Nephro Update Europe 2019
20 – 21 September, Prague

Hypertension

Ton Rabelink, Netherlands

Blood pressure targets

State of the Art

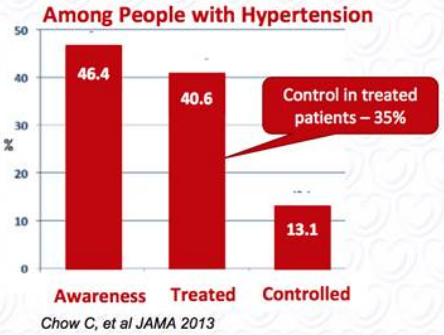
Global Impact of an Elevated Blood Pressure

In 2015, elevated systolic BP was the leading preventable cause of premature death globally

10 million deaths
Over 200 million disability adjusted life years

Ischemic Heart Disease: 4.9m
Hemorrhagic Stroke: 2.0m
Ischemic Stroke: 1.5m

Forouzanfar MH, et al JAMA 2017



www.escardio.org/guidelines

Williams B, Mancia G et al. Eur Heart J (2018); doi:10.1093/eurheartj/ehy339
Williams B, Mancia G et al. J Hypertens (2018); doi:10.1097/HJH0000000000001940

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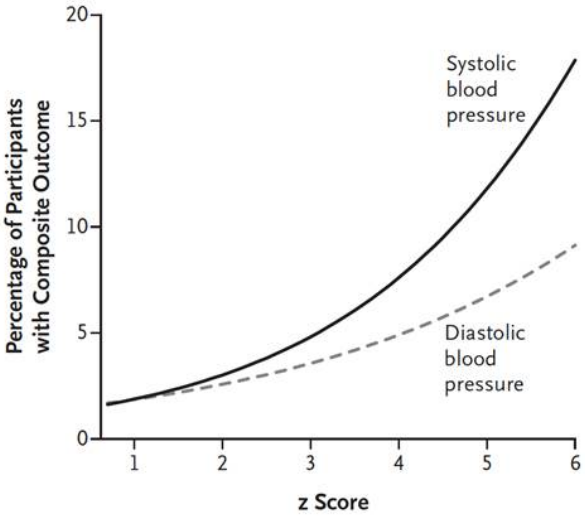
Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes



data from 1.3 million adults in a general outpatient population, multivariable Cox survival analysis to determine the effect of the burden of systolic and diastolic hypertension on a composite outcome of myocardial infarction, ischemic stroke, or hemorrhagic stroke over a period of 8 years.

Flint et al., N Engl J Med. 2019 Jul 18;381(3):243-251

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The controversy between AHA and ESC guidelines

Blood Pressure, mm Hg				
Systolic		Diastolic	ACC/AHA[b]	ESC/ESH[c]
<120	and	<80	Normal	Optimal
120-129	and	<80	Elevated	Normal
	and/or	80-84	Stage 1 hypertension	
		85-89		High normal
130-139	and/or	85-89		
140-159	and/or	90-99	Stage 2 hypertension	Grade 1 hypertension
≥160-179	and/or	≥100-109		Grade 2 hypertension
≥180	and/or	≥110		Grade 3 hypertension

Vasan, JAMA Nov 6, 2018 Volume 320

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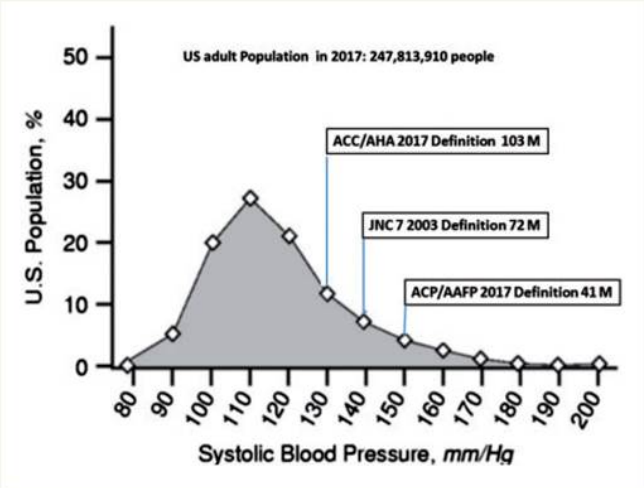
Changing definition of hypertension in guidelines: how innocent a number game?

Franz H. Messerli[1]*, Stefano F. Rimoldi[1], and Sripal Bangalore[2]



Take home figure Number of adults in the USA said to have hypertension depending on definition by various guidelines.

Messerli et al., Eur Heart J. 2018 Jun 21;39(24):2241-2242

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The similarities between AHA and ESC guidelines

	2017 ACC/AHA	2018 ESC/ESH
Main Areas of Commonality		
Diagnosis of hypertension	Emphasis on accuracy of BP measurements. Use of out-of-office BP monitoring (ABPM or HBPM) to confirm the diagnosis of hypertension.	Emphasis on accuracy of BP measurements. Either office BP measurement on repeated visits, HBPM , or ABPM to confirm the diagnosis of hypertension.
Equivalence of office BP readings to ABPM and HBPM values	Office BP 140/90 mm Hg equivalent to a 24hr ABPM mean of 130/80 mm Hg and HBPM average of 135/85 mm Hg.	Office BP 140/90 mm Hg equivalent to a 24hr ABPM mean of 130/80 mm Hg and HBPM average of 135/85 mm Hg.
Importance of CV risk assessment	Use of ACC/AHA 2013 pooled cohort ASCVD risk score to guide drug treatment of hypertension, especially in stage 1 hypertension (10-year risk of an ASCVD event ≥10%).	Use of SCORE CV risk assessment (10-year risk of a first fatal atherosclerotic event) to consider drug treatment in patients with high normal BP (in very high risk patients with established CVD) and to guide use of statin therapy in all patients.
Lifestyle interventions	Lifestyle interventions as core management for prevention and treatment of high BP, with emphasis on use of lifestyle interventions for all patients with elevated BP or hypertension.	Similar lifestyle interventions and emphasis on use of lifestyle interventions for all patients with high normal BP or any grade of hypertension.
Drug treatment strategy	Core treatment based on 4 major groups of drugs (ACE-inhibitor or ARB, CCB, or thiazide/thiazide-like diuretic). Use of β-blockers when there are compelling indications. Initial treatment with 2-drug therapy for most adults with hypertension, but especially in African-Americans and adults with stage 2 hypertension and an average SBP/DBP >20/10 mm Hg above their BP target. Single pill combination therapy recommended to improve adherence.	Core treatment based on 4 major groups of drugs (ACE-inhibitor or ARB, CCB, or thiazide/thiazide-like diuretic). Use of β-blocker when there are compelling indications. Initial treatment with 2-drug therapy for most adults with hypertension. Single pill combination therapy recommended to improve adherence and BP control.

Vasan, JAMA Nov 6, 2018 Volume 320

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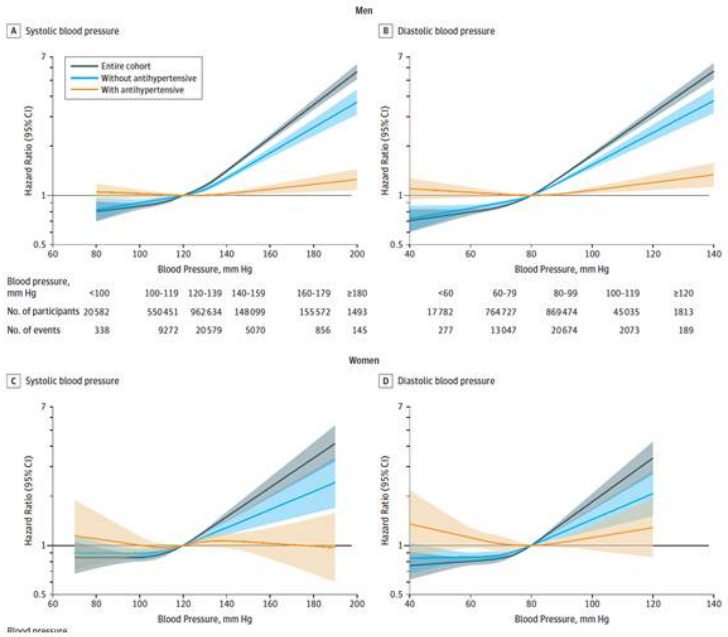
Association of Blood Pressure Classification in 2.488101 Korean young Adults According to the 2017 ACC/AHA guidelines with Subsequent Cardiovascular Disease Events



Son et al., JAMA. 2018 Nov 6;320(17):1783-1792.

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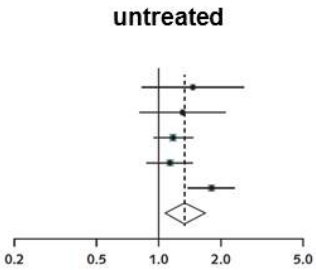
Cardiovascular Events and Mortality in White Coat Hypertension A Systematic Review and Meta-analysis

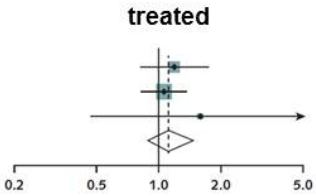
Jordana B. Cohen et al

Figure 3. All-cause mortality risk in WCH and WCE.

Study, Year (Reference)	Total Participants, *n*	HR (95% CI)
Mancia et al, 2013 (26)	1589	1.46 (0.83–2.57)
Sung et al, 2013 (27)	1257	1.30 (0.81–2.09)
Asayama et al, 2014 (28)	8237	1.17 (0.94–1.47)
Stergiou et al, 2014 (29)	6458	1.13 (0.87–1.46)
Banegas et al, 2018 (30)	63 910	1.79 (1.38–2.32)
Overall (I^2 = 41.1%; P = 0.095)		1.33 (1.07–1.67)



Study, Year (Reference)	Total Participants, *n*	HR (95% CI)
Stergiou et al, 2014 (29)	6458	1.19 (0.82–1.73)
Banegas et al, 2018 (30)	63 910	1.06 (0.82–1.37)
Spannella et al, 2018 (43)	120	1.58 (0.47–5.30)
Overall (I^2 = 0.0%; P = 0.747)		1.11 (0.89–1.46)



Cohen et al., Ann Intern Med. 2019 Jun 11. doi: 10.7326/M19-0223

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Blood pressure and organ donation

KDIGO guidelines
for living donor selection state that normal BP, as defined by guidelines for the general population in the country or region where donation is planned, is acceptable for donation.

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Diagnostic Performance of Blood Pressure Measurement Modalities in Living Kidney Donor Candidates

Sherif Armanyous,1 Yasushi Ohashi,1 Michael Lioudis,1 Jesse D. Schold,2 George Thomas,1 Emilio D. Poggio,1 and Joshua J. Augustine1

Hypertension was diagnosed in 90 (16%) prospective donors by JNC-7 criteria and 198 (34%) prospective donors by ACC/AHA criteria

Clin J Am Soc Nephrol 14: 2019.

Nephro Update Europe 2019

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Table 3. Empirical new BP thresholds derived to optimize the sensitivity and specificity of diagnosing hypertension as determined using 24-hour BP monitoring

BP Classification	Office Systolic BP	Office Diastolic BP	Automated Systolic BP	Automated Diastolic BP
JNC-7	123	82	120	78
ACC/AHA	119	79	116	76

JNC-7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; ACC/AHA, American College of Cardiology/American Heart Association.

Using these lower cutoffs, the sensitivity for detecting hypertension improved from 79%to 87% for JNC-7 and from 32%to 87% by ACC/AHA definition

Clin J Am Soc Nephrol 14: 2019.

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The controversy between AHA and ESC guidelines

The European guideline recommends a target of less than 140/90 mm Hg, with flexibility for individualized management depending on treatment tolerance and impact on renal Function and electrolyte levels.

The US guideline recommends a target below 130/80 mm Hg, largely based on the favorable CVD and all-cause mortality experience in SPRINT participants with CKD at baseline

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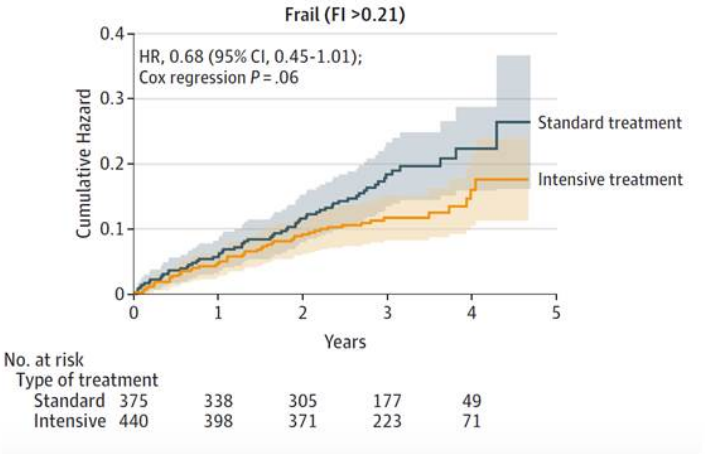
Intensive vs Standard Blood Pressure Control in Adults Aged ≥75 Years



- 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

Williamson JAMA. 2016;315(24):2673-2682

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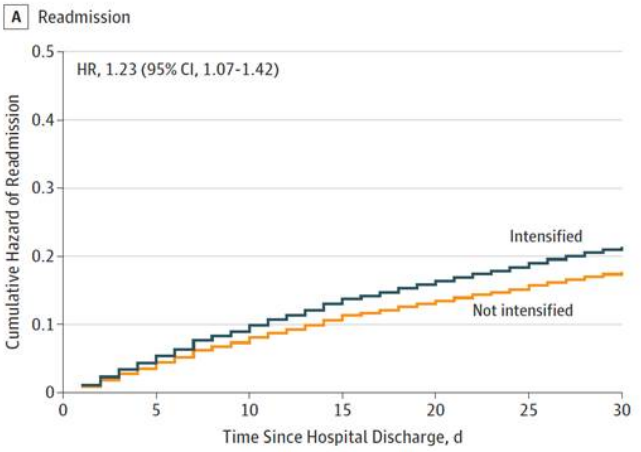
Clinical OutcomesAfter Intensifying Antihypertensive Medication Regimens Among Older Adults at Hospital Discharge

Timothy S. Anderson,

Figure. Cumulative Hazard Plots Comparing Outcomes With Exposure to Antihypertensive Regimen Intensifications at Hospital Discharge



JAMA Intern Med. doi:10.1001/jamainternmed.2019.3007

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Brain injury

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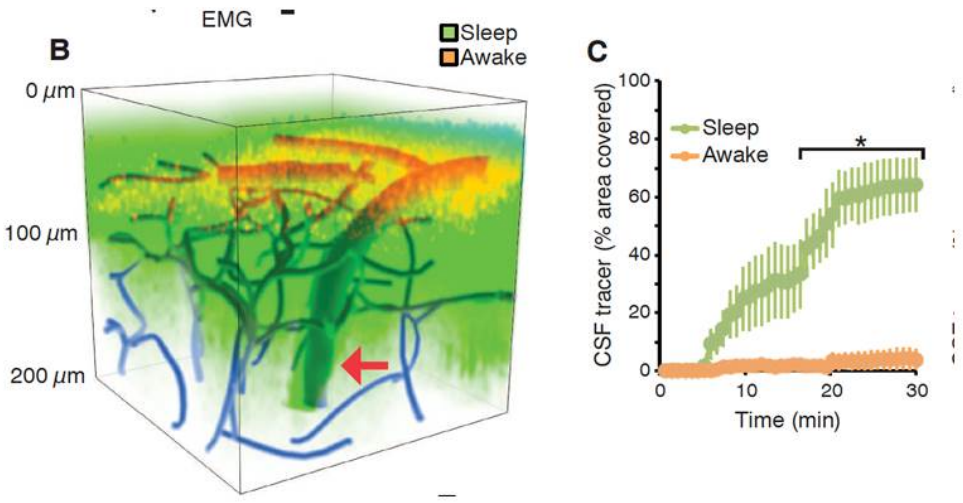
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,1



Xie et al., Science. 2013 Oct 18;342(6156):373-7

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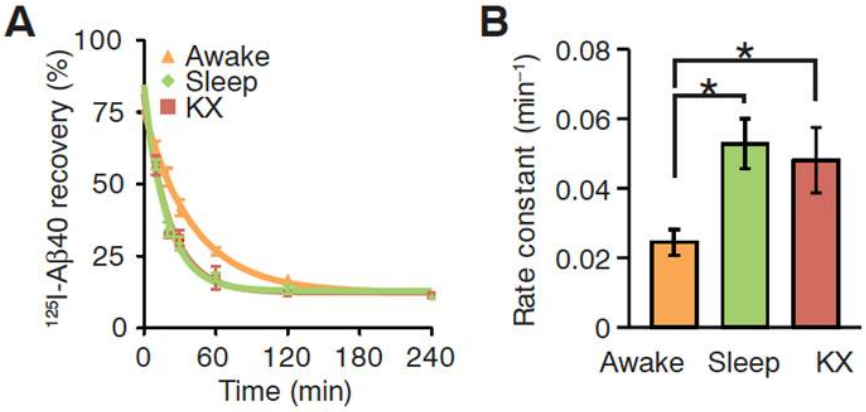

Xie et al., Science. 2013 Oct 18;342(6156):373-7

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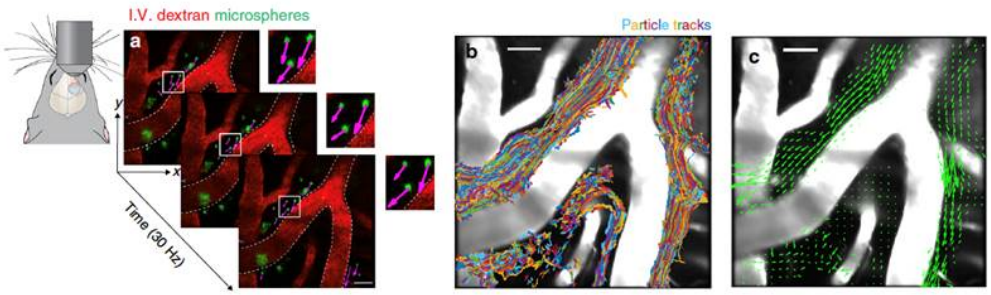
Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension

Humberto Mestre 1,2, Jeffrey Tithof 3, Ting Du1,4, Wei Song1, Weiguo Peng1,5, Amanda M. Sweeney1, Genaro Olveda1, John H. Thomas3, Maiken Nedergaard1,5 & Douglas H. Kelley 3



Mestre et al., Nat Commun. 2018 Nov 19;9(1):4878

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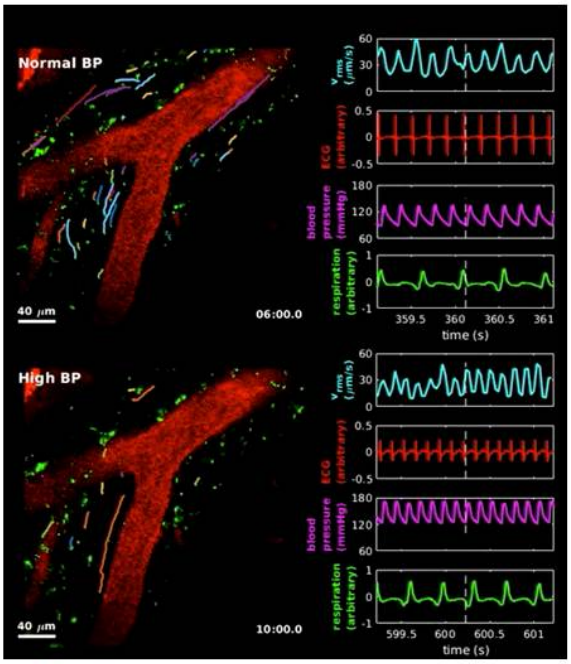

Mestre et al., Nat Commun. 2018 Nov 19;9(1):4878

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Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia

Keenan A.Walker, PhD; A. Richey Sharrett,MD,…….; Rebecca F. Gottesman, MD, PhD

Walker et al., JAMA. 2019 Aug 13;322(6):535-545

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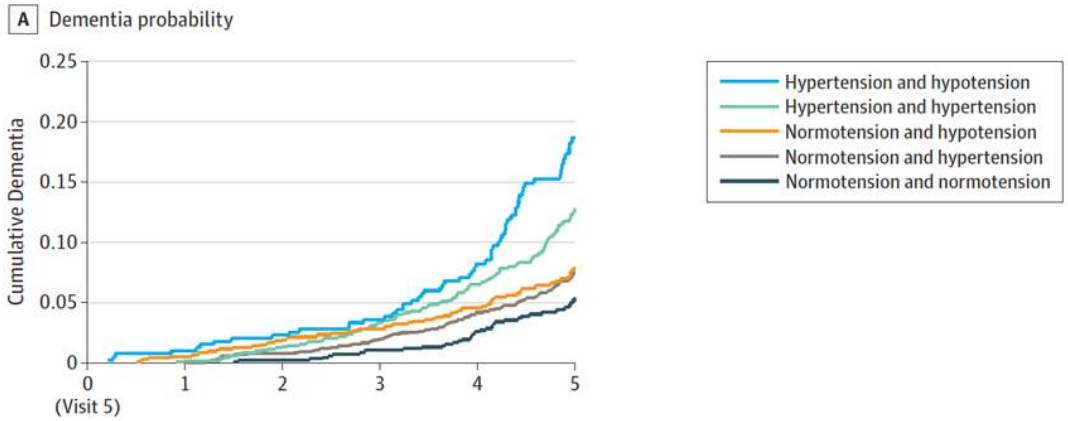

Walker et al., JAMA. 2019 Aug 13;322(6):535-545

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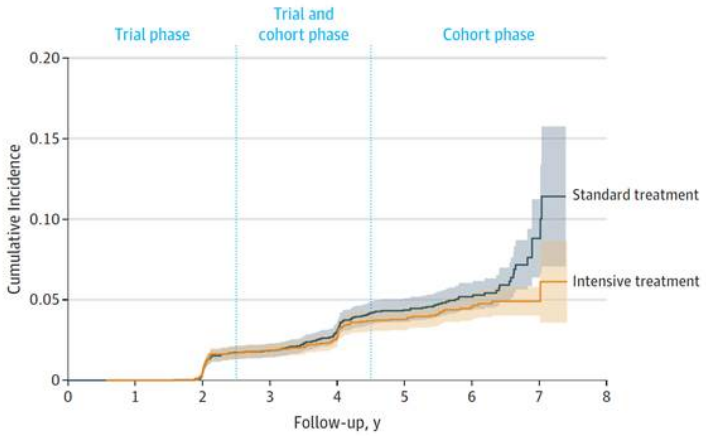
Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia:A Randomized Clinical Trial

The SPRINT MIND Investigators

Figure 2. Probable Dementia by Treatment Group



No. at risk									
Standard treatment	4285	4282	4168	3886	2829	2107	989	87	0
Intensive treatment	4278	4277	4171	3917	2893	2189	1027	93	0

SPRINT MIND Investigators for the SPRINT Research GroupJAMA. 2019 Feb 12;321(6):553-561

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

The SPRINT MIND Investigators

Research Original Investigation Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia

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

	Treatment Group					
	Intensive		Standard			
Outcomes	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
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.

SPRINT MIND Investigators for the SPRINT Research GroupJAMA. 2019 Feb 12;321(6):553-561

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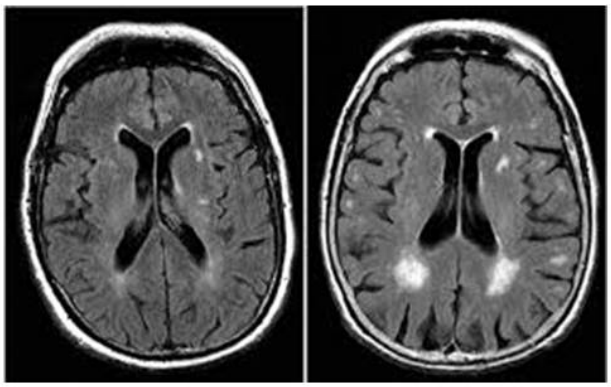
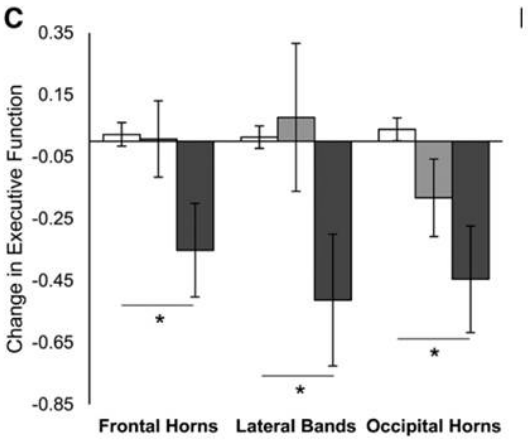
Cognitive Impact of Cerebral Small Vessel Disease Changes in Patients With Hypertension

Joan Jiménez-Balado,





Hypertension. 2019;73:342-349

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INtensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional DecIINe In The ElderIY (INFINITY)

3 Years post-randomization, 24-hour BPs were 131/65 mmHg and 146/74 mmHg in the intensive-BP and standard-BP groups, respectively.

In the intensive-BP group, white matter lesions were reduced by 40% (0.29% vs. 0.48%, P=0.03), compared to the standard-BP group.

Presented at ACC.19 by William B White (Farmington, CT, USA)

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In the intensive-BP group, white matter lesions were reduced by 40% (0.29% vs. 0.48%, P=0.03), compared to the standard-BP group.

Reduced cerebrovascular damage was not significantly linked to differences in mobility decline.

In the intensive-BP group, only 1 out of 6 cognitive parameters (sequential reaction time) was significantly improved (-23±16 ms vs. 33±15 ms) compared to the standard-BP group.

Falls and syncope were not significantly different between the two treatment groups.

Presented at ACC.19 by William B White (Farmington, CT, USA)

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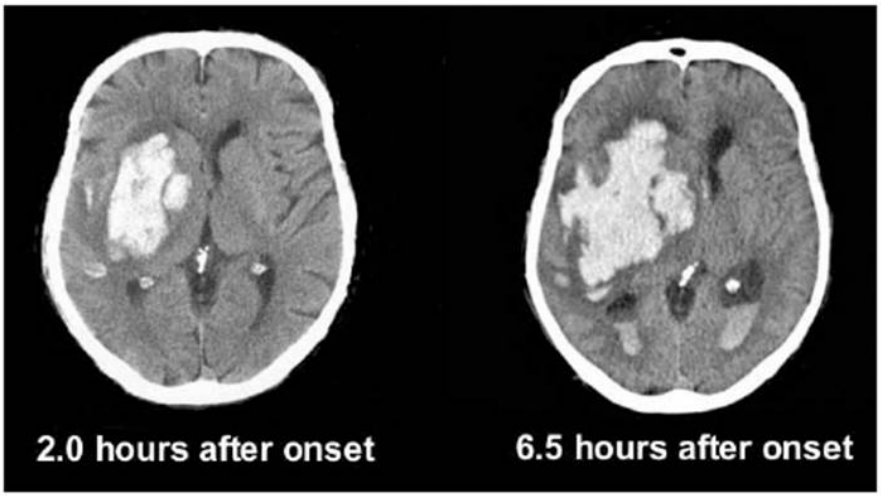
Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage



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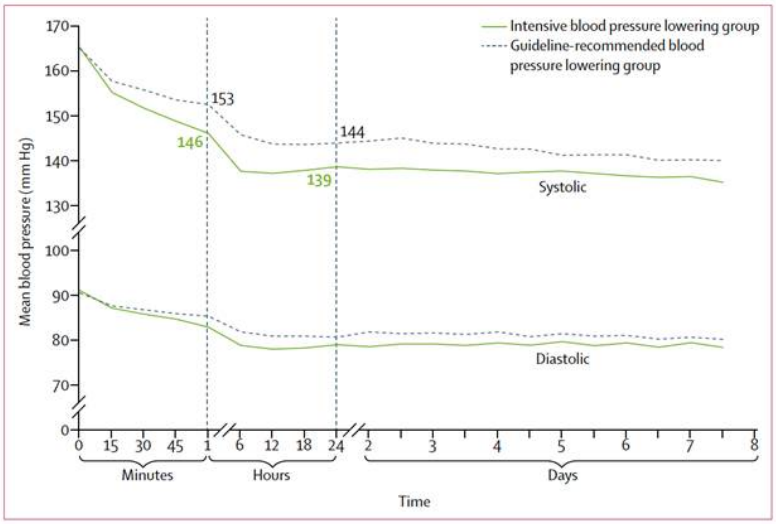
Intensive blood pressure reduction with intravenousthrombolysis therapy for acute ischaemic stroke (ENCHANTED)

Craig S Anderson et al



Anderson et al., Lancet. 2019 Mar 2;393(10174):877-888

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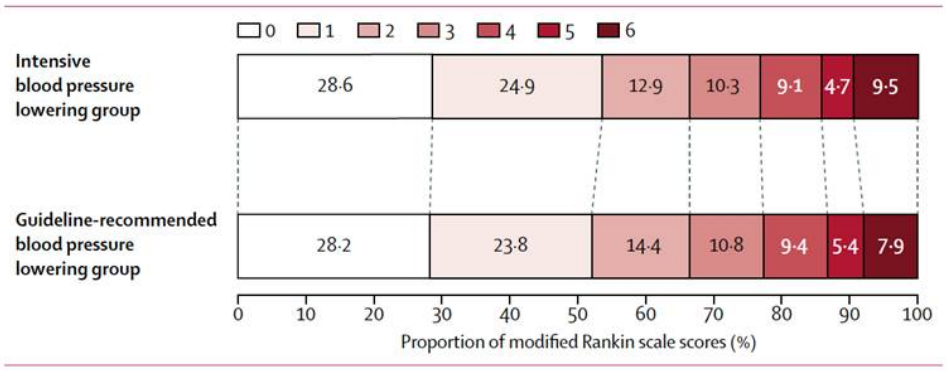
Craig S Anderson et al



Anderson et al., Lancet. 2019 Mar 2;393(10174):877-888

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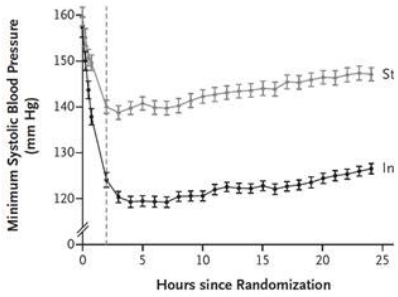
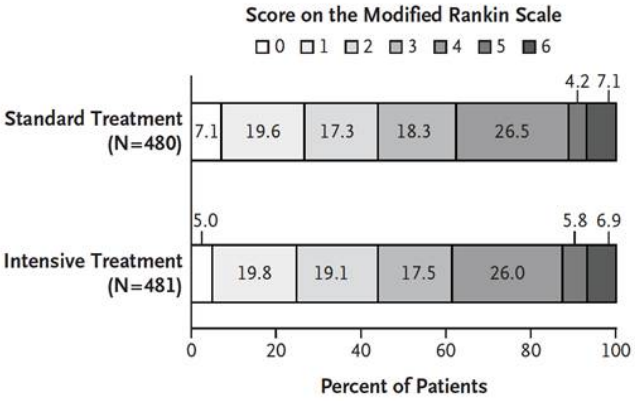
Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage





- Average BP level at presentation 200 mmHg
- Titration of BP using nicardipine and labetalol
- No advantage, but also no disadvantage

Qureshi, N Engl J Med 2016;375:1033-43

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The sartan recall

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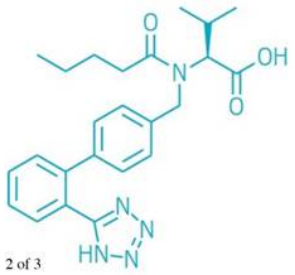
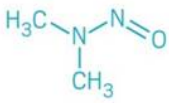
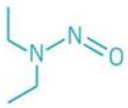




NDMA



NDEA

More than 61 million prescriptions/year in the US alone

Concentrations found cause in 1 of 100,000 users cancer after 70y years of exposure

Byrd et al., N Engl J Med. 2019 Apr 25;380(17):1589-1591

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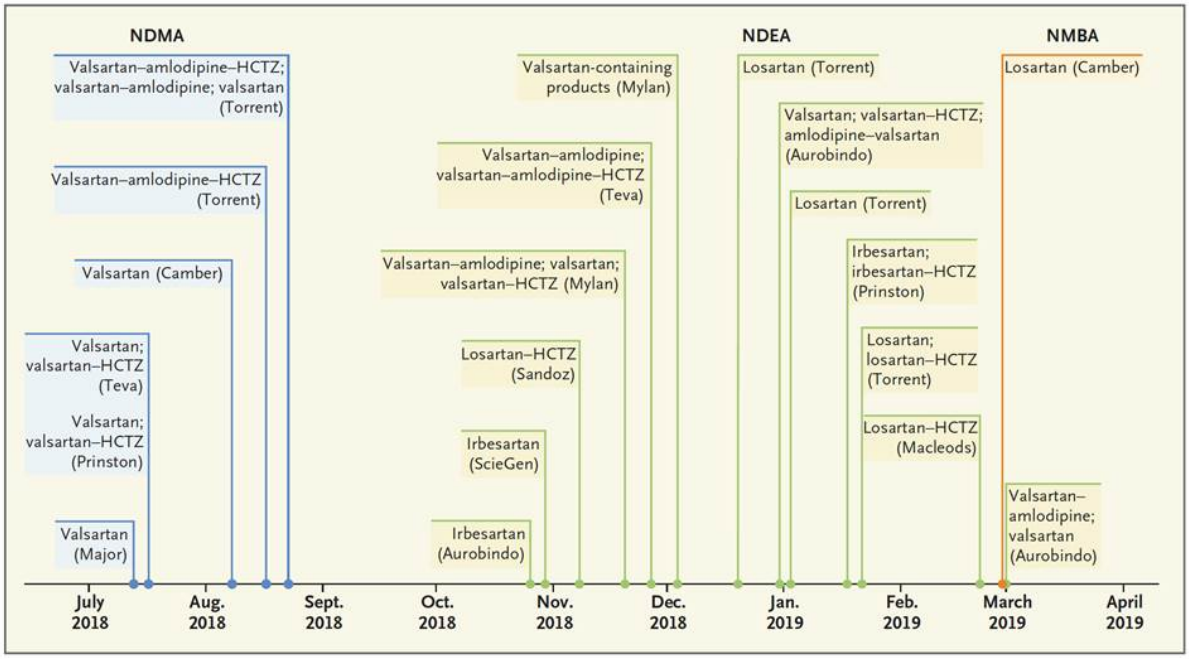
Anatomy of the Angiotensin- Receptor Blocker Recalls

J. Brian Byrd, M.D., M.S.C.I., Glenn M. Chertow, M.D., M.P.H., and Vivek Bhalla, M.D.



Recalls of Angiotensin-Receptor Blockers.

Byrd et al., N Engl J Med. 2019 Apr 25;380(17):1589-1591

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Treatment-resistant hypertension

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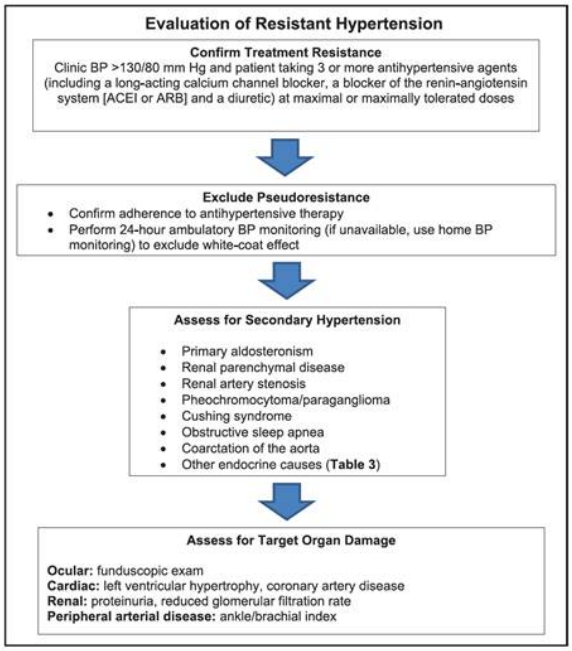
Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association



Carey et al., Hypertension. 2018 Nov;72(5):e53-e90.

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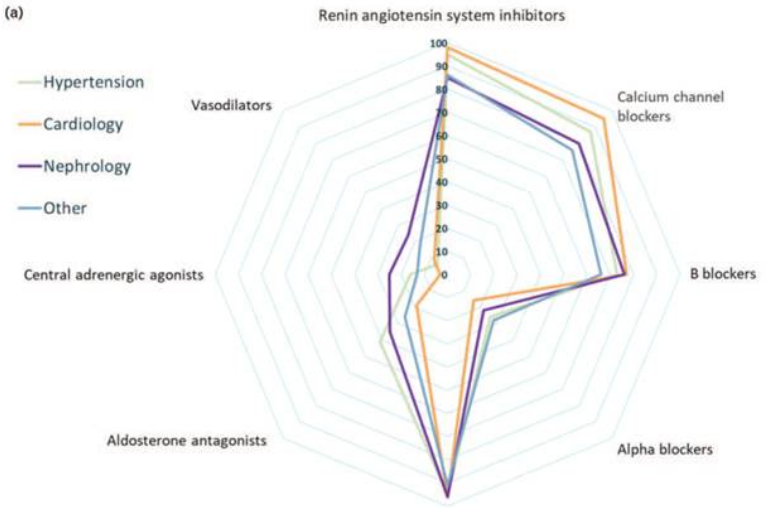
Clinical characteristics, antihypertensive medication use and blood pressure control among patients with treatment-resistant hypertension:

Cheryl Carcel,b,c, Bruce Neala,b,d, Suzanne Oparile, Kris Rogersa, Krzysztof Narkiewiczf, Ji Guang Wangg, Ernesto L. Schiffrinh, Neil Poulteri, Michel Azizij,k,l, and John Chalmersa,c



Carcel et al., J Hypertens. 2019 Aug 13. doi: 10.1097/HJH.0000000000002184

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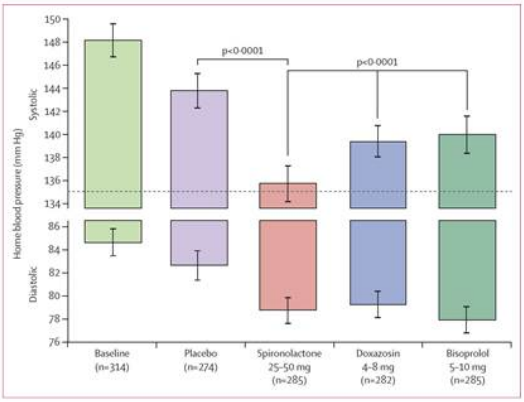
The efficacy of mineralocorticoid receptor blockade in resistant hypertension



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

Williams, Lancet 2015; 386: 2059–68

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State of the Art
Renal denervation for therapy resistant hypertension

- Early uncontrolled and unblinded trials reported large reductions in blood pressure following renal denervation in patients with uncontrolled hypertension.
- the randomised, sham-controlled SYMPLICITY 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.

Bhatt et al., N Engl J Med. 2014 Apr 10;370(15):1393-401.

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Catheter-Based Renal Denervation in Patients with Hypertension

Meta-analysis included 977 patients from 6 sham-controlled trials

582 randomized to renal sympathetic denervation (RSD) and 395 to sham

Three 2nd generation RSD trials were designed and performed with more attention to procedural technique and patient selection

Mean patients age: 52.8 to 64.5 years

Median follow-up: 2 to 6 months

24-hour ambulatory systolic blood pressure (SBP) reduction:
SBP reduction in all trials: 3.65 mm Hg, $p < 0.001$
SBP Reduction in 2nd generation trials: 4.85 mm Hg, $p < 0.001$

Office SBP reduction:
SBP reduction in all trials: 5.53 mm Hg, $p < 0.001$
SBP reduction in 2nd generation trials: 7.07 mm Hg, $p < 0.001$

Adverse events associated with RSD were rare.

Sardar, P. et al. J Am Coll Cardiol. 2019;73(13):1633–42.

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Malignant hypertension and TMA

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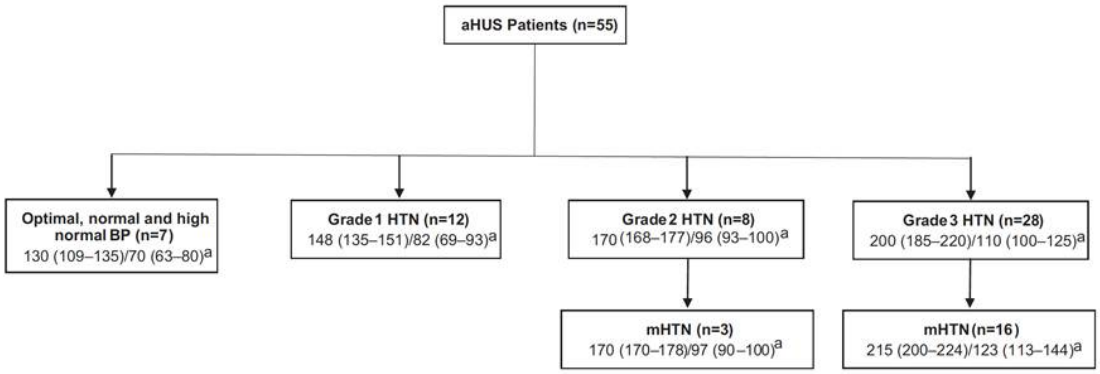
Severe and malignant hypertension are common in primary atypical hemolytic uremic syndrome

Teresa Cavero et al on behalf of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)



Eculizumab improves renal survival irrespective of HTN

Kidney International (2019) doi.org/10.1016/

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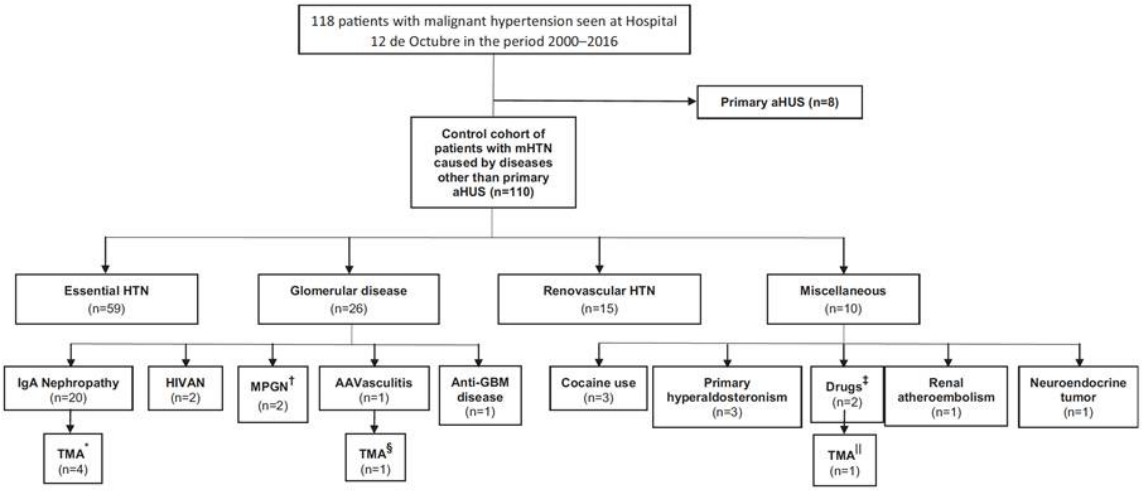

Cavero et al., Kidney Int. 2019 May 31. pii: S0085-2538(19)30582-4

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Hyperaldosteronism

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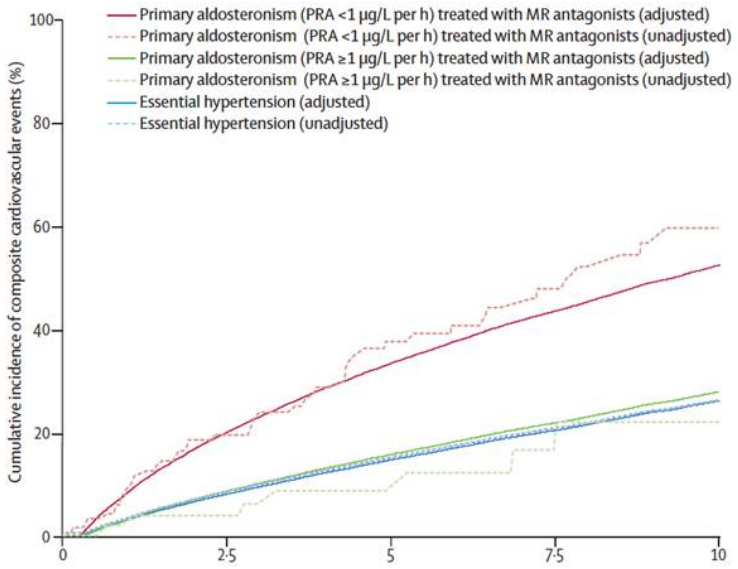
Cardiovascular Outcomes in Medically Primary Aldosteronism



Hundemer et al., Lancet Diabetes Endocrinol. 2018 Jan;6(1):51-59

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Clinical Outcomes After Unilateral Adrenalectomy for Primary Aldosteronism

Table 3. Clinical Success: Cure, Clear Improvement, and No Clear Success

Variable	Total Cohort (n = 435)	Clinical Success		
		Cure (n = 118 [27.1%])	Clear Improvement (n = 135 [31.0%])	No Clear Success (n = 182 [41.8%])
Preoperative				
SBP, mean (SD), mm Hg	150 (20)	143 (17)	150 (17)	155 (22)
DBP, mean (SD), mm Hg	90 (13)	88 (11)	90 (12)	91 (15)
Preoperative hypertension grade, No. (%)[a]				
0	111 (25.5)	49 (41.5)	27 (20.0)	35 (19.2)
1	180 (41.4)	41 (34.7)	70 (51.9)	69 (37.9)
2	105 (24.1)	24 (20.3)	27 (20.0)	54 (29.7)
3	39 (9.0)	4 (3.4)	11 (8.1)	24 (13.2)
No. of antihypertensives/d, median (range)[b]	3 (0 to 8)	2 (0 to 6)	3 (1 to 8)	3 (0 to 7)
DDD (n = 405)[b]				
Median (range)	3.7 (0.0 to 25.3)	2.2 (0.0 to 15.7)	4.1 (0.5 to 25.3)	4.3 (0.0 to 22.3)
No. of pills/d (n = 407)[b]				
Median (range)	3 (0 to 10)	2 (0 to 7)	4 (1 to 10)	4 (0 to 9)

Vorselaars et al., JAMA Surg. 2019 Apr 1;154(4):e185842.

Nephro Update Europe 2019

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Preoperative				
No. of antihypertensives/d, median (range)[b]	1 (0 to 6)	0	2 (1 to 5)	2 (0 to 6)
DDD (n = 402)[b]				
Median (range)	1.0 (0.0 to 11.7)	0	2.0 (0.1 to 11.7)	2.0 (0.0 to 9.8)
No. of pills/d (n = 407)[b]				
Median (range)	1 (0 to 9)	0	2 (0 to 8)	2 (0 to 9)
Preoperative-Postoperative Change[c]				
SBP, mean (SD), mm Hg	17 (21)	21 (18)	25 (18)	9 (22)
DBP, mean (SD), mm Hg	7 (14)	9 (11)	12 (12)	3 (15)

Vorselaars et al., JAMA Surg. 2019 Apr 1;154(4):e185842.

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Hypertension & metabolism

Nephro Update Europe 2019

Uric acid and hypertension: state of the art

An elevated uric acid level consistently predicts the development of hypertension.

An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.

Raising the uric acid level in rodents results in hypertension.

Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.

Feig, N Engl J Med 2008;359:1811-21.

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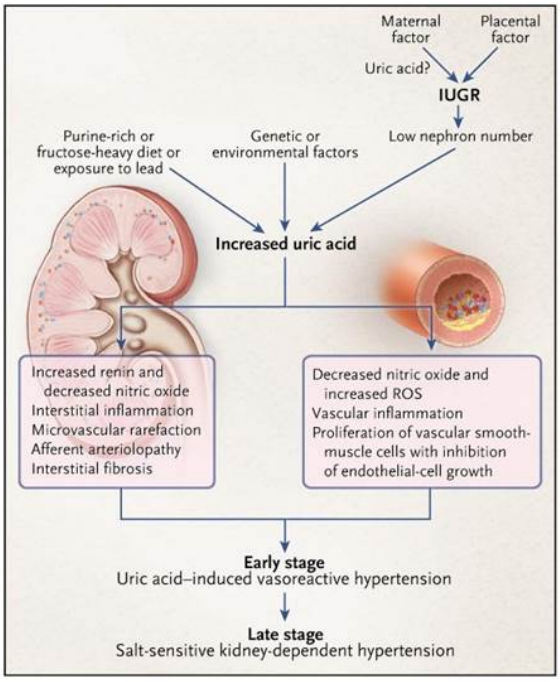
Uric acid and hypertension: state of the art



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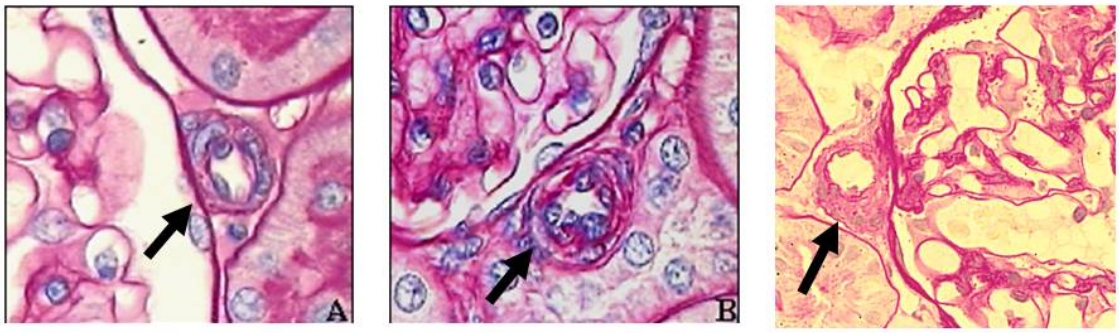
Hyperuricemia Induces Preglomerular Vascular Disease

Normal Rat **Hyperuricemic Rat** **Essential Hypertension**



Mazzali et al., Am J Physiol Renal Physiol. 2002 Jun;282(6):F991-7

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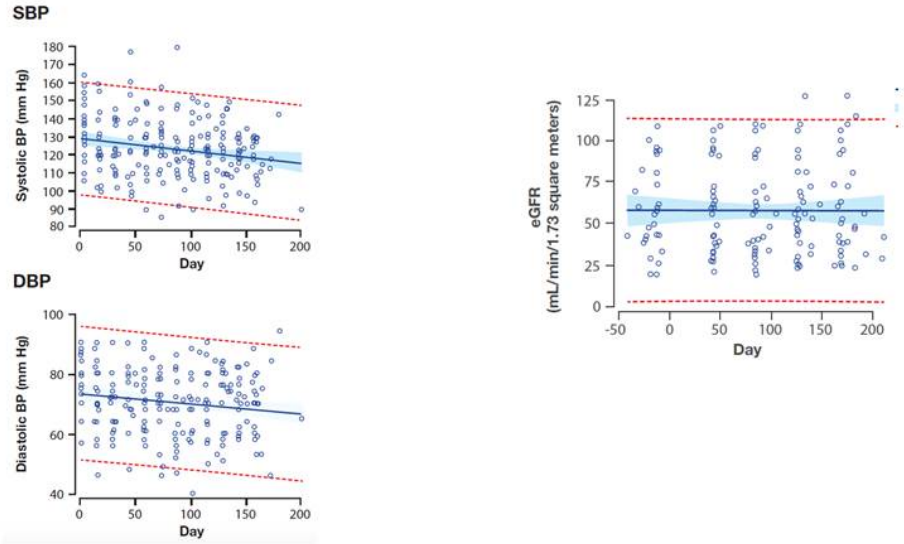
Pegloticase Treatment Significantly Decreases Blood Pressure in Patients With Chronic Gout

Richard J. Johnson, Hyon K. Choi, Anthony E. Yeo, Peter E. Lipsky



Johnson et al., Hypertension. 2019 Jul;74(1):95-101

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