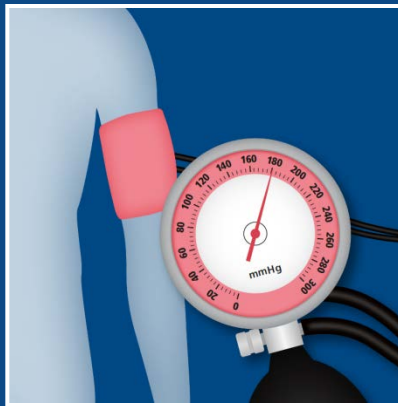


Nephro Update Europe 2017

6-7 October, Vienna

Hypertension



Ton Rabelink, Netherlands

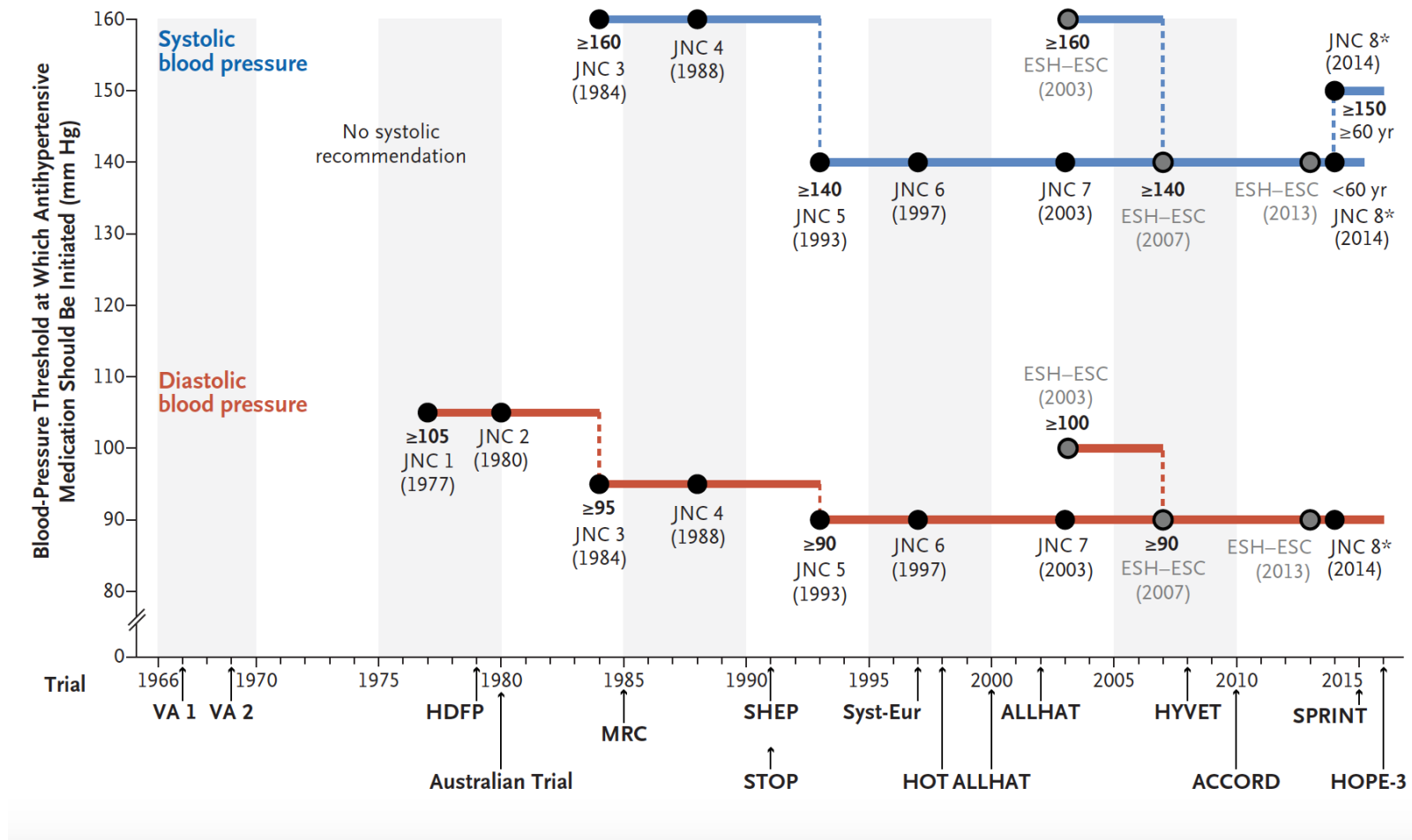
Hypertension

- The blood pressure target
- Therapy-resistant hypertension and devices
- Update on drug therapy
- Capita selecta
- New pathophysiology

Hypertension

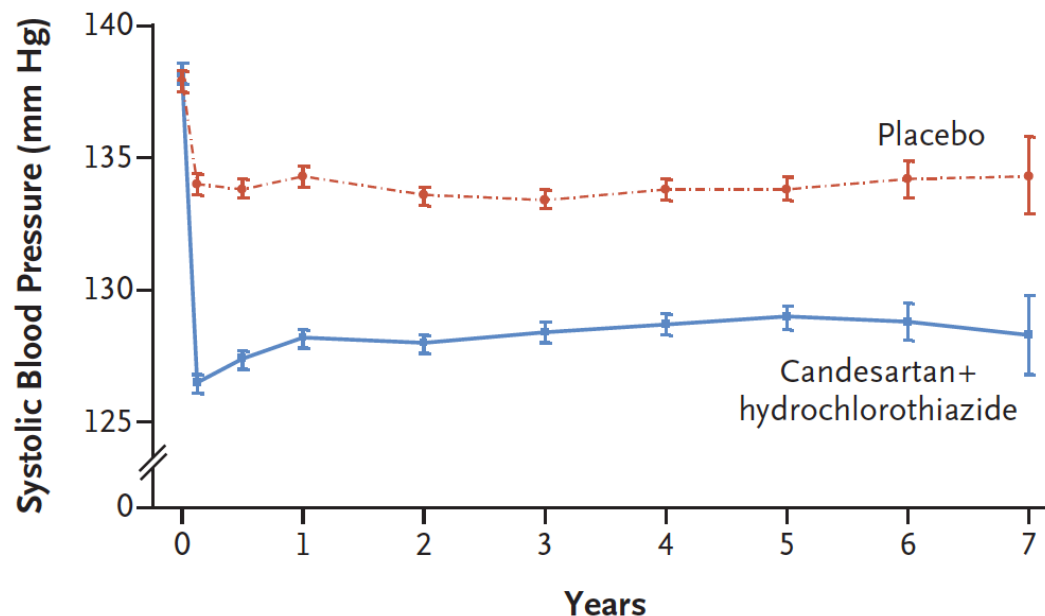
- **The blood pressure target**
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State of the Art



* JNC VIII: SBP goal to less than 150 mm Hg for patients aged 60 years or older

HOPE-3 study

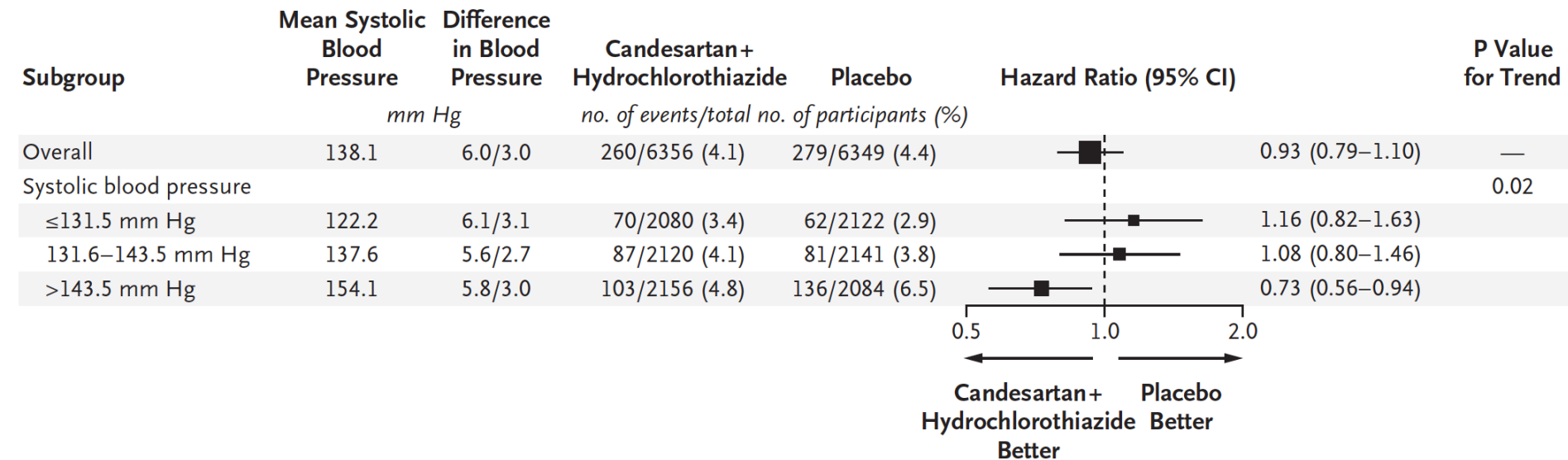


- 12,705 participants at intermediate risk who did not have cardiovascular disease
- either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo.
- BP at baseline 138/82 mmHg

Lonn N Engl J Med 2016;374:2009-20.

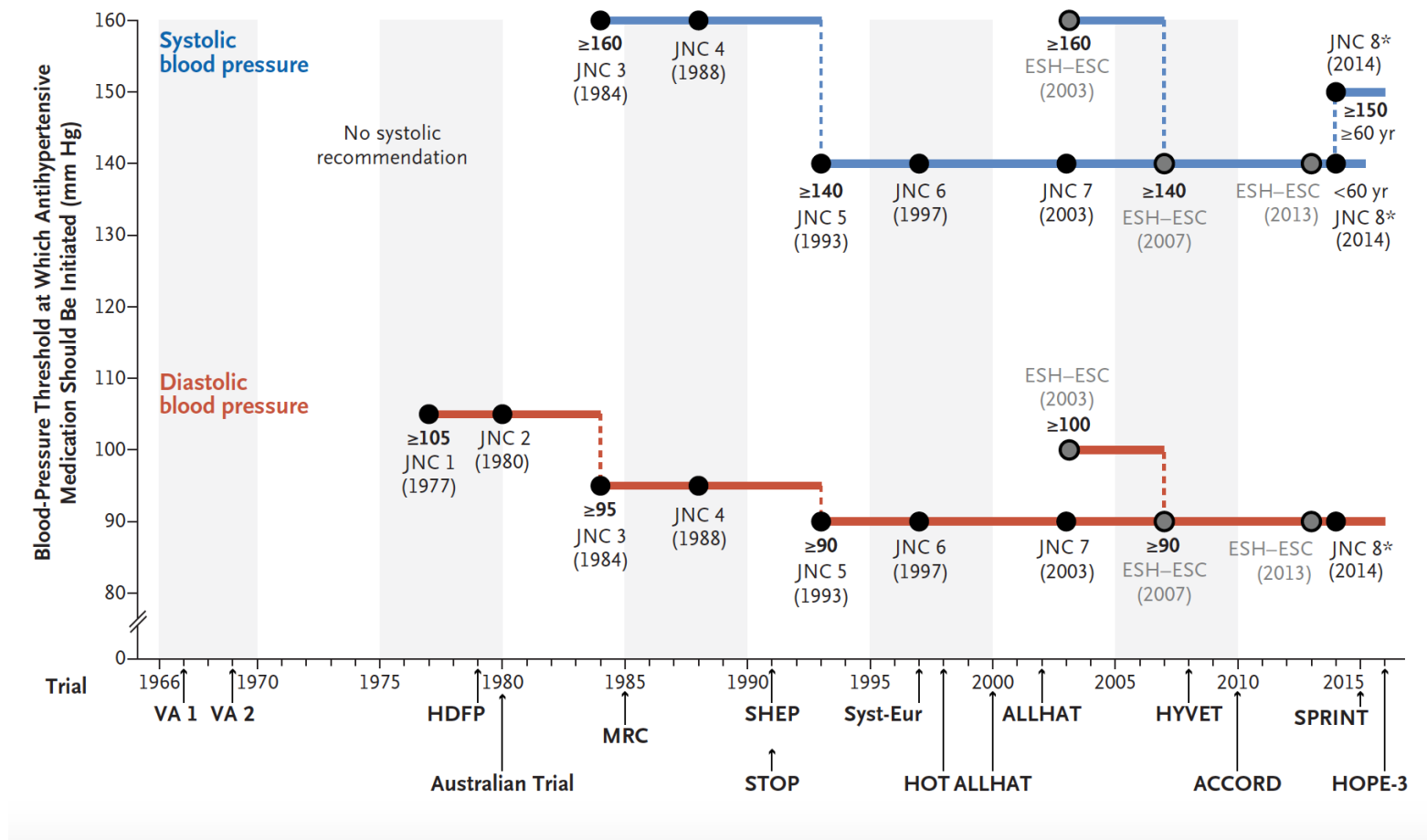
HOPE-3 study

A First Coprimary Outcome



Lonn N Engl J Med 2016;374:2009-20.

State of the Art

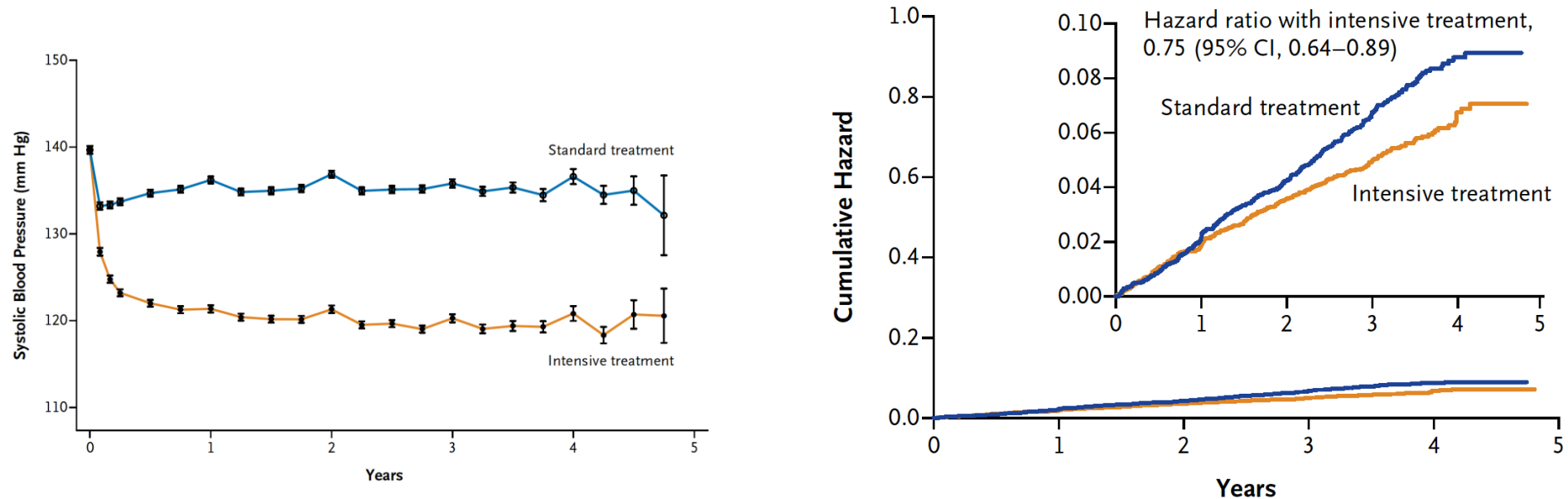


*** JNC VIII: SBP goal to less than 150 mm Hg for patients aged 60 years or older**

M Pfeffer, N Engl J Med 2016;375:1756-66.

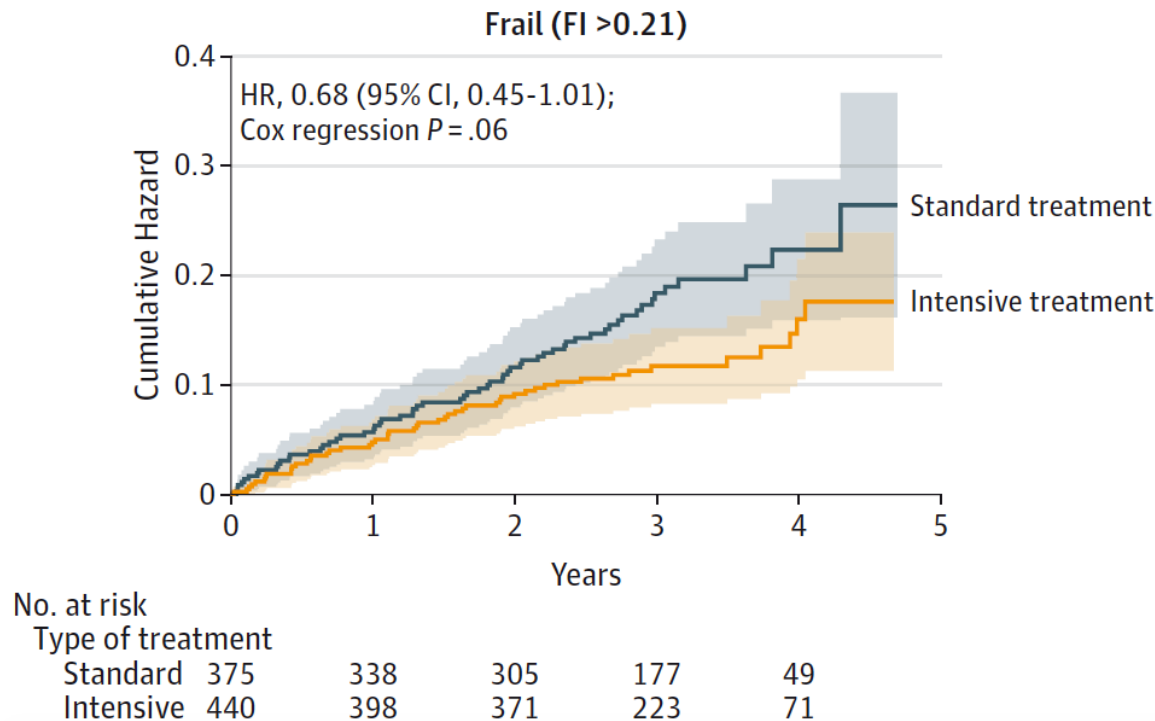
The SPRINT study

A Primary Outcome



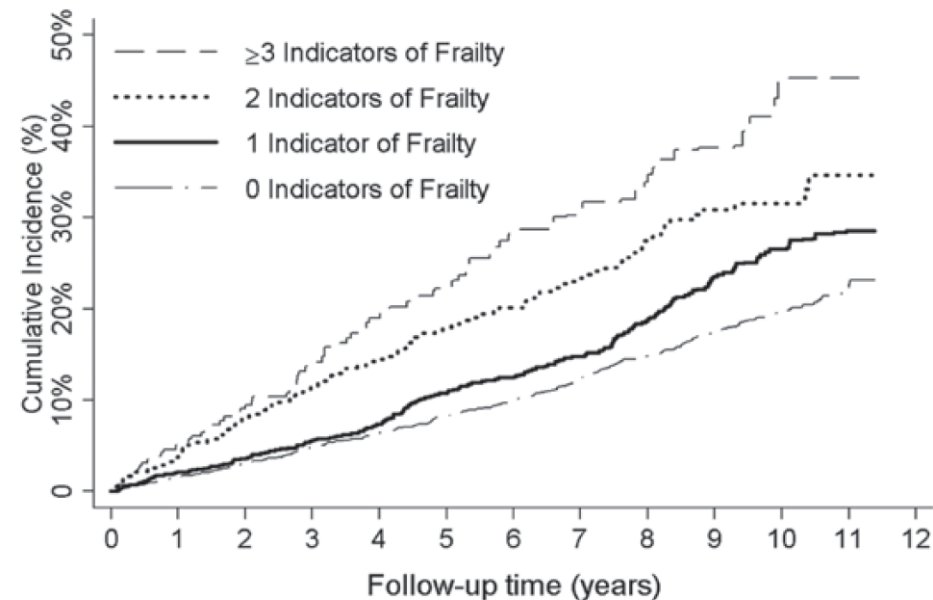
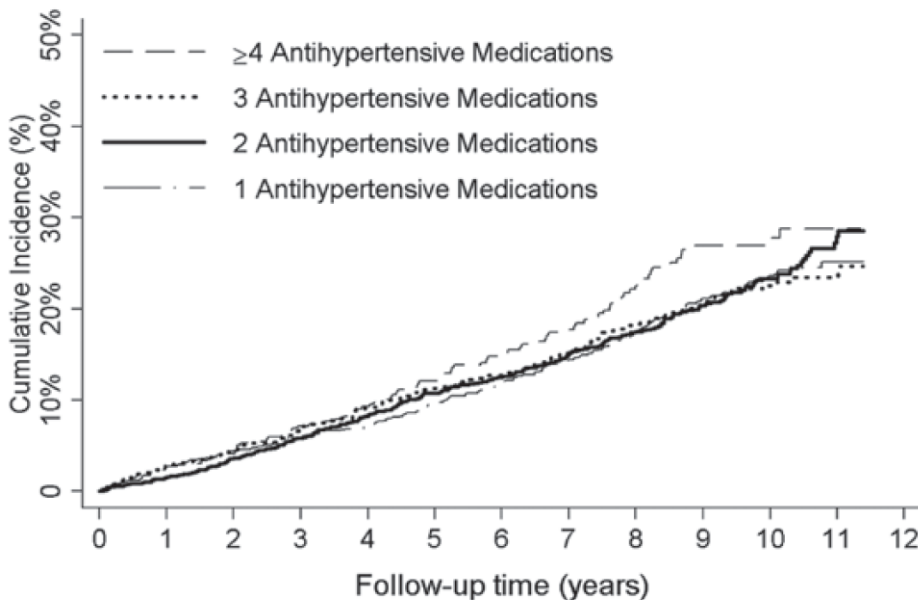
- Pts with high risk for cardiovascular events but without diabetes (n =9361, mean age 68 yrs), targeting a systolic blood pressure of less than 120 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause

Intensive vs Standard Blood Pressure Control in Adults Aged ≥ 75 Years



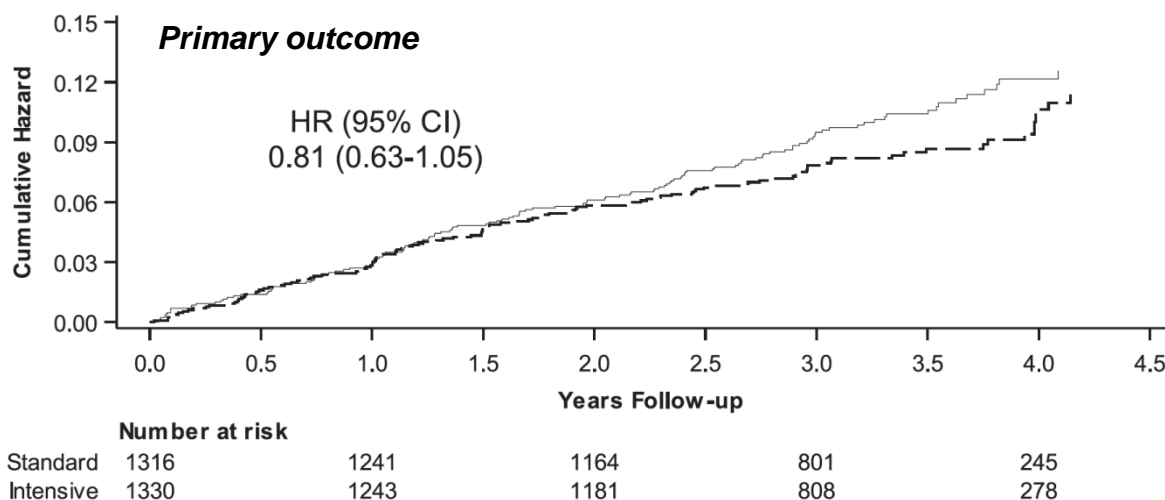
- CV protection is preserved even in the frail elderly
- Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment
- 4.9% vs 5.5% for injurious falls

Frailty, but not BP or number of antihypertensive medication classes, are associated with increased risk for serious fall injuries among elderly



- 5236 patients from REGARDS cohort > 65 yrs, linked to medicare claims

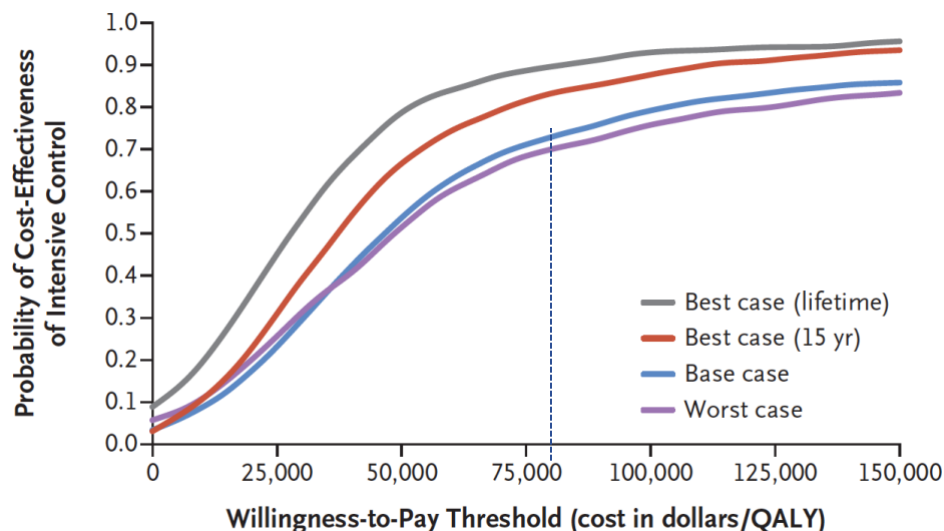
Intensive blood pressure control in CKD



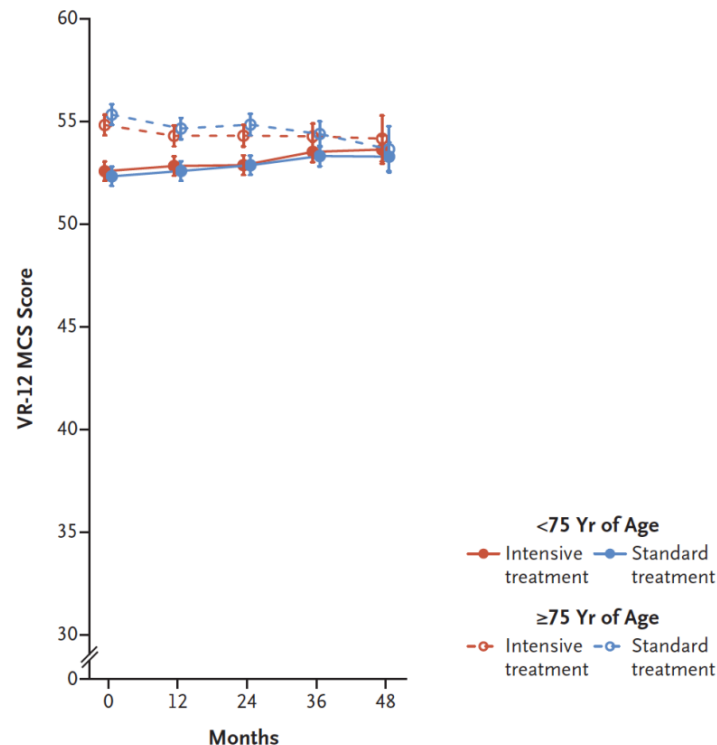
- Baseline eGFR 47 ml/min; baseline RR 147/75 mmHg
- eGFR decrease of >50% or development of ESRD, occurred in 15 (1.1%) in the intensive group and 16 (1.2%) in the standard group

eGFR Reduction from Month 6, % ^a	No. of Events (% per 1 yr) ^b		Intensive Treatment Versus Standard Treatment	
	Intensive Treatment, n=1330	Standard Treatment, n=1316	HR (95% CI)	P Value
50	7 (0.17)	4 (0.10)	1.65 (0.48 to 5.62)	0.42
40	15 (0.37)	14 (0.36)	1.01 (0.49 to 2.10)	0.98
30	44 (1.09)	35 (0.91)	1.19 (0.76 to 1.85)	0.44

Cost effectiveness and patient satisfaction on intensive blood pressure lowering



Base case (i.e., reduced adherence after 5 yrs, no effects at 15 yrs), worst case (i.e., nonadherence and no effects after 5 yrs), best case (5 yrs adherence and persistence of effects for 15 yrs), and lifetime best case (lifetime adherence and treatment effects).



Veterans RAND 12-Item Health Survey (VR-12)

Bres et al, *N Engl J Med* 2017;377:745-55.

Take-Home Message

- Targeting a systolic blood pressure < 120 mmHg reduces CV death and all cause mortality
- Is cost effective and does not reduce QoL
- Is safe in (frail) elderly and mild CKD

The mean diastolic blood pressure achieved in the intensive group was 62 mm Hg, or 5 mm Hg less than in the standard group.

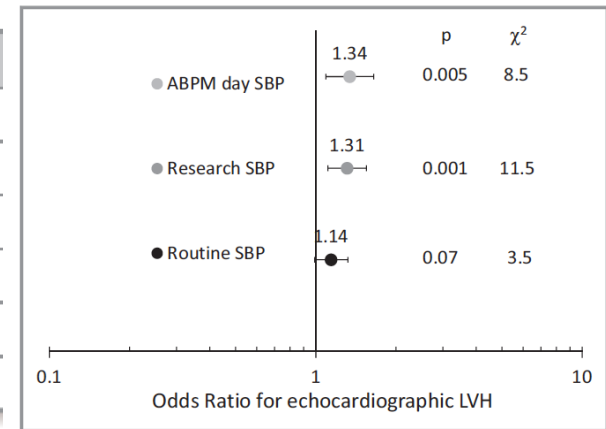
Discussion

- Method of BP measurement in studies (Agarwal, J Am Heart Assoc. 2017;6:e004536

Discussion

- Method of BP measurement in studies

Variable	Bias (95% CI)
Research grade, routine SBP	−12.7 (−14.7 to −10.7)
Research grade, routine DBP	−12.0 (−13.4 to −10.7)
Research grade, day ABPM SBP	−7.9 (−9.4 to −6.4)
Research grade, day ABPM DBP	−11.7 (−12.7 to −10.8)
Routine clinic, day ABPM SBP	4.8 (2.9–6.7)
Routine clinic, day ABPM DBP	0.3 (−0.9 to 1.5)



BP target 120/80 mmHg is equivalent to 132/92 mmHg office BP

Agarwal, J Am Heart Assoc. 2017;6:e004536

Discussion

- the SPRINT trial excluded a relevant proportion of the
- high-risk hypertensive population, in particular patients with diabetes or previous stroke.

Discussion

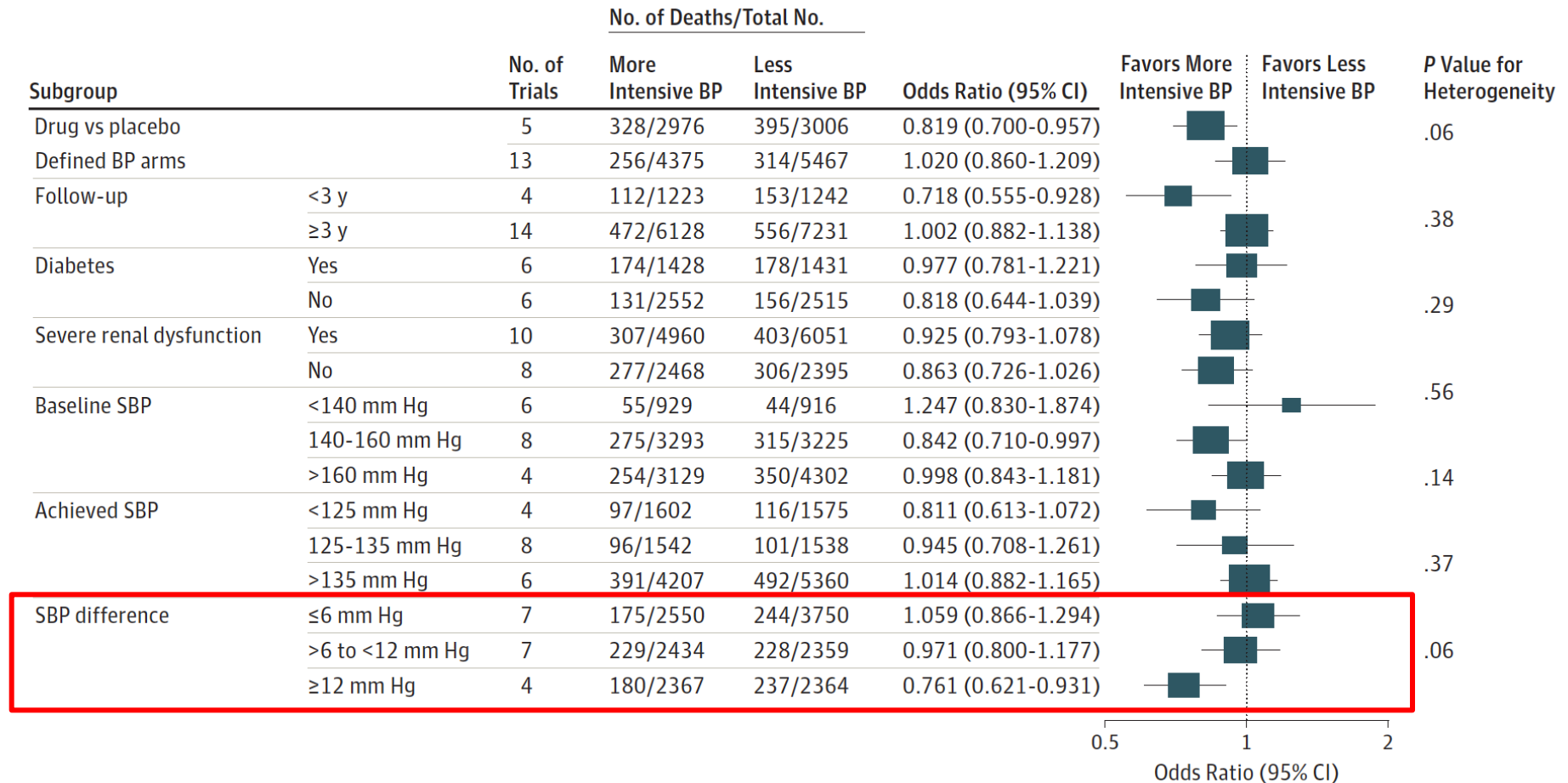
- ACCORD study in type II DM, using similar strategy did not find such benefits
- (but recently did demonstrate a beneficial effect on LVH; Soliman Hypertension. 2015;66:1123-1129)
- data from the EMPAREG-OUTCOME trial indicated that reducing SBP to values close to 130mmHg was probably one of the factors contributing to the beneficial results found in this study

Discussion

- **Posthoc analysis** of SPRINT presented at ESC 2017 shows when initial BP > 160 mmHg, no longer CV protective effect and small increase in all cause mortality

More Intensive vs Less Intensive BP Lowering and Risk of Mortality in CKD Stages 3 to 5

A Systematic Review and Meta-analysis



Discussion

- *Personal opinion:*
- -pushing BP a bit further to 130 mmHg systolic seems reasonable in the intermediate risk patient, even in elderly.
- Be more cautious in diabetes with TOD and CKD 4-5
- May be delta BP more important than absolute number achieved, particularly when baseline BP is high

Hypertension

- The blood pressure target
- **Therapy-resistant hypertension and devices**
- Update on drug therapy
- Capita selecta
- New pathophysiology

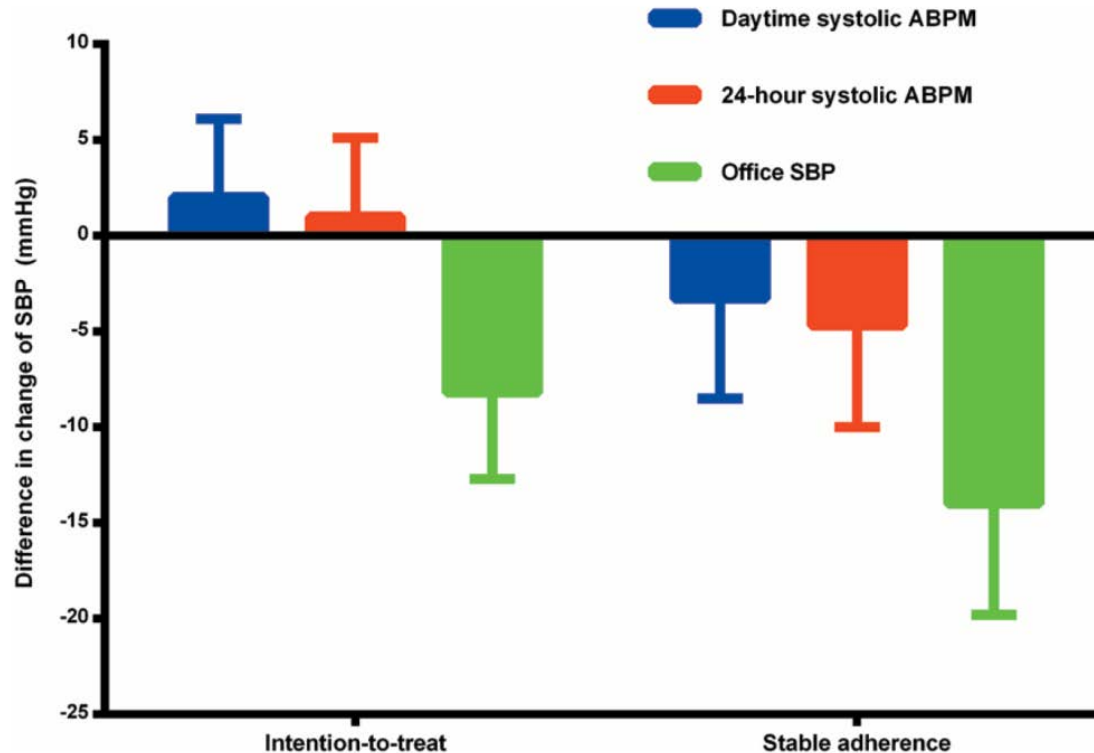
State of the Art

Renal denervation for therapy-resistant hypertension

- early uncontrolled and un-blinded trials reported large reductions in blood pressure following renal denervation in patients with uncontrolled hypertension**
- the randomised, sham-controlled SYMPPLICITY HTN-3 trial showed no significant blood-pressure-lowering benefits**
- incomplete ablation of the renal nerves, non-adherence to antihypertensive medications, and patient selection might have influenced these results**

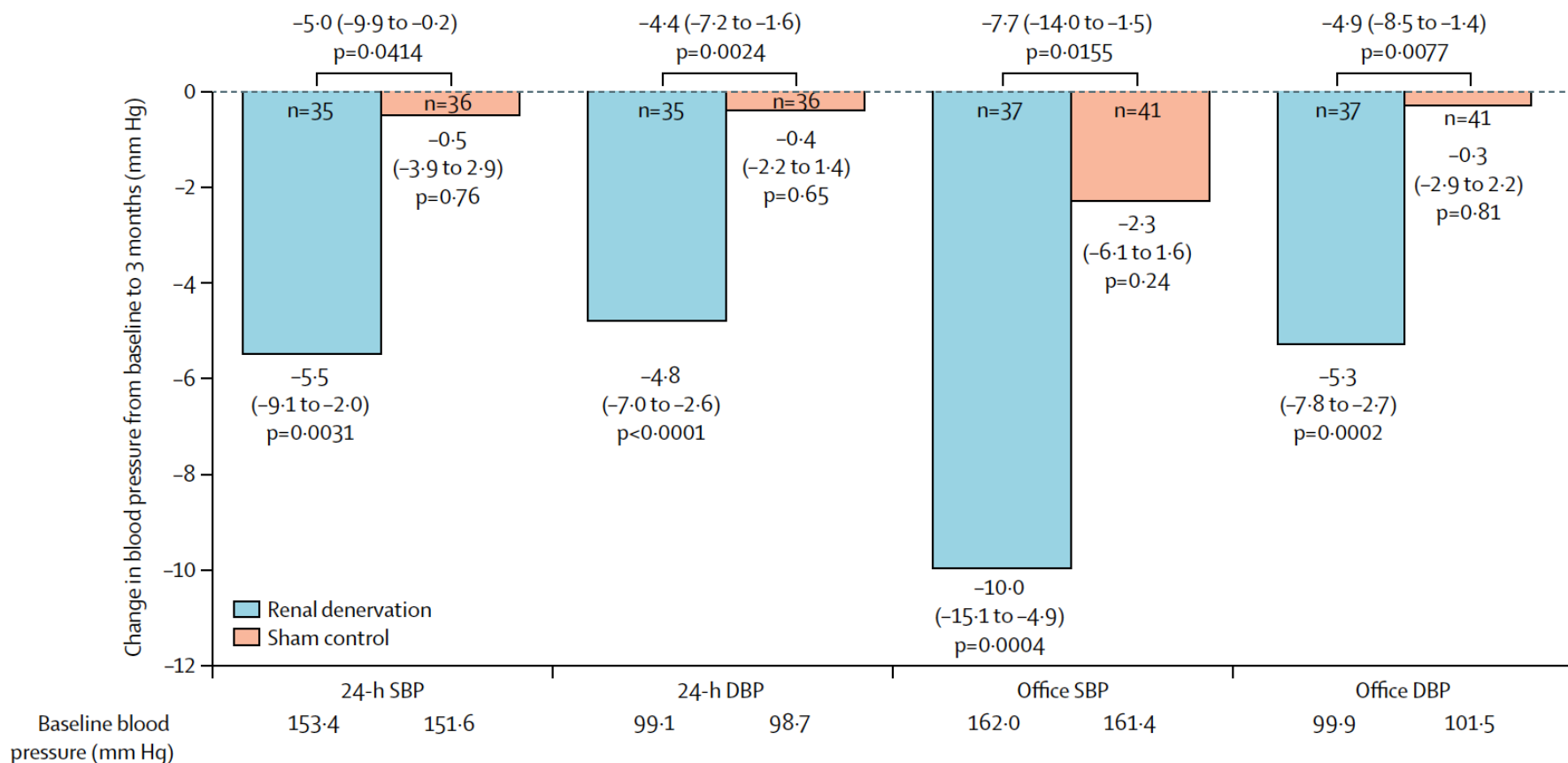
State of the Art

Does therapy resistant hypertension exist ?



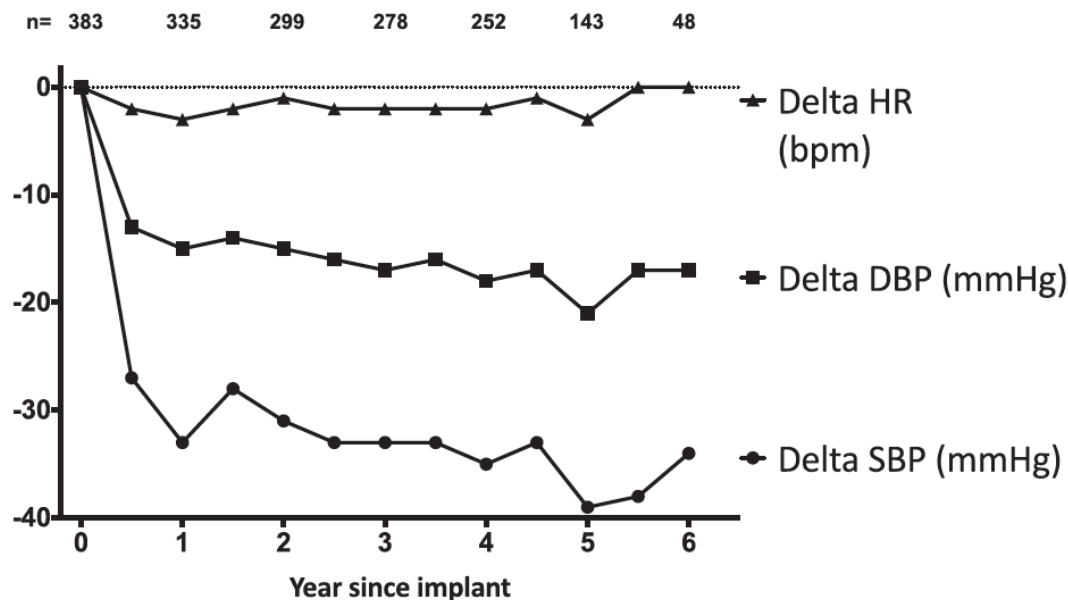
SYMPATHY trial: effect of denervation over standard treatment in intention-to-treat analysis (n=139) and proven adherence (n=54)

Renal denervation in uncontrolled hypertension in the absence of antihypertensive medications



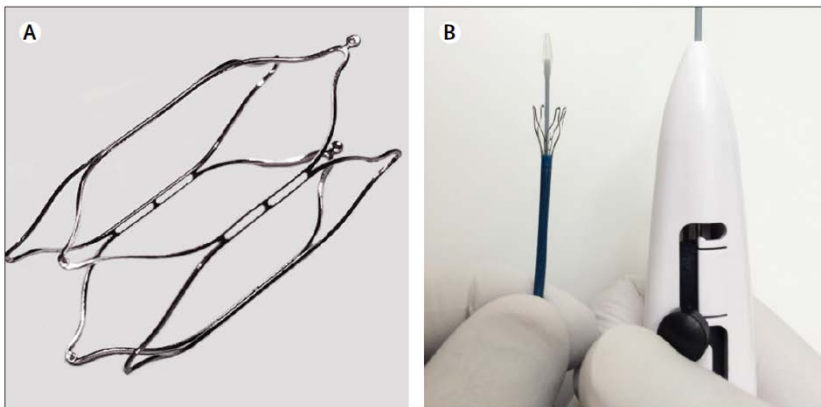
- Sham procedure controlled, new device with reproducible denervation
- N=80, BP systolic 150-180 mmHg,; no medication

Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy

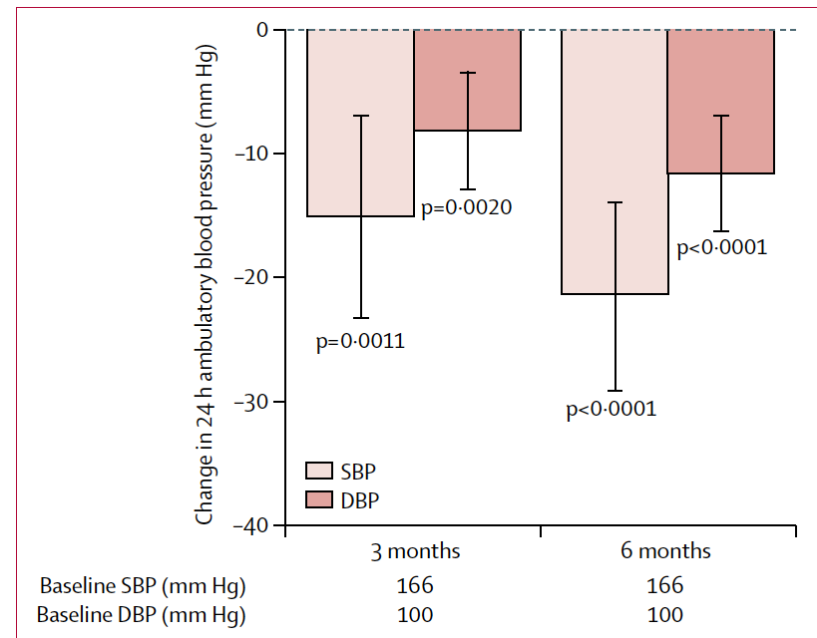


- 143 patients with 5 years of follow-up
- office systolic BP fell from 179 ± 24 mm Hg to 144 ± 28 mm Hg, and office diastolic pressure from 103 ± 16 mm Hg to 85 ± 18 mm Hg.
- In $\approx 25\%$ of patients, it was possible to reduce the number of medications from a median of 6 to a median of 3.
- next generation device Barostim Neo study ongoing

Endovascular baroreflex amplification for resistant hypertension



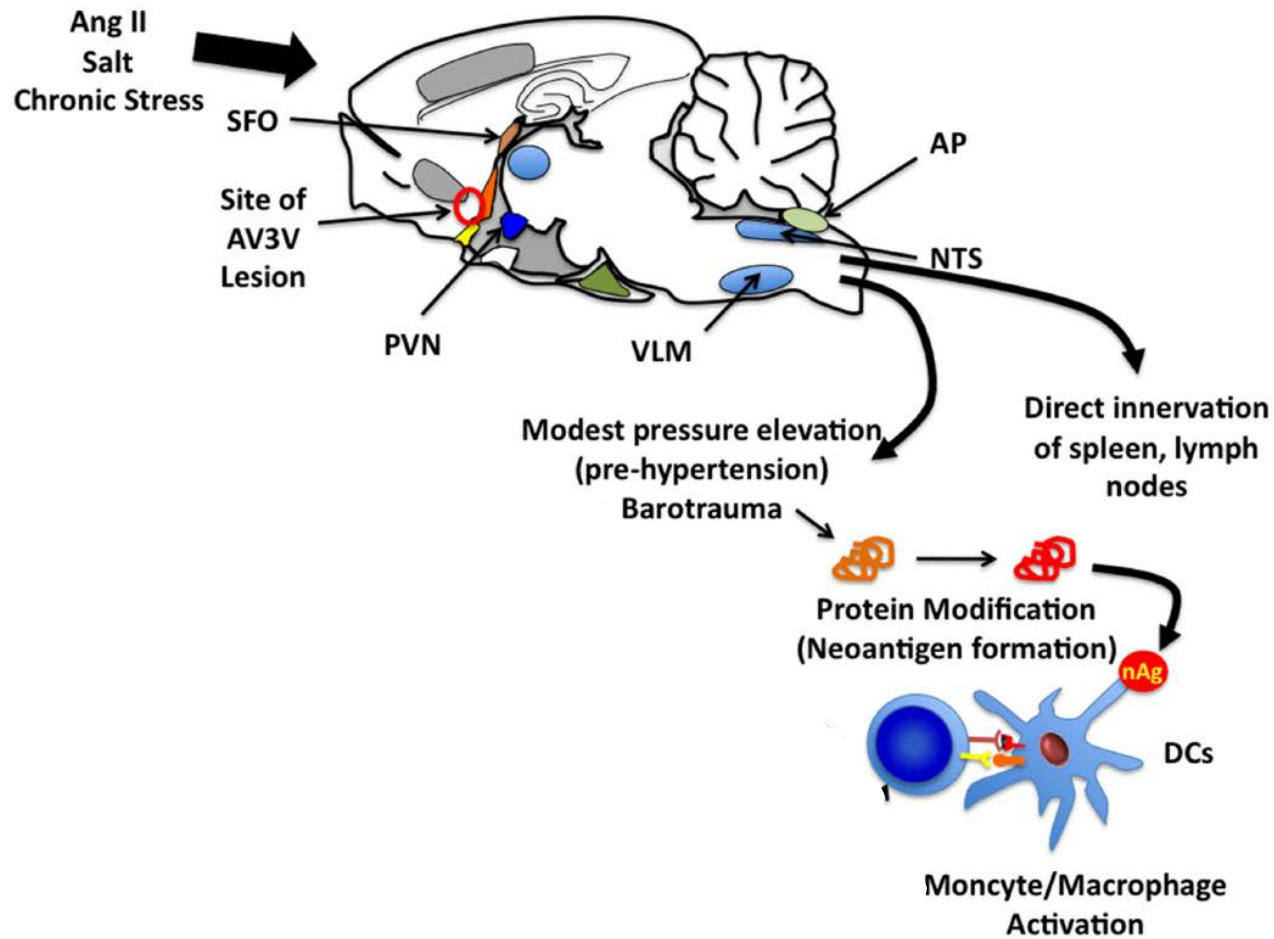
- 30 patients
- maximally tolerated doses of at least three antihypertensive drugs, including a diuretic.
- at least 80% adherence to antihypertensive medication, for at least 30 days before enrolment, mean office systolic blood pressure 160 mm Hg or greater



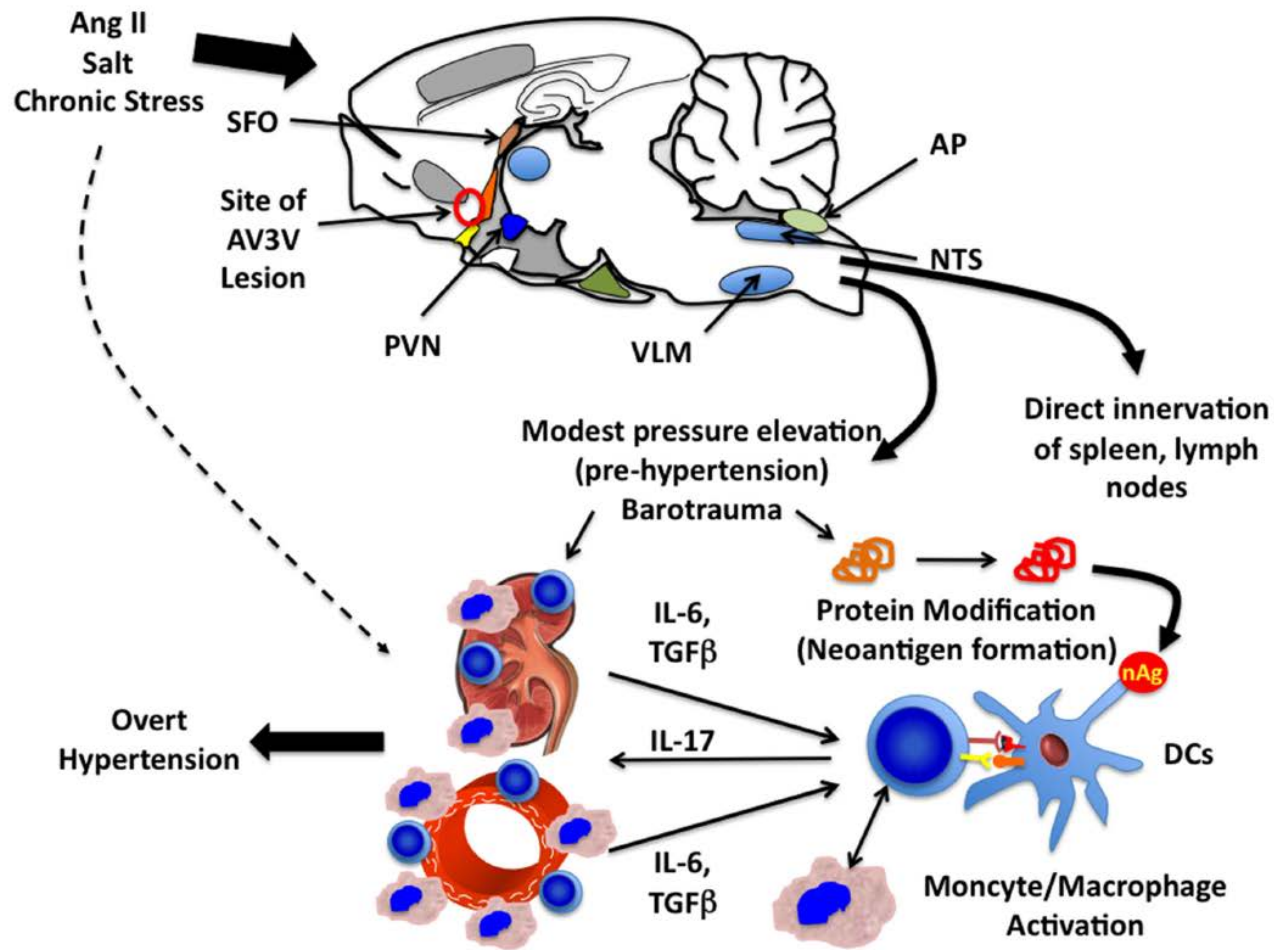
Spiering, Lancet. 2017 ;S0140-6736(17)32337-1 Epub ahead of print

One more thing.....

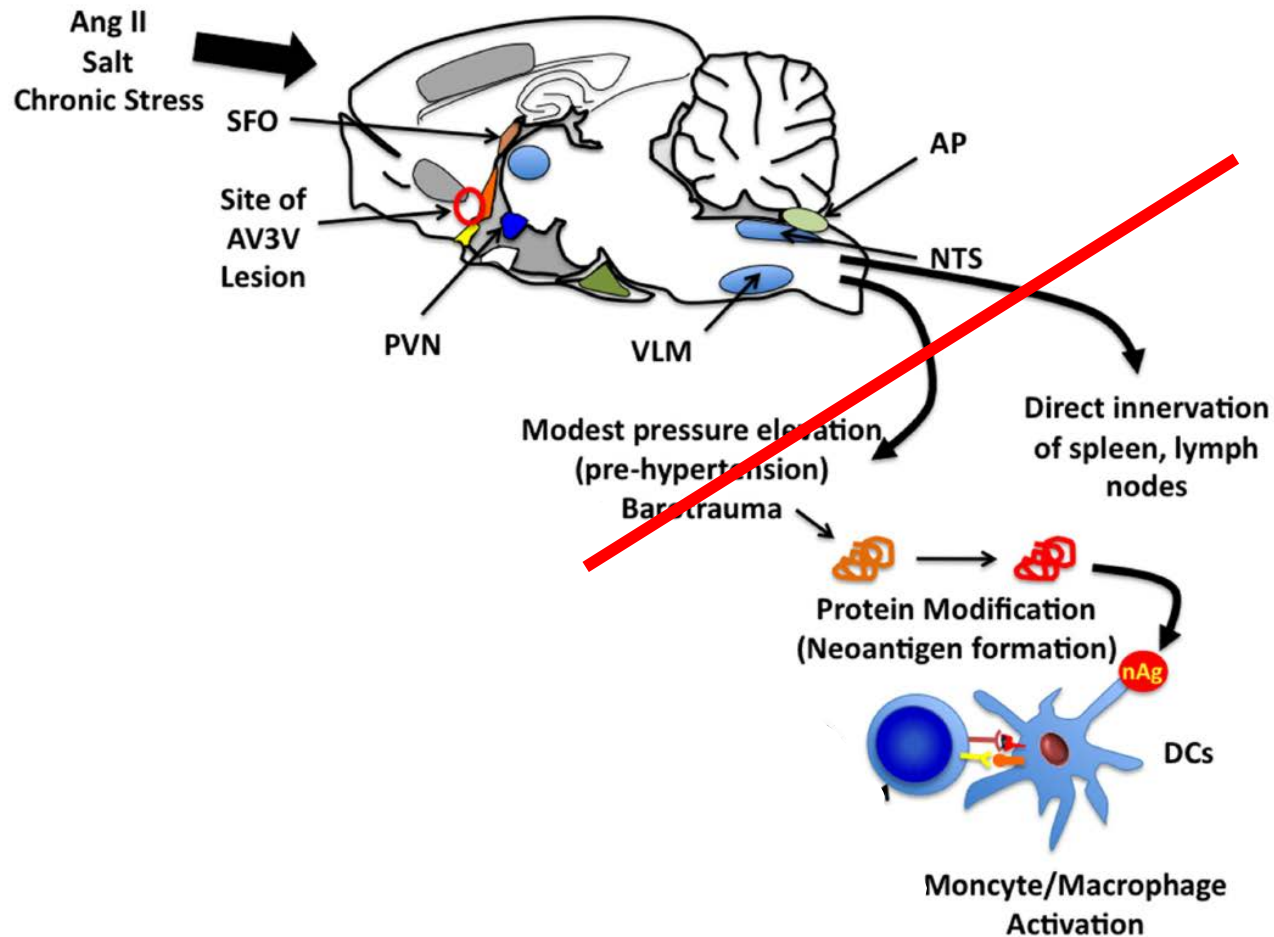
hypertension is an inflammatory disease



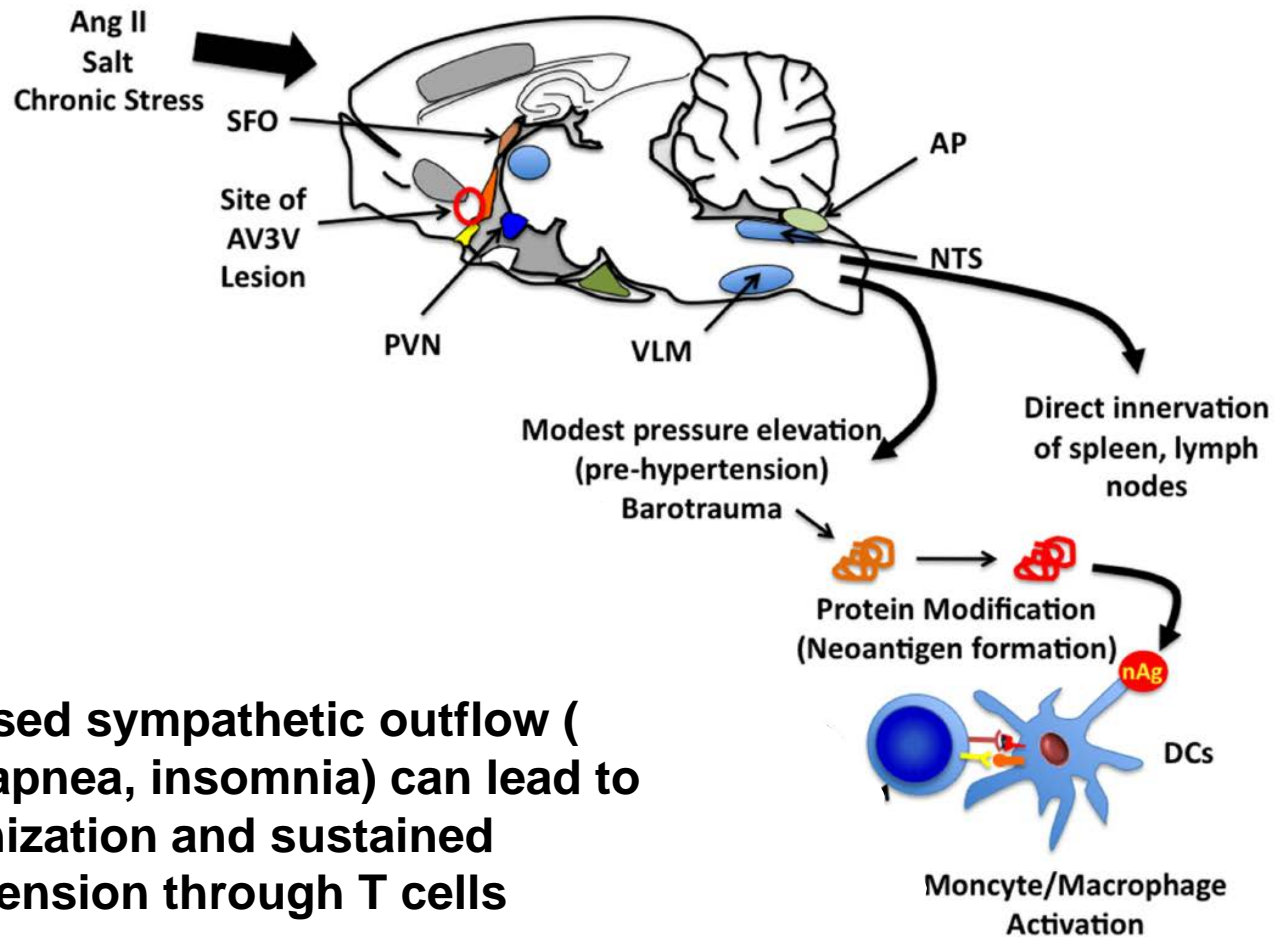
hypertension is an inflammatory disease



hypertension is an inflammatory disease

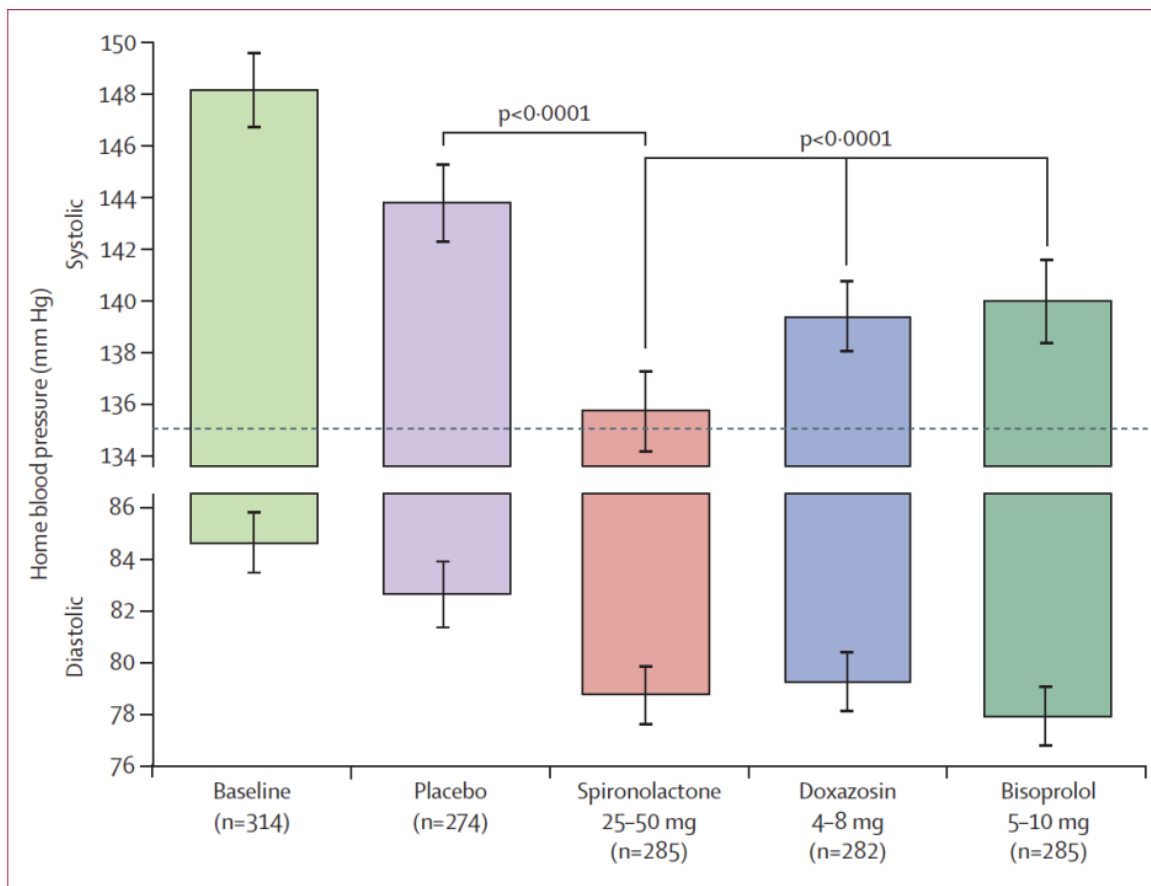


hypertension is an inflammatory disease



- Increased sympathetic outflow (sleep apnea, insomnia) can lead to immunization and sustained hypertension through T cells

The efficacy of mineralocorticoid receptor blockade in resistant hypertension



- **PATHWAY-2: 285 patients with hypertension on 3 BP lowering agents**
- **ESC congress 2017: Spironolactone most effective in sodium retaining, higher Aldo patients. Amiloride mimicks effect of spironolactone.**

Take-Home Message

- Therapy-resistant hypertension is mostly due to non-adherence
- Salt sensitivity may constitute an important component of BP treatment resistance and MRA should be considered then.
- Device-based sympathetic nerve activity reducing therapy should be developed as an alternative or complementary strategy to BP lowering agents and not only as rescue therapy

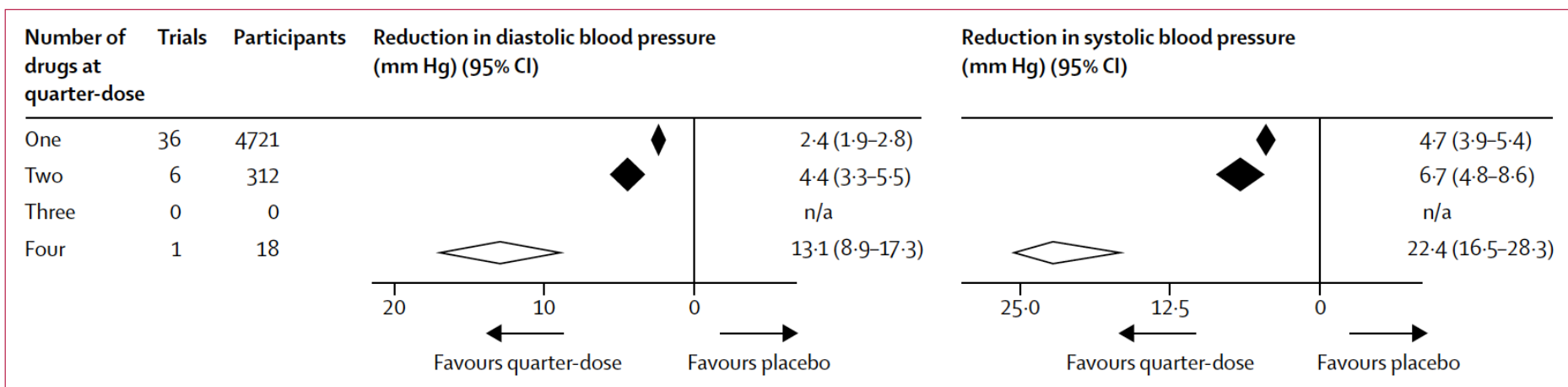
Hypertension

- The blood pressure target
- Therapy-resistant hypertension and devices
- **Update on drug therapy**
- Capita selecta
- New pathophysiology

What is the optimal dose of BP lowering agents ?

- **a systematic review of 354 trials of BP-lowering therapy showed that half-standard-dose achieved almost 80% of BP lowering,**
- **BP-lowering effect of different classes of drugs was additive.**
- **Less side effects with half the standard dose**

Quarter-dose quadruple combination therapy for initial treatment of hypertension



- Systematical review of the literature on placebo-controlled, quarter-dose BP-lowering
- QUADPILL study (n-22; irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg in one capsule, cross over)

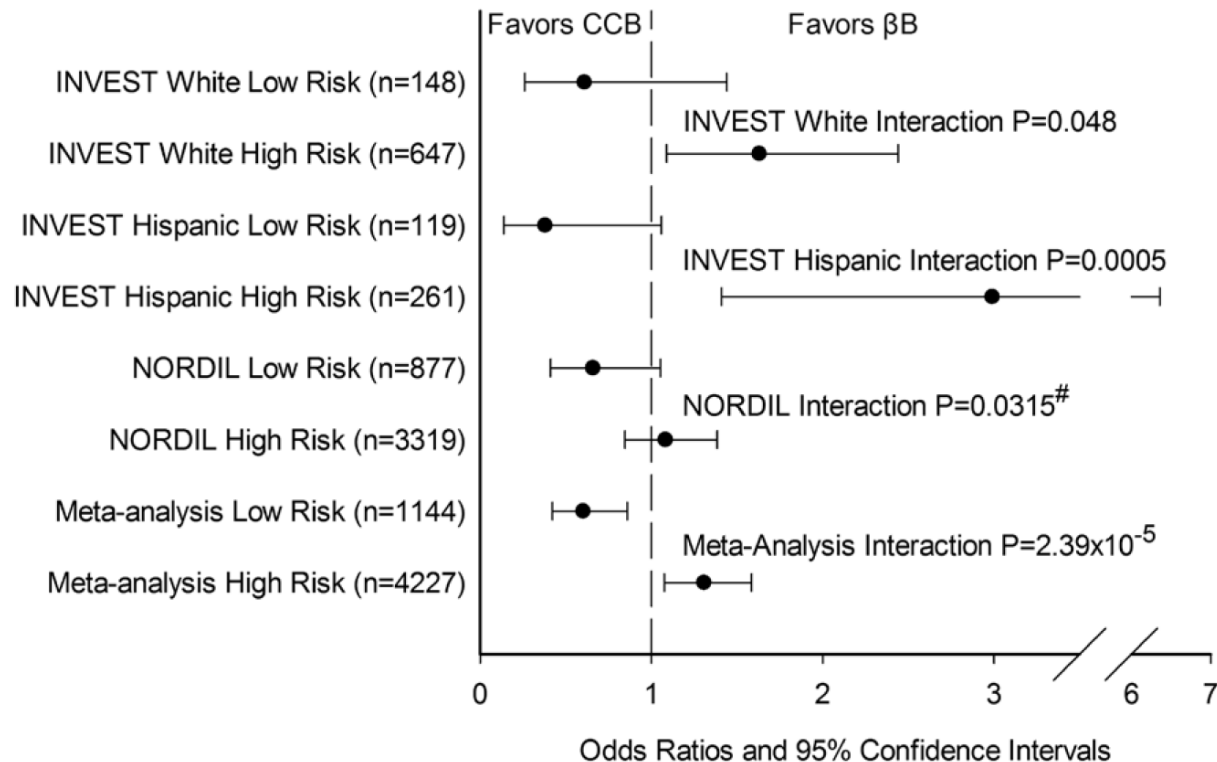
Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD; UMPIRE study

Table 2. Effect of Treatment on Adherence to Primary and Secondary End Points

Outcomes	Fixed-Dose Combination (n = 1002)	Usual Care (n = 1002)	Treatment Effect (95% CI) ^a	P Value
Primary end points				
Adherence, No./total (%) ^b	829/961 (86)	621/960 (65)	1.33 (1.26 to 1.41)	<.001
Systolic blood pressure, mm Hg	129.2 (128.1-130.2)	131.7 (130.7-132.8)	-2.6 (-4.0 to -1.1)	<.001
Low-density lipoprotein cholesterol, mg/dL	84.2 (82.5-85.8)	88.4 (86.7-90.0)	-4.2 (-6.6 to -1.9)	<.001
Secondary end points				
Adherence at 12 mo, No./total (%)	827/935 (88)	602/925 (65)	1.36 (1.29 to 1.43)	<.001
Diastolic blood pressure, mm Hg	72.8 (72.2-73.5)	75.2 (74.7-75.8)	-2.5 (-3.3 to -1.6)	<.001
Total cholesterol, mg/dL	156.6 (154.6-158.5)	159.1 (157.1-161.1)	-2.5 (-3.3 to 0.3)	.08
High density lipoprotein cholesterol, mg/dL	44.2 (43.7-44.6)	43.7 (43.2-44.2)	0.5 (-0.2 to 1.1)	.14
Triglycerides, mg/dL	142.3 (137.8-146.9)	138.8 (134.2-143.4)	3.6 (-2.9 to 10.0)	.28
Plasma creatinine, mg/dL	1.07 (1.06-1.08)	1.04 (1.03-1.05)	0.03 (0.01 to 0.05)	.002

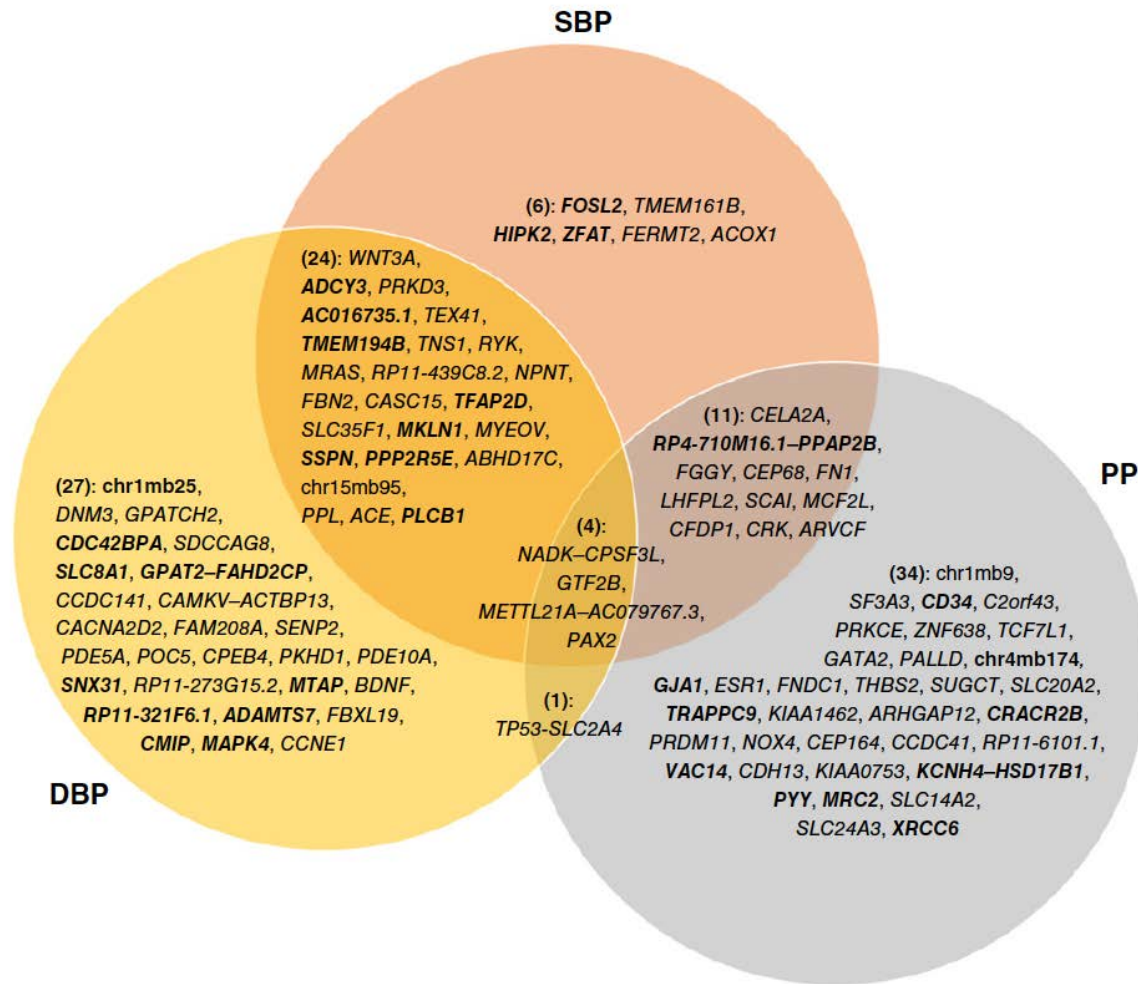
Participants were randomly assigned (1:1) to an FDC-based strategy (n=2004) FDC-based strategy (n=1002) containing either (1) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol (CAD) or (2) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide (CVA) or to usual care (n=1002).

Genetic risk factors to predict treatment response



- A genetic risk score was constructed from the top 3 loci in INVEST studies and replicated in the NORDIC study (SIGLEC12 rs16982743 and A1BG rs893184)

Towards precision medicine and new drugs: BP loci

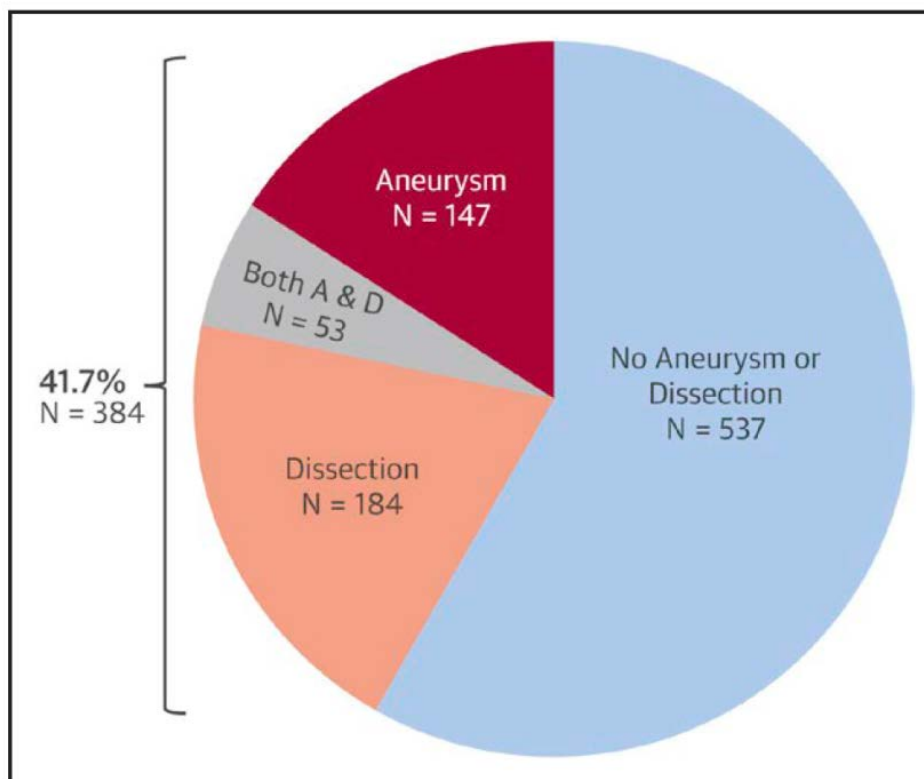


- Exome sequencing of 152,249 subjects correlated to SBP, DBP and PP

Hypertension

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- New pathophysiology

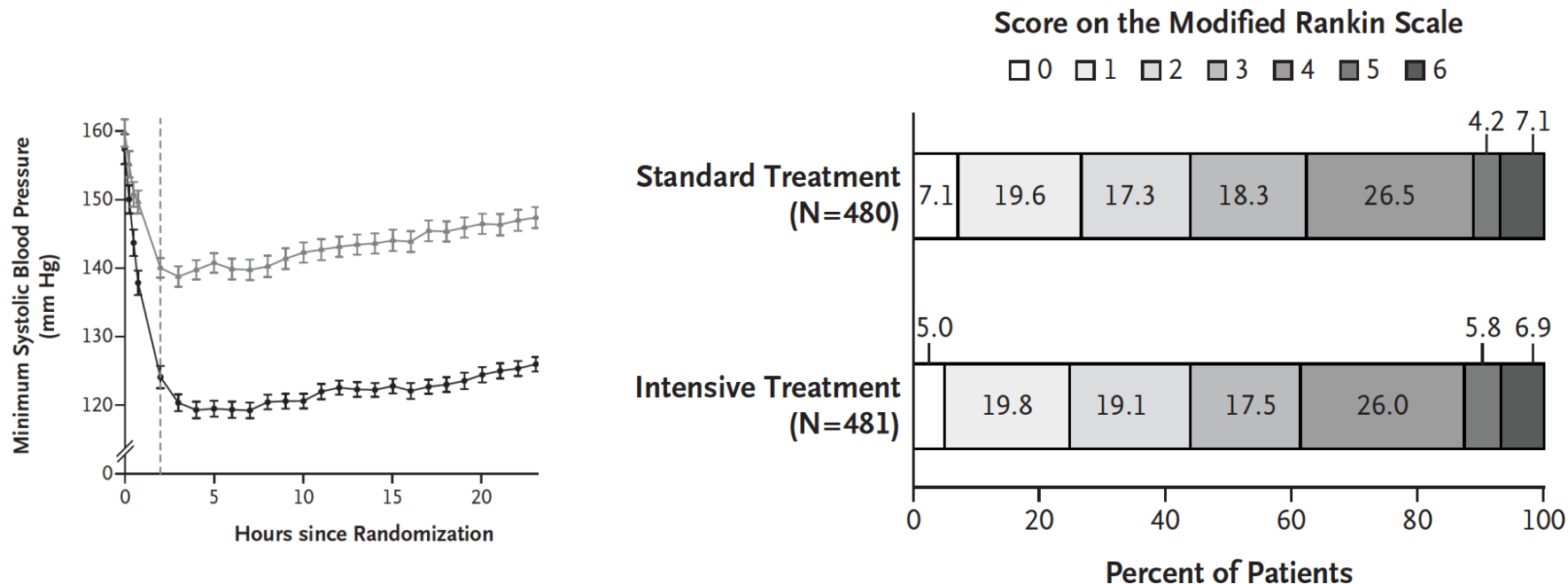
Fibromuscular dysplasia: new insights from the ARCADIA



- CTA is the preferred method of imaging because of the higher spatial resolution and thus greater sensitivity and specificity than with MRA
- FMD is not an isolated condition of 1 vascular territory but a systemic disease with t also aneurysms and dissections
- Every FMD patient should undergo a head to pelvis CTA (or MRA)

Olin, Hypertension. 2017;70:488-489, Plouin, Hypertension. 2017;70:652–658

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

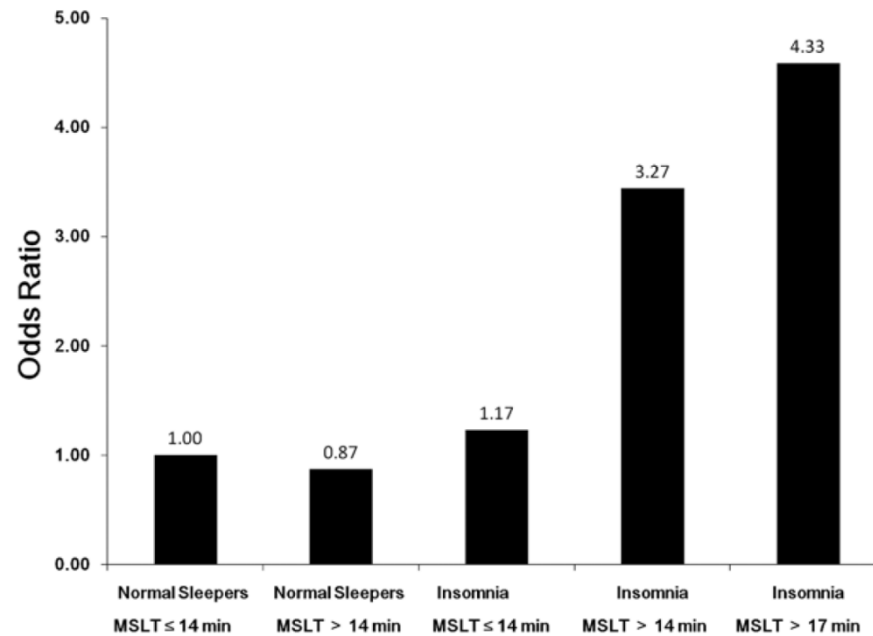


- The trial was based on evidence that hematoma expansion and the rate of subsequent death or disability might be reduced with very early and more aggressive reduction in the systolic blood-pressure level. Average BP level at presentation 200 mmHg
- Titration of BP using nicardipine and labetalol
- No advantage, but also no disadvantage

Hypertension in pregnancy: a risk factor for the child?

- prospective data collected on 15,778 Norwegian young adults shows that those born following hypertensive pregnancies had higher blood pressure than those born to mothers with normotensive pregnancies (mean difference of 2.7/1.5 mmHg for systolic and diastolic BP)
- siblings born to mothers who had experienced both a hypertensive pregnancy and a normotensive pregnancy had similar increases in blood pressure when they reached adult life
- Therefore, higher BP in offspring is genetic and there is no effect of exposure from maternal hypertension.

Insomnia and Hypertension



- 219 chronic insomniacs, 96 controls
- insomnia with day time hyperarousal, as measured by long Multiple Sleep Latency Test (MSLT) is associated with a very high risk for hypertension

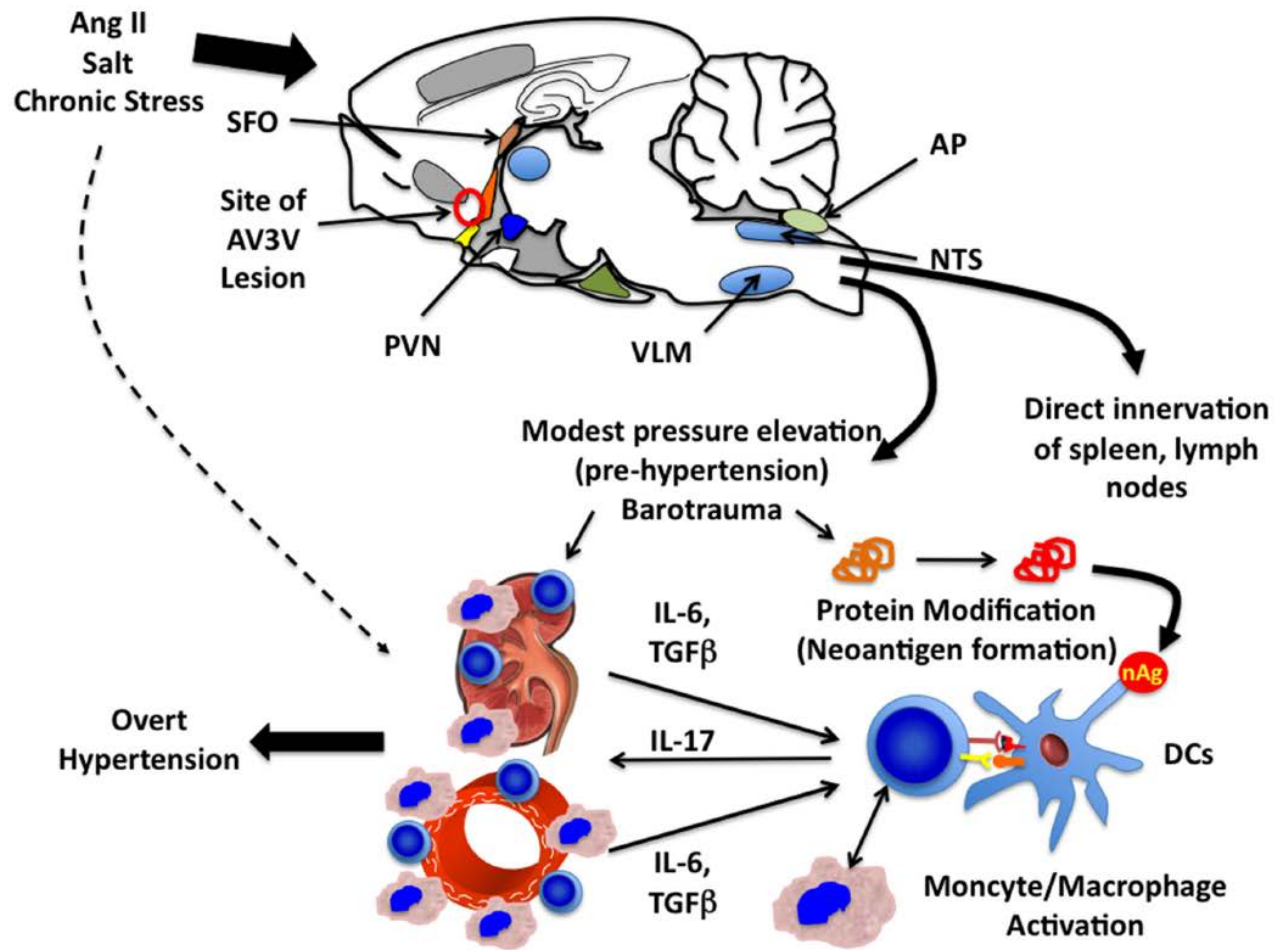
Take-Home Message

- No new drugs this year
- Dose (very) low, and in (fixed) combination (*and always add diuretic*)
- Genetic profiling of drug therapy in hypertension is coming
- In patients with FMD do once a screening for multiple vessel disease
- It is okay to lower BP in cerebral heamorrhage

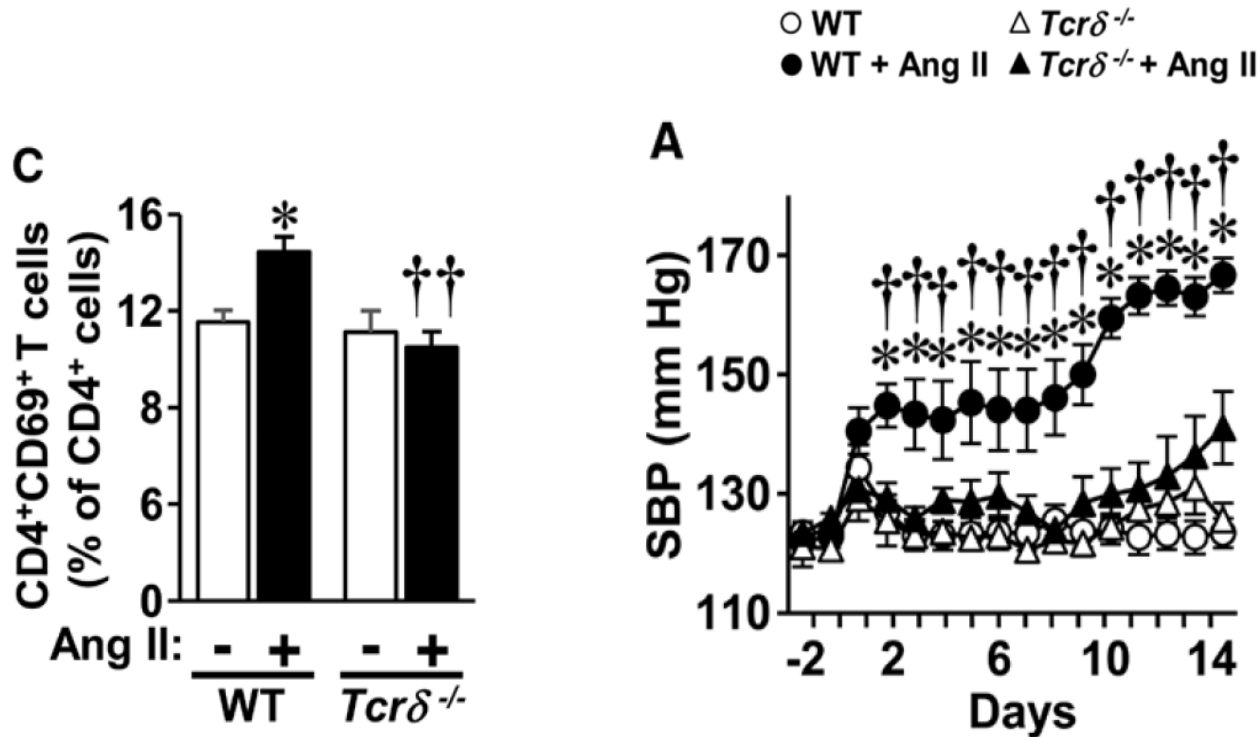
Hypertension

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hypertension is an inflammatory disease

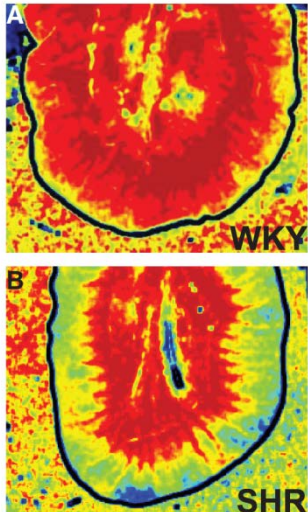
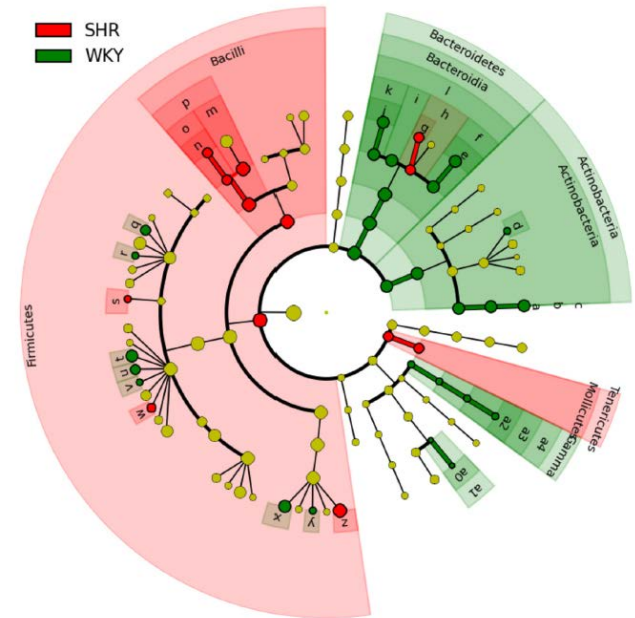
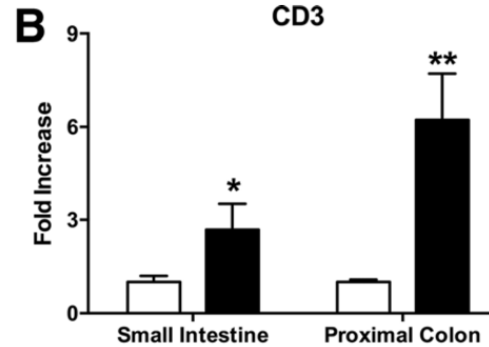
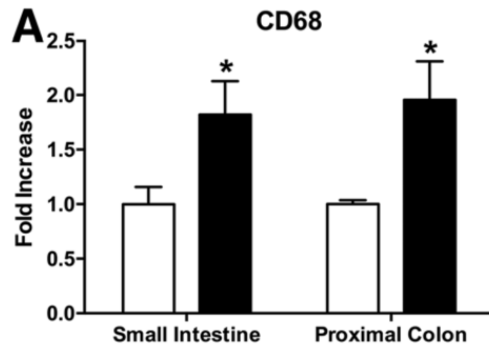


$\gamma\delta$ T Cells mediate Ang II hypertension



- T cells with rapid innate-like responses positioning them at the initiation phase of immune responses
- $\gamma\delta$ T cells mediate Ang II-induced SBP elevation, vascular injury, and T-cell activation in mice.

The gut microbiome, inflammation and hypertension



- The increase in blood pressure in spontaneously hypertensive rat was associated with gut dysbiosis and inflammation
- Hypertension is associated with increased sympathetic drive to the gut
- All these things can be reversed by ACEi

Take-Home Message

- Hypertension is increasingly seen as a T cell immune disease
- Secondary to sympathetic activation and increased Ang II activity

List of References

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List of Abbreviations

- SBP systolic blood oressure
- JNC Joint National Committee
- BP blood pressure
- PP pulse pressure
- MRA mineralocorticoid Receptor Antagonist
- LVH; left ventricular hypertrophy