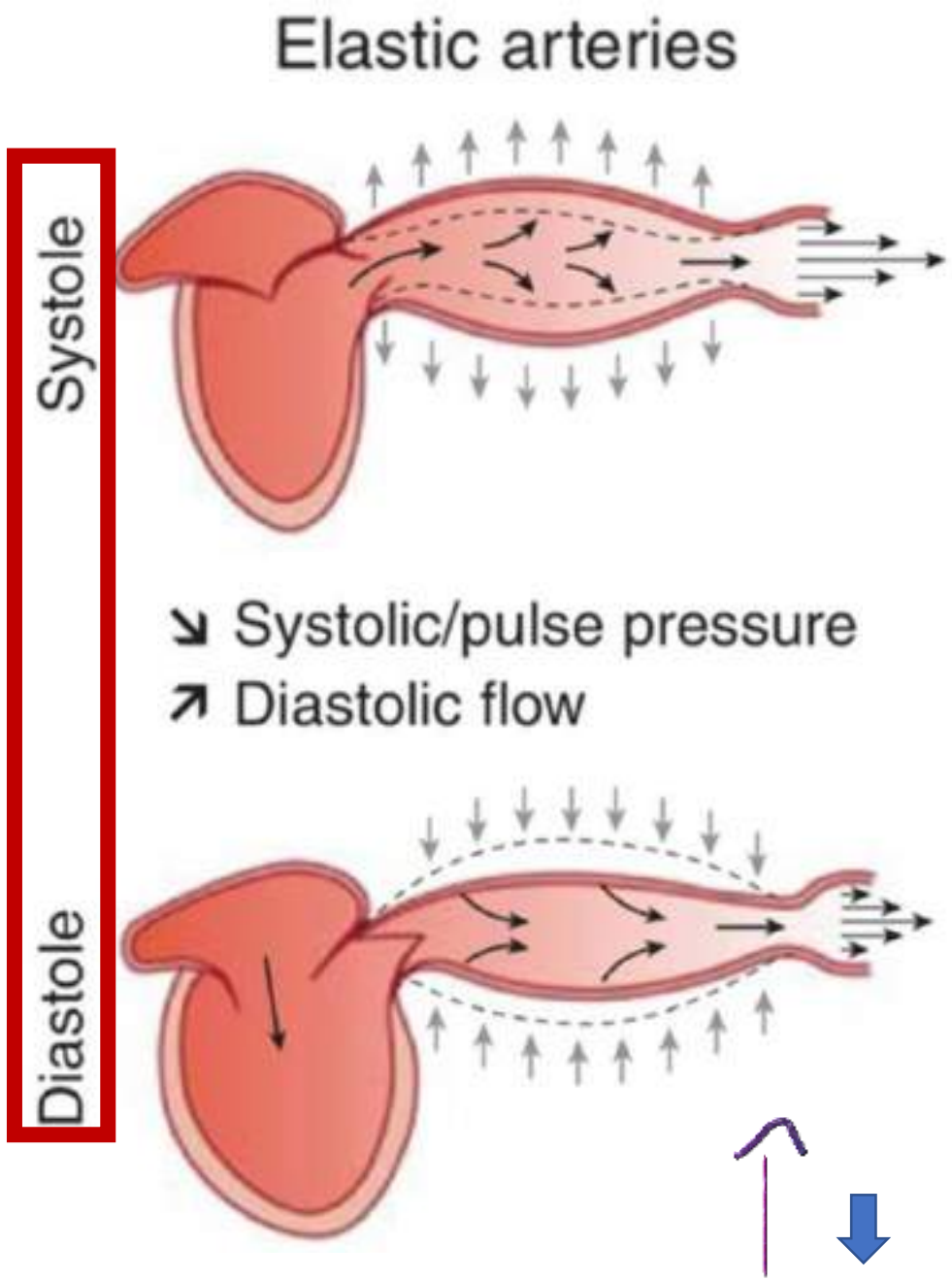

Compliant thoracic aorta
= dampens ventricular ejection pulsatility

Proximal pulsatile pressure/flow

Continuous distal pressure/flow

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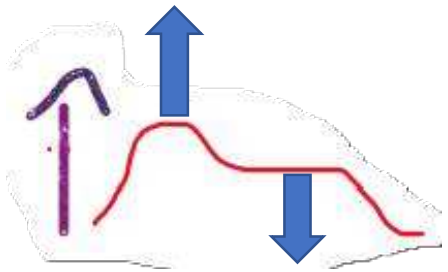
Briet M. et al. Arterial stiffness and pulse pressure in CKD and ESRD. Kidney Int. (2012) 82:388–400. doi: 10.1038/ki.2012.131

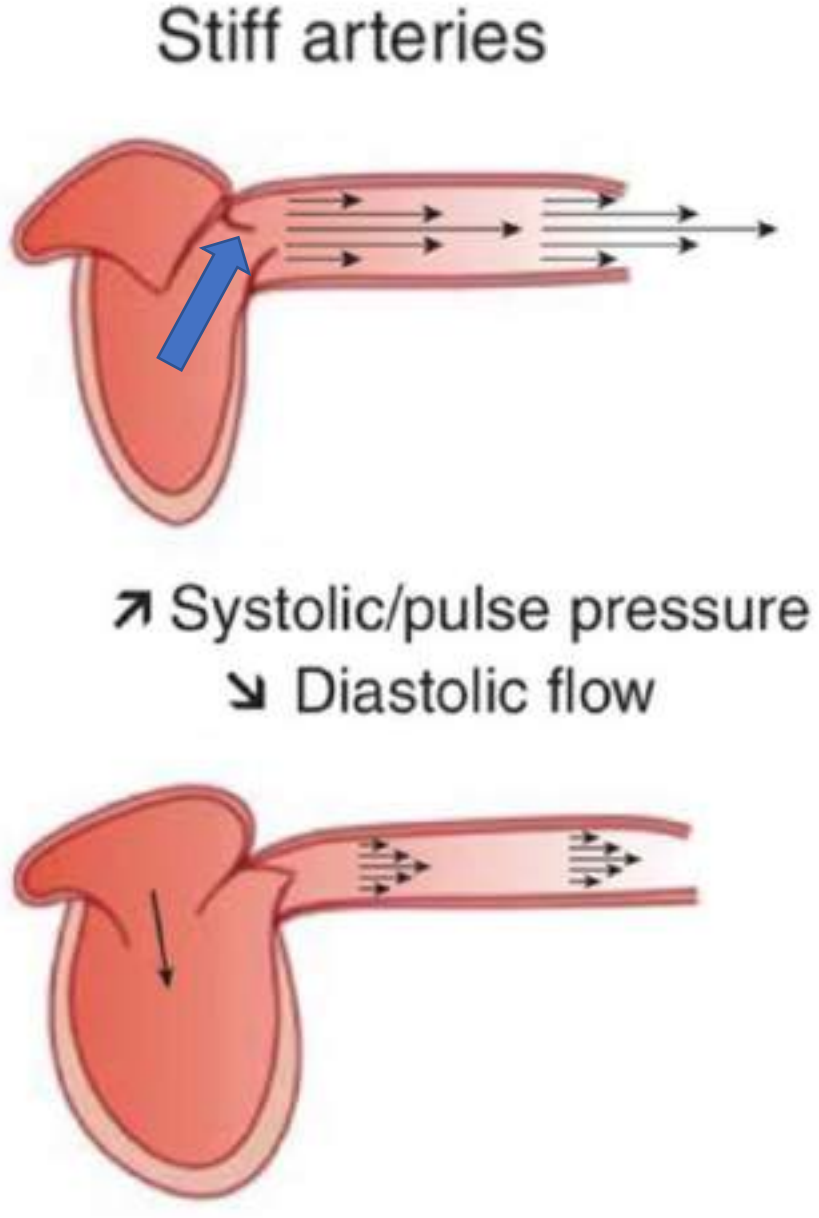
IN SYSTOLE:

↑ **higher pressure** necessary **to stretch** a more **rigid aorta**.

Larger proportion of **stroke volume** flows **through** the **arterial system** and peripheral **tissues**.

= **intermittent distal flow** and pressure.





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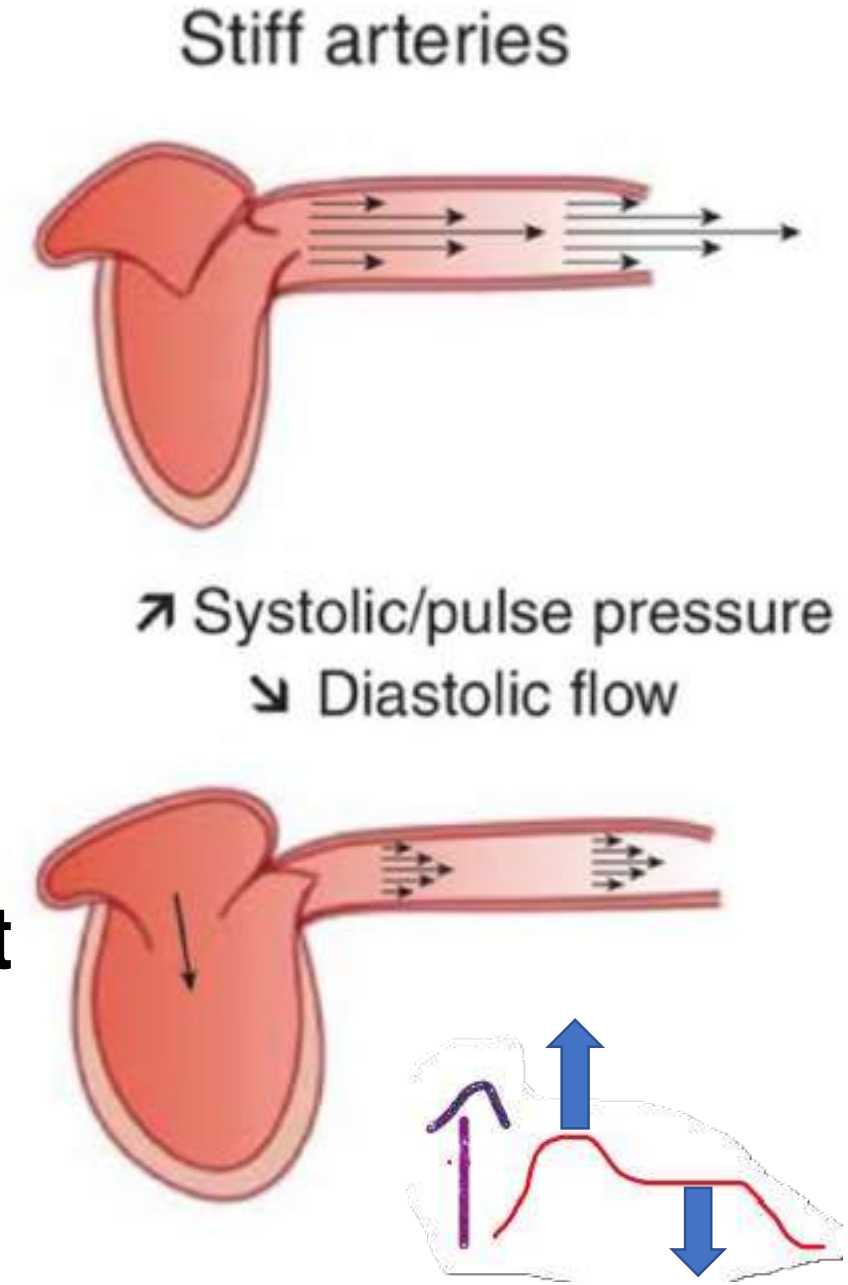
IN SYSTOLE:

= **exaggerated flow** and **pressure pulsatility** at **the site of distal small resistance**

brain-kidney: inward remodeling reduce lumen diameter to protect microcirculation from pulsatile stress

= **shorter capillary transit time.**

= **reduces metabolic exchanges.**



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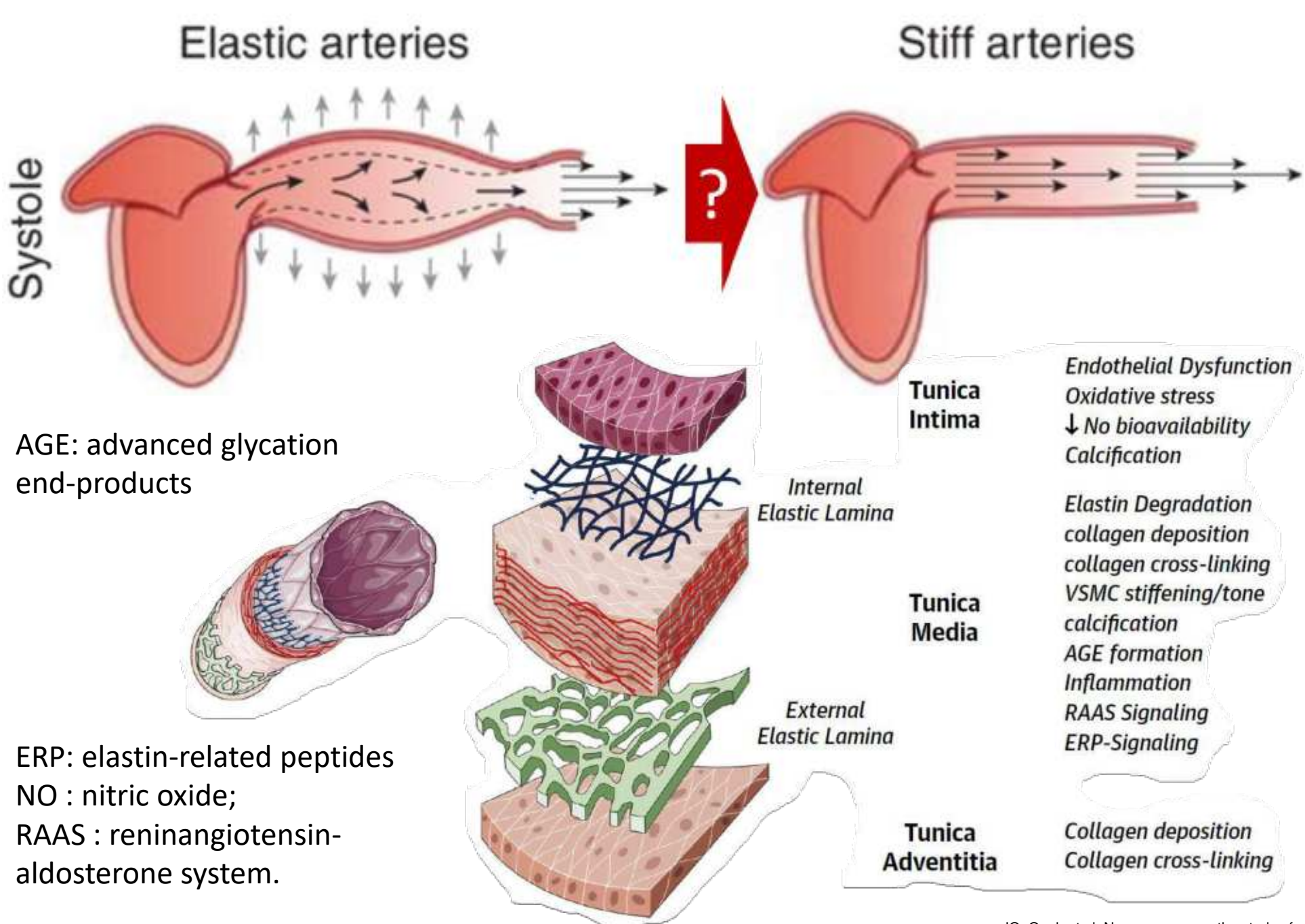


AGE: advanced glycation end-products

ERP: elastin-related peptides
NO : nitric oxide;
RAAS : reninangiotensin-aldosterone system.

Julio A. Chirinos et al. Large-Artery Stiffness in Health and Disease.J Am Coll Cardiol 2019;74:1237–63.

S. Laurent et al. Arterial Stiffness and Hypertension in the Elderly. Frontiers in Cardiovascular Medicine doi:10.3389/fcvm.2020.544302.

JO. Onuh et al. New progress on the study of aortic stiffness in age-related hypertension. J Hypertens. 2020 October;38(10):1871–1877.

Pathophysiology:

- Over time, endothelial dysfunction occurs, inducing an elevation in endothelin-1 and decreasing bioavailability of nitric oxide, which affects arterial dilation.
- Other neurohormonal mechanisms include a decline in the renin-angiotensin aldosterone system, with plasma renin levels by age 60 declining to 40% to 60% of younger individuals.
- Plasma aldosterone levels also decrease, predisposing individuals to drug-related hyperkalemia.
- Some authors have described increased peripheral plasma norepinephrine related to age which is thought to be a compensatory mechanism for reduction in beta-adrenergic responsiveness with aging.

Pathophysiology:

- The aging changes in the kidney are increased salt sensitivity due to a decline in the activity of the sodium/potassium and calcium adenosine triphosphate pumps, which prompts vasoconstriction and vascular resistance.

Special Conditions

Orthostatic Hypotension:

- Reduced baroreflex sensitivity with age and loss of artery compliance causes orthostatic hypotension, defined as a reduction in SBP by at least 20 mmHg or DBP by at least 10 mmHg within 3 minutes of standing.
- Orthostatic hypotension carries a prevalence of 18% in older adults and is associated with increased falls and cerebrovascular effects.
- It was showed that beta-blockers were associated with increased likelihood of developing orthostatic hypotension.
- The older adults rely on an increased cardiac output due to increased heart rate, as opposed to changes in their stiff arteries to achieve postural homeostasis.
- There is also evidence of orthostatic HTN and its association with cerebrovascular events in older adults.

Postprandial Hypotension:

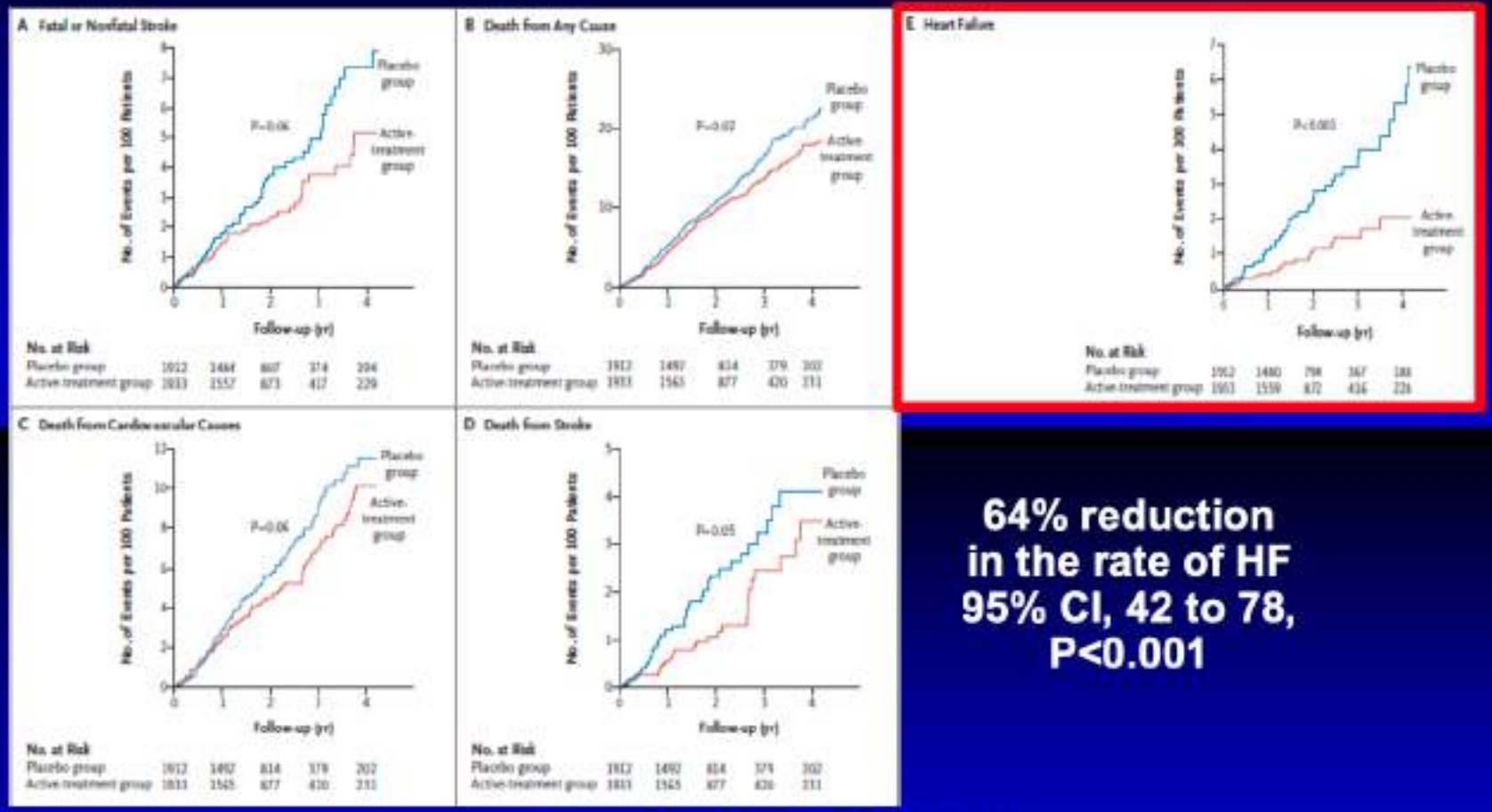
- Postprandial hypotension in geriatric patients is an under recognized cause of syncope.
- The mechanism is unclear, but it appears to be related to reduced sympathetic response to a meal.
- Ambulatory BP monitoring and symptoms can give a diagnose.
- The patient can be advised to increase water intake before eating or substituting six smaller meals daily for three larger meals.
- Older adults have an increase frequency of postprandial hypotension.
- Patients with HF, syncope, Parkinson's disease, end-stage renal disease on dialysis, autonomic dysfunction can have postprandial hypotension.
- Frail older adults with postprandial hypotension increase their postprandial BP and heart rate when walking.

Treatment

Evidence:

- Systolic Hypertension in the Elderly Program (SHEP)
- Systolic Hypertension in Europe trial (Syst-Eur)
- Hypertension in the Very Elderly Trial (HYVET)
  - All these three trials defined ISH as SBP ≥160 and DBP <90 mmHg.
  - Based on the data mainly from HYVET study, the 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the management of HTN stated that there is evidence for benefits of lowering the SBP to <150 mmHg in older adults with initial SBP of >160 mmHg.
- Recently, SPRINT trial added to this evidence base and showed the benefits of a lower BP goal of SBP <120 mmHg in patients aged over 75 years

Treatment of Hypertension in Patients 80 Years or Older



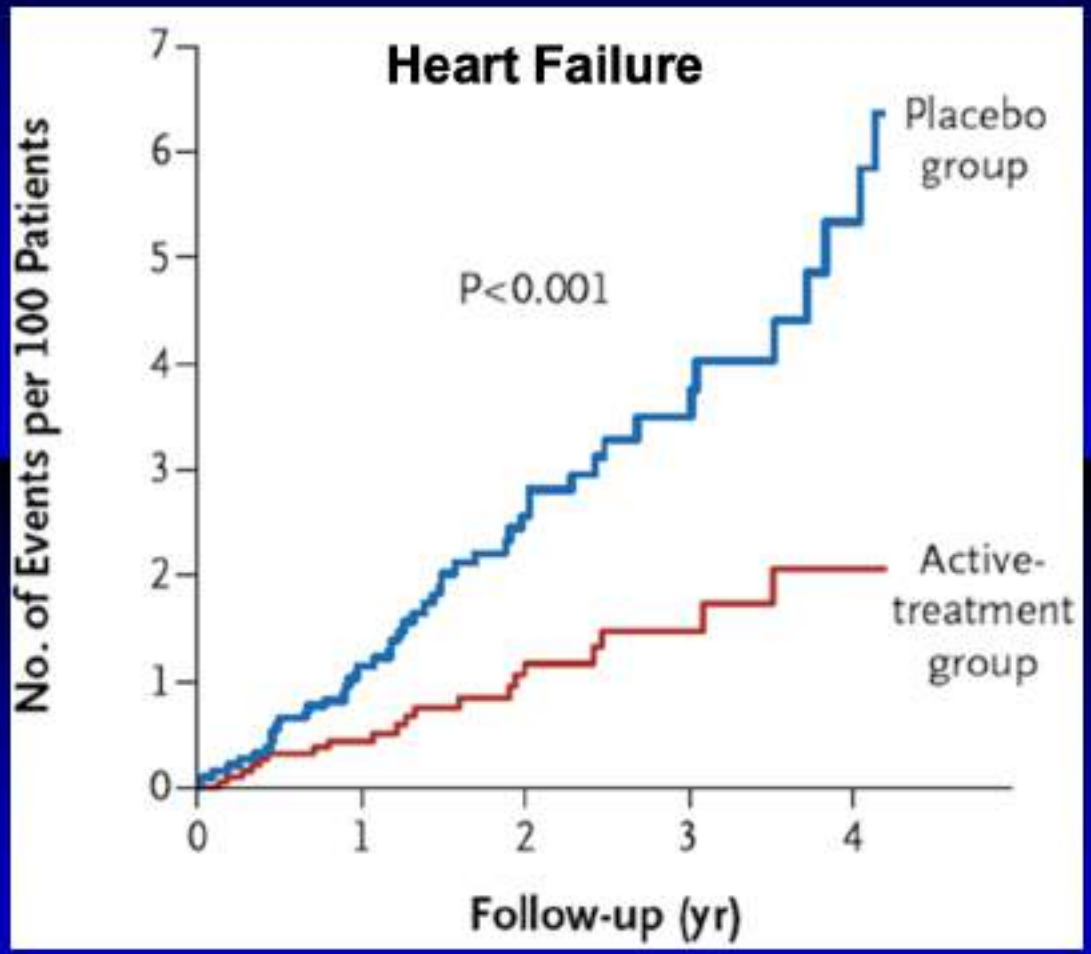
64% reduction in the rate of HF 95% CI, 42 to 78, P<0.001

Diuretics ±ACE inhibitors

HYVET – NEJM 2008;358:1887-98

Hypertension in the Very Elderly Trial (HYVET)

N=3845 patients > 80 years of age;
indapamide + perindopril to achieve target of 150/80 mmHg vs. Placebo



Beckett et al, N Engl J Med 2008;358

Target:

- Despite this convincing evidence of the benefit of antihypertensive treatment in older adults with HTN, the optimal BP target has remained unclear in this population.
- This mostly derives from the higher vulnerability of older adults to develop complications from the antihypertensives such as orthostasis, falls and renal dysfunction due to their burden of comorbidities, advanced age and frailty.
- Choosing a target blood pressure in older adults with hypertension requires discussion between physician and the patient taking into consideration several factors such as the burden of comorbidity, life expectancy, clinical judgment, and patient preference.

Target:

- While the SPRINT and HYVET studies support blood pressure control even in frail individuals, analysis of NHANES data by Odden et al suggest that impaired walking speed (a surrogate for frailty) may assist in risk stratifying frail seniors.
- In slower walkers (<0.8 m/s), elevated SBP and DBP (≥140/90) were not associated with mortality.
- Observational data suggests that BP reductions in the frail individuals may be harmful.

Target:

- A meta-analysis identified that between 40 to 69 years of age, each difference of 20 mmHg in the SBP or 10 mmHg increase of DBP is associated with more than 2-fold difference in stroke-related death, death due ischemic heart disease and from other vascular etiologies.
- Differences were about half as extreme between ages 80 to 89 years. Data from The Second National Health and Nutrition Examination Survey (NHANES II) and SHEP trial showed that in the elderly, there is a linear relationship between CVD risk, specifically in stroke, and increasing SBP (the absolute stroke risk in the place group of the SHEP trial was 8.2% over 5 years, compared to the 5% present in the patients that received treatment).
- The HYVET randomized control trial enrolled individuals age ≥ 80 with a SBP of at 160 mmHg to receive indapamide or placebo, and demonstrated a 21% relative reduction in all-cause mortality and a 23% relative reduction in CVD mortality after a median of 1.8 years under treatment.

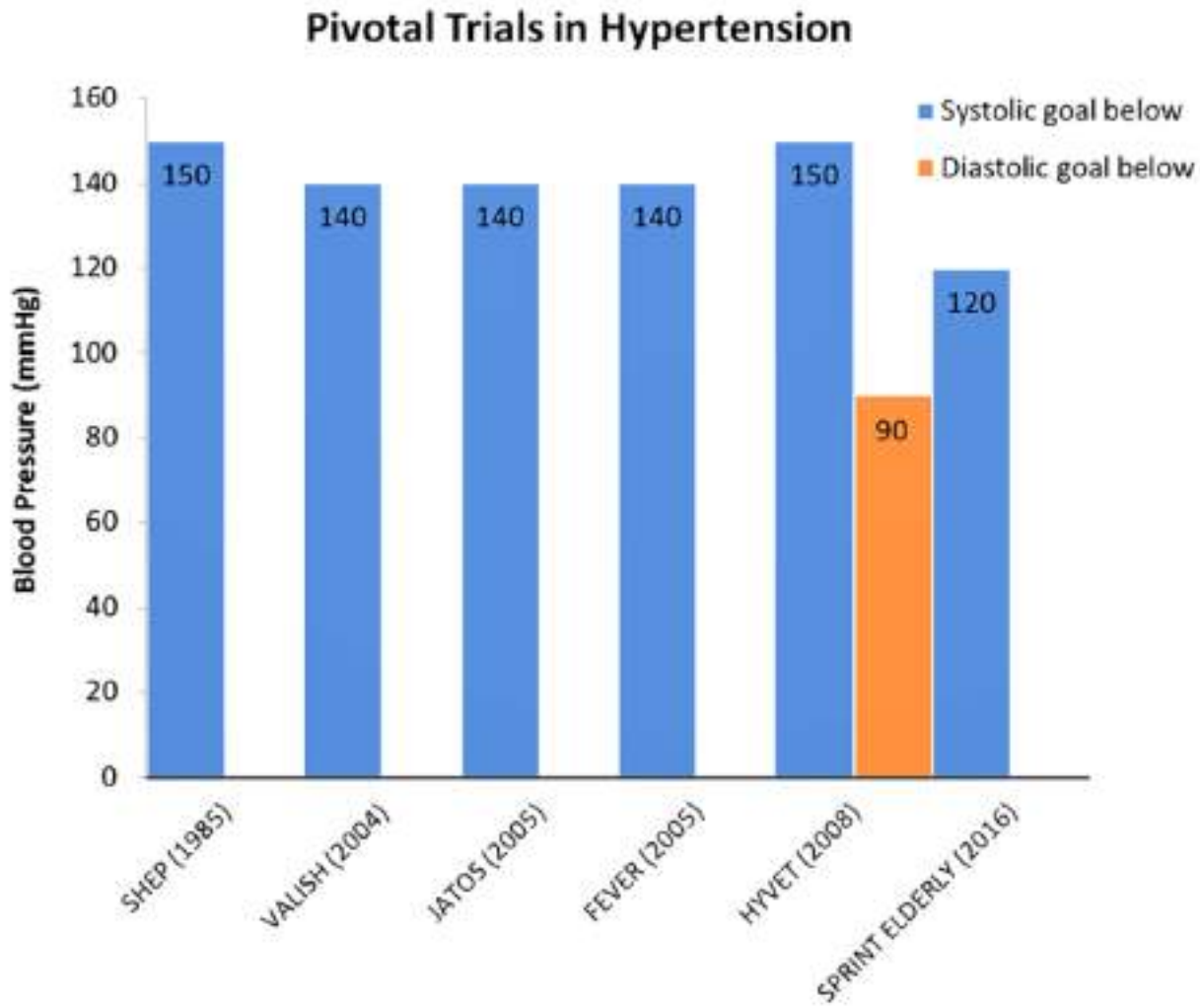


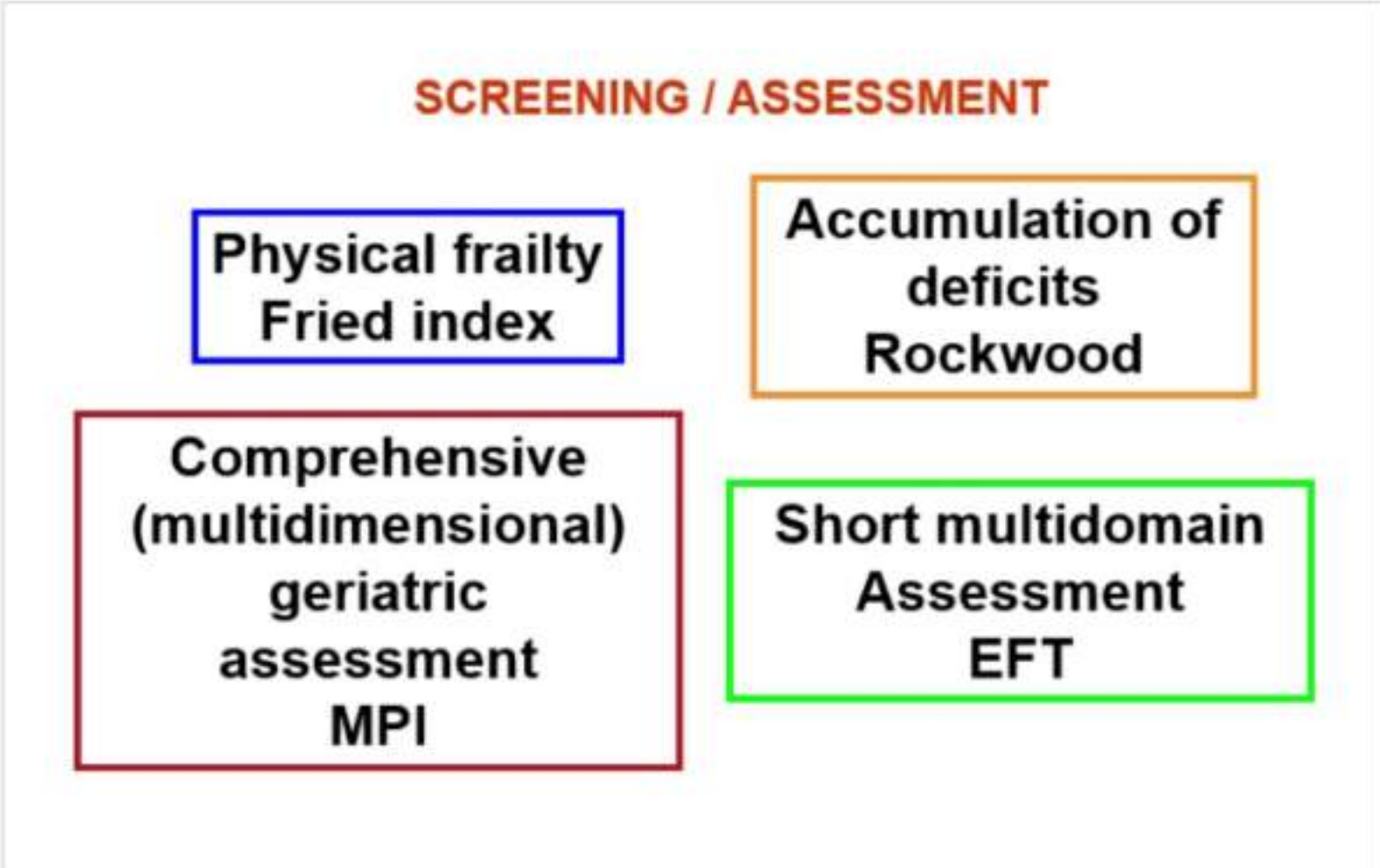
FIGURE 1 Blood pressure goals in pivotal clinical trials: demonstrated in chronologic order from 1985 to 2016 the systolic and diastolic blood pressure goals in mmHg. We are able to appreciate a remarkable difference in SPRINT ELDERLY compared to prior

TABLE 1 Chronological order of the guidelines for the management of high blood pressure in adults and the elderly

Organization	Year	Population	Target Blood Pressure	Considerations for the elderly
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[55]	2003	All adults except those with diabetes or chronic kidney disease Adults with diabetes or chronic kidney disease	<140/90 mmHg <130/80 mmHg	Encourage low sodium and alcohol-free lifestyle Avoid DBP <50-60 mmHg
ACCF/AHA 2011 for the elderly[32]	2011			
European Society of Hypertension/European Society of Cardiology (ESH/ECS)[44]	2013	All adults except those with diabetes Adults with diabetes	140-150 mmHg systolic; consider <140 mmHg if the patient is fit and healthy <85 mmHg DBP	Ages ≥80 years, the patient's mental capacity and physical heath should also be considered if targeting to <140 mmHg Screen for Orthostatic Hypotension before initiating therapy Avoid DBP < 55 mmHg
Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[56]	2014	Adults age < 60 years and those >18 with diabetes or chronic kidney disease	<140/90 mmHg	Adults age ≥ 60 years Goal: <150/90 mmHg If CKD or DM <140/90 mmHg
American Heart Association/American College of Cardiology (ACC)/Centers for Disease Control and Prevention (AHA/ACC/CDC)[59]	2014	All adults	<140/90 mmHg	No age-specific guidelines
American Society of Hypertension/ International Society of Hypertension (ASH/ISH)[58]	2014	Adults ages 18-79 years	<140/90 mmHg; <130/80 mmHg BP target may be considered in younger adults	Adults ages ≥80 years Diagnose of HTN only if SBP >150 mmHg Goal: <150/90 mmHg
Department of Veterans Affairs/Department of Defense (VA/DoD)[60]	2014	All adults Adults with diabetes	<150/90 mmHg <150/85 mmHg	No age-specific guidelines
American Heart Association/American College of Cardiology/American Society of Hypertension (AHA/ACC/ASH)[61]	2015	Adults with CAD, except as noted below Adults with MI, stroke, TIA, carotid artery disease, peripheral artery disease or abdominal aortic aneurysm	<140/90 mmHg <130/80 mmHg	Adults ages >80 years Goal: <150/90 mmHg
American College of Cardiology/American Heart Association (ACC/AHA)[1]	2017	All adults	<130/80 mmHg	≥65 + ambulatory: Goal <130 mmHg ≥65 + high burden of comorbidity, limited life expectancy, clinical judgment, patient preference: assess risk/benefit
Hypertension Canada[62]	2017	All adults	<140/90 mmHg	Age 60-79: goal <140/90 mmHg Age > 79: goal <150/90
American College of Physicians-elderly[48]	2017			≥60 years: goal <150 mmHg If TIA <140 mmHg
European Society of Hypertension/European Society of Cardiology[2] (ESH/ECS)	2018	All Adults	<140/90 mmHg	≥60 years: goal <150/90 mmHg, if tolerate <140 mmHg do not change therapy

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; MI, myocardial infarction; TIA, transient ischemic attack.

Figure 2. Screening/assessment of frailty.



The figure indicates some of the validated screening/assessments for frailty according to the subtype of frailty investigated. EFT: essential frailty toolset; MPI: multidimensional prognostic index

TABLE 21. Adapting BP-lowering strategies in patients older than 80 years according to their functional/autonomy status

Characteristics	Group 1 Fit	Group 2 Slowed but autonomous for most activities	Group 3 Severely dependent
Diagnosis	-ADL (Katz) ≥5/6 and -absence of clinically significant dementia (MMSE≤20/30) and -routine walking activities	-Profile between Groups 1 and 3	-ADL (Katz) ≤2/6 or -severe dementia or -(MMSE ≤10/30), chronic bedridden or -end of life
Therapeutic strategy	- As recommended below	-Individualize treatment	-Individualize treatment -Prioritize therapeutic strategies according to comorbidities and polypharmacy issues

Katz Index of Independence in Activities of Daily Living (ADL) is a scale rated from 0 (completely dependent) to 6 (completely autonomous). This scale comprises 6 ADL: Bathing, Dressing, Toileting, Transferring, Feeding and Continence. For each ADL, '0' means that the person is unable to do it without assistance, 0.5 need of some assistance, 1 no need of any assistance [970]. MMSE, Mini mental status evaluation.

Recommendations and statements	CoR	LoE
Patients 65 to 79 years old		
The recommended office threshold for initiation of drug treatment is 140/90 mmHg.	I	A
The primary goal of treatment is to lower BP to <140/80mmHg	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	I	B
Patients 65 to 79 years old with ISH		
The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.	I	A
However, a reduction of office SBP in the 130 to 139 mmHg range may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
In dedicated RCTs in older patients with ISH, CCBs and Thiazide/Thiazide-like diuretics have been mainly used. However, all other major drug classes can be used, because of the frequent co-existence of compelling indications and the need of combination therapy to control SBP.	I	A
Initiation of treatment with a two-drug combination is also recommended in most older patients with ISH, who are not frail.	I	C
Patients ≥80 years old		
The recommended office SBP threshold for initiation of drug treatment is 160 mmHg.	I	A
However, a lower SBP threshold in the 140 to 160 mmHg range may be considered.	II	C
Office BP should be lowered to a SBP in the 140 to 150 mmHg range and to a DBP <80mmHg.	I	A
However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B
Additional recommendations		
In frail patients, initiation of drug treatment and the treatment	I	C
Do not aim to target office SBP below 120 mmHg or DBP below target for office SBP and DBP should be individualised. 70 mmHg during drug treatment.	III	C
However, in patients with low office DBP, i.e. below 70 mmHg, SBP should be still lowered, albeit cautiously, if on-treatment SBP is still well above target values	II	C
Reduction of treatment can be considered in patients age 80 years or older with a low SBP (<120mmHg or in the presence of severe orthostatic hypotension or a high frailty level	III	C
Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥ 80 years, is not recommended, if treatment is well tolerated.	III	B
In older patients, treatment should start with lower doses and uptitration should be slower.	I	C
The search for orthostatic hypotension in old patients should be systematic, even in the absence of symptoms. Back titration or discontinuation of BP lowering drugs should be considered in patients with orthostatic hypotension.	I	C
In old patients with hypertension there should always be an assessment of functional/autonomy status including cognitive function.	I	C
In patients with reduced functional/autonomy status and/or dementia treatment should be individualized.	I	C

Non-pharmacologic Interventions :

- Regular physical activity
- Weight control
- Smoking cessation
- Stress reduction
- Avoidance of excessive alcohol intake
- Reduction is sodium intake
- Potassium supplementation!!!
- Calcium or magnesium supplements
- Consumption of probiotics, fiber, flaxseed, increased protein intake,
- Consumption of garlic, dark chocolate, tea, coffee, and fish oil.

Non-pharmacologic Interventions :

- Behavioral therapies:
  - Transcendental meditation
  - Yoga
  - Taiichi
  - Biofeedback
- Treatment of co-morbidities:
  - Sleep apnea
  - Renal artery stenosis
  - Prostatism
  - Primary aldosteronism

Treatment:

- Review the patients medications to ensure they are not on any medications which can cause HTN:
  - Non- steroidal anti-inflammatory drugs
  - Steroids
  - Angiogenesis inhibitors
  - Tyrosine kinase inhibitors
  - Atypical antipsychotics, antidepressants, amphetamines
  - Hormone replacement therapy
  - Immunosuppressants
  - Decongestants
  - Use of recreational drugs, caffeine, tea and herbal supplements should also be inquired.

Pharmacologic Treatment:

- Factors to consider prior to selecting a medication:
  - Comorbidities
  - Frailty
  - Ability to follow instructions
  - Complexity of the current regimen
  - Supporting care (ie, spouses and family)
  - Electrolytes and renal function
- Thiazide diuretics, angiotensin-converting-enzyme inhibitor (ACEI), angiotensin II receptor blockers (ARB), and calcium channel blocker (CCB), have all shown benefit on CVD outcomes in older age patients.
- Unless clinically indicated by comorbidities, beta blockers should not be used as first line medications because they may worsen CVD outcomes in those over 60 years of age.
- Loop diuretics and alpha-blockers should also be avoided given their association with falls.

Pharmacologic Treatment:

- ALLHAT trial which suggested that low-dose daily chlorthalidone was most effective in the population.
- Anglo- Scandinavian Cardiac Outcomes Trial-blood-pressure-lowering arm (ASCOT-BPLA) which showed significant overall mortality benefit in subjects aged >60 years when given a combination of CCB and ACE-I.
- Commonly, BP remains uncontrolled on monotherapy and a combination of different agents is needed to achieve adequate BP control.
- Any of the four first line BP medications can be combined, however based on multiple RCTs RAAS blockers and CCB/thiazide is the preferred combination.
- Single pill combination can be utilized with the added benefit of improving medication compliance.
- The medications should then be up titrated, with additional medications added as needed to achieve BP targets.

Pharmacologic Treatment:

- Initiation of any medication should be done with assessment of orthostatic hypotension and gradual titration according to tolerance.
- Renal function should be assessed to detect possible increases in serum creatinine and reductions in GFR as a result of BP-related reductions in renal perfusion.
- Hypokalemia is also an important side effects of diuretics which needs to be monitored.
- The medical team needs to be cognizant of treatment related side effects which may occur more frequently than reported in clinical trials.

Conclusion:

- Hypertension in the elderly should be treated to reduce morbidity and mortality.
- Blood pressure targets in older adults should be tailored on an individualised basis, according to the presence of orthostatic hypotension, comorbidities, potential polytherapy, and the potential presence of frailty.
- A major concern when treating older patients with antihypertensive drugs should be hypotension, particularly orthostatic hypotension and post-prandial hypotension.
- Teratment should be individulaised for every single patient.