News in HTA management in 2013-2014?

JM Krzesinski

ULg-CHU Liège

Topics discussed on HTA

- European, American and International guidelines
- Quality of BP measurements
- Non pharmacological aspects
- Management of special situations

  (ARAS, Resistant HTA, Hemodialysis)

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Journal of Hypertension 2013, 31:1281–1357

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2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

JAMA. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

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Clinical Practice Guidelines for the Management of Hypertension in the Community
A Statement by the American Society of Hypertension and the International Society of Hypertension

Journal of Hypertension 2014, 32:3–15

Michael A. Weber[a], Ernesto L. Schiffrin[b], William B. White[c], Samuel Mann[d], Lars H. Lindholm[e], John G. Kenerson[f], John M. Flack[g], Barry L. Carter[h], Barry J. Materson[i], C. Venkata S. Ram[j], Debbie L. Cohen[k], Jean-Claude Cadet[l], Roger R. Jean-Charles[m], Sandra Taler[n], David Kountz[o], Raymond Townsend[p], John Chalmers[q], Agustin J. Ramirez[r], George L. Bakris[s], Jiguang Wang[t], Aletta E. Schutte[u], John D. Bisognano[v], Rhian M. Touyz[w], Dominic Sica[x], and Stephen B. Harrap[y]

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Journal of Hypertension 2013, 31:1281–1357

New guidelines ESH 2013

- Stimulation of out of the office BP measurements
- No initiation of anti HTA treatment in high normal BP situations
- Simplification of the BP targets which are less strict in many groups
- Delay before starting antiHTA treatment in the very old (>80y) and higher BP target than before
- Less tight BP targets even in diabetic, CKD or high CV risk patients
- Coming back of the beta-blockers as first line treatment
- Modification of the management of resistant patients

When proposing out of the office measurement?

Clinical indications for HBPM or ABPM
• Suspicion of white-coat hypertension
- Grade I hypertension in the office
- High office BP in individuals without asymptomatic organ damage and at low total CV risk
• Suspicion of masked hypertension
- High normal BP in the office
- Normal office BP in individuals with asymptomatic organ damage or at high total CV risk
• Identification of white-coat effect in hypertensive patients
• Considerable variability of office BP over the same or different visits
• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
• Elevated office BP or suspected pre-eclampsia in pregnant women
• Identification of true and false resistant hypertension
Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status
• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes
• Assessment of BP variability

Home BP

- WCHTA
- Masked HTA
- Pregnancy inducedHTA
- Highly variable HTA
- Resistant HTA

MAPA

- Dipping
- Discordance office and home BP values
- Variability approach

When starting the treatment?

Recommendations	Class[a]	Level
Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes.	I	A
Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range.	I	B
Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	IIa	B
In elderly hypertensive patients drug treatment is recommended when SBP is ≥160 mmHg.	I	A

2013 ESH/ESC Guidelines for the management of arterial hypertension

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

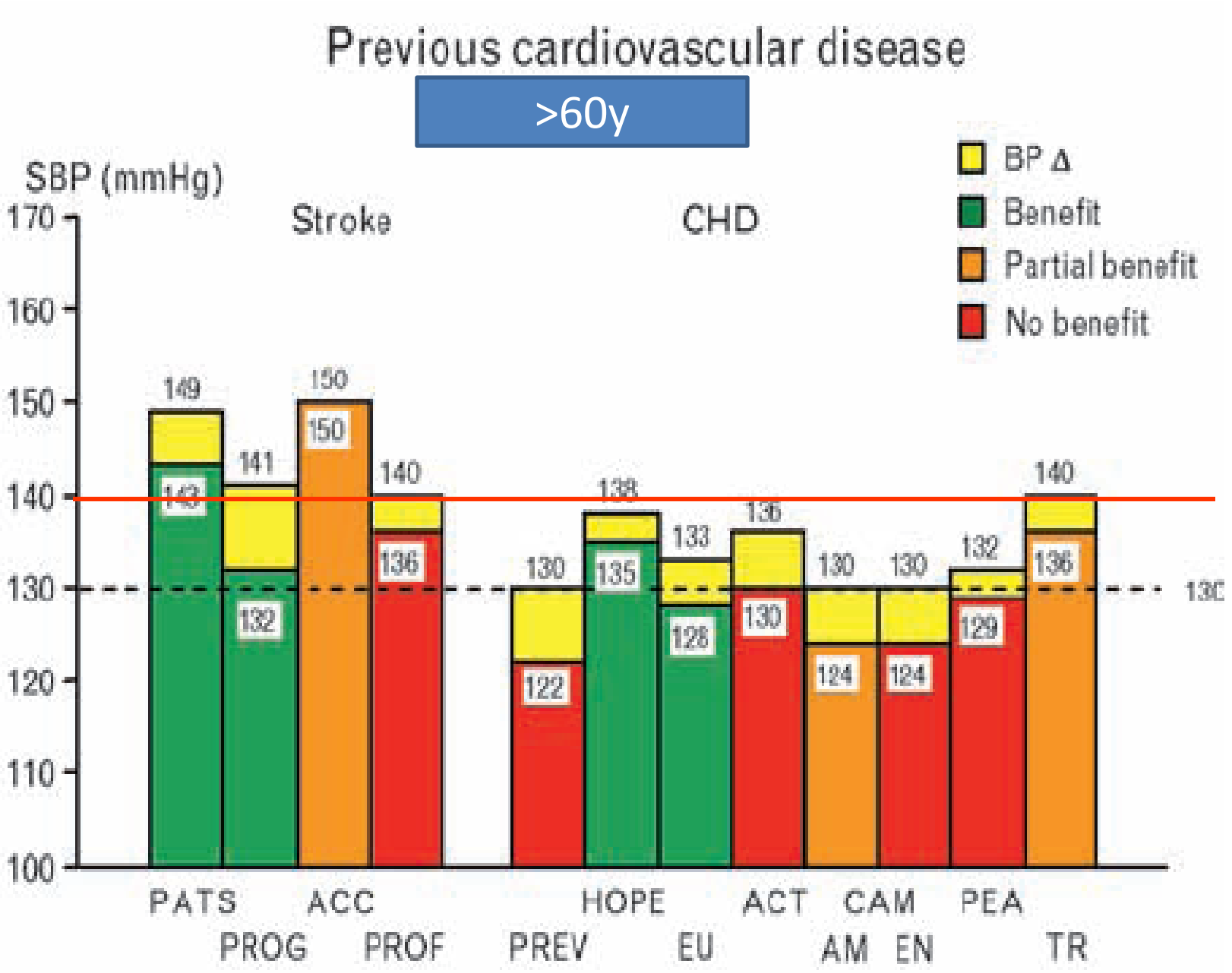
ESH–ESC and JNC 7 Summary: Target BP Goals (2003 and 2007)

Type of hypertension	BP goal (mmHg)
Uncomplicated	<140/90
Complicated	
Diabetes mellitus	<130/80
Kidney disease	<130/80
Other high risk (stroke, myocardial infarction)	<130/80

Task Force of ESH–ESC. J Hypertens 2007;25:1105–87
Chobanian et al. JAMA 2003;289:2560–72

New BP targets

- **SBP < 140/90 mmHg** in all adults < 80 ans (with or without CV complications)
- In people **older than 80 ans** and in good health: start antiHTA drugs when SBP> 160 mmHg with a BP target between 140 and 150 mmHg.
- In **Diabetes**, target <140/85 mmHg
- In **CKD**, target <140/90 mmHg except when proteinuria (130/90 mmHg)


Previous cardiovascular disease
>60y
SBP (mmHg)
Stroke
CHD
BP Δ
Benefit
Partial benefit
No benefit
170
160
150
140
130
120
110
100
149
143
141
132
150
150
140
136
130
122
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135
133
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Tight Versus Standard Blood Pressure Control in Patients With Hypertension With and Without Cardiovascular Disease

Gianpaolo Reboldi, Fabio Angeli, Giovanni de Simone, Jan A. Staessen, Paolo Verdecchia; on behalf of the Cardio-Sis Investigators

Abstract—An excessive blood pressure (BP) reduction might be dangerous in high-risk patients with cardiovascular disease. In the Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (Cardio-Sis), 1111 nondiabetic patients with systolic BP ≥150 mm Hg were randomly assigned to a systolic BP target <140 mm Hg (standard control) or <130 mm Hg (tight control). We stratified patients by absence (n=895) or presence (n=216) of established cardiovascular disease at entry. Antihypertensive treatment was open-label and tailored to each patient's needs. After 2-year follow-up, the primary end point of the study, electrocardiographic left ventricular hypertrophy, occurred less frequently in the tight than in the standard control group in the patients without (10.8% versus 15.2%) and with (14.1% versus 23.5%) established cardiovascular disease (*P* for interaction=0.82). The main secondary end point, a composite of cardiovascular events and all-cause death, occurred less frequently in the tight than in the standard control group both in patients without (1.47 versus 3.68 patient-years; *P*=0.016) and with (7.87 versus 11.22 patient-years; *P*=0.049) previous cardiovascular disease. In a multivariable Cox model, allocation to tight BP control reduced the risk of cardiovascular events to a similar extent in patients with or without overt cardiovascular disease at randomization (*P* for

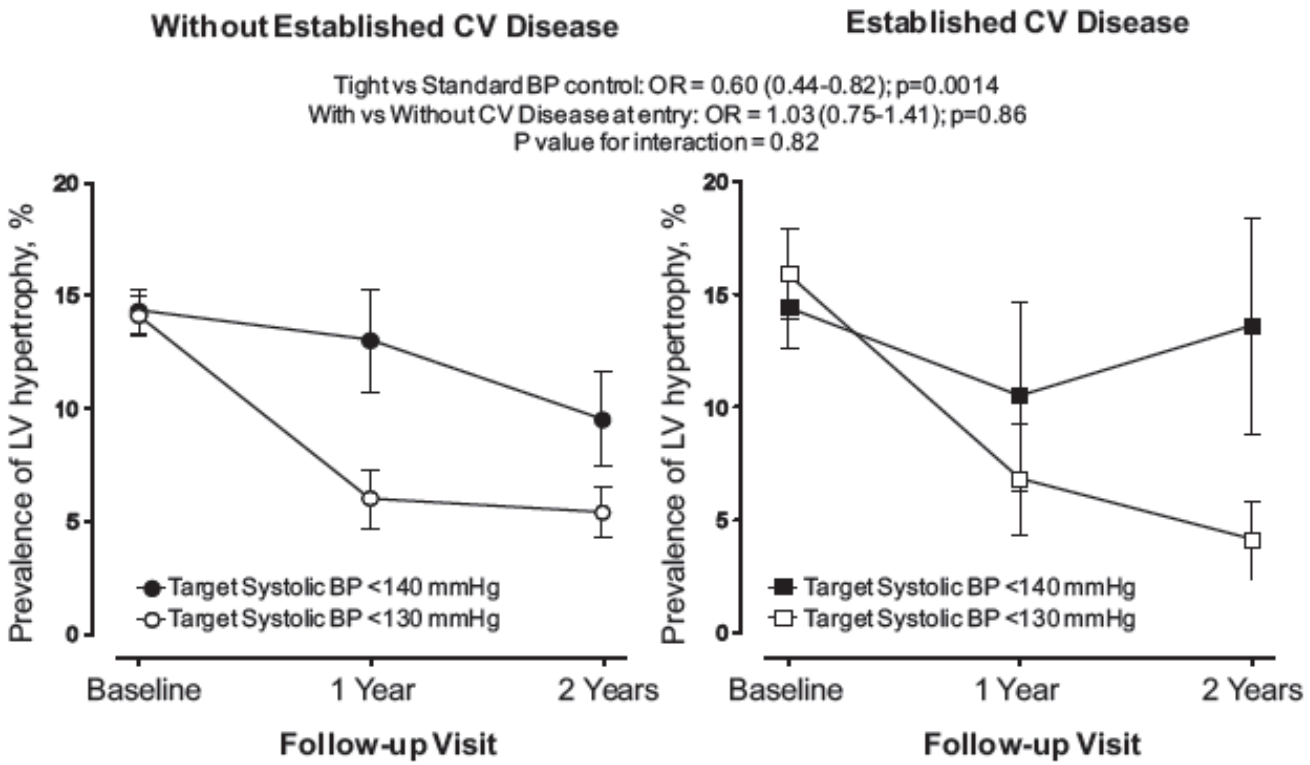
Table 1. Main Characteristics of Patients With and Without Established Cardiovascular Disease at Entry

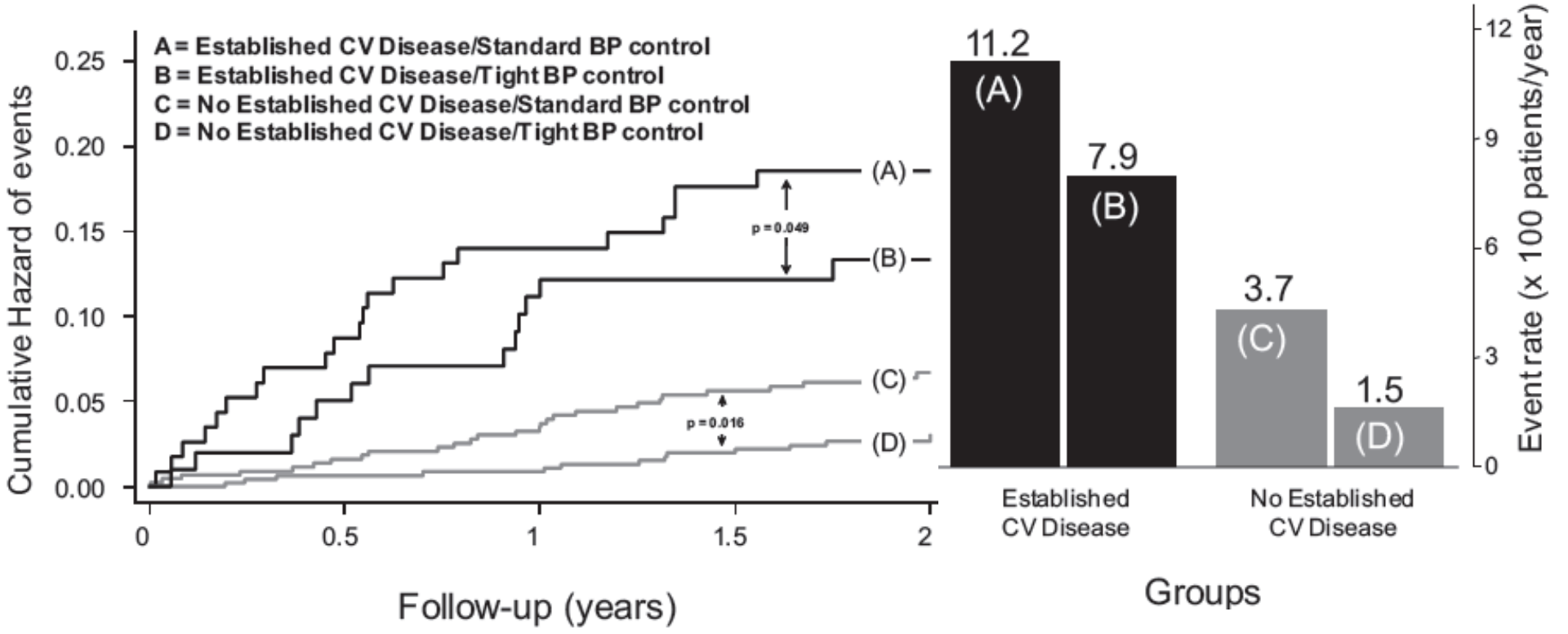
Characteristics	Without Established Cardiovascular Disease (n=895)			With Established Cardiovascular Disease (n=216)		
	Standard BP control (n=438)	Tight BP control (n=457)	*P* Value	Standard BP control (n=115)	Tight BP control (n=101)	*P* Value
Age, y	66 (7.3)	66 (6.8)	0.46	69.8 (7.1)	71.7 (7.6)	0.07
Women, %	62.3	60.1	0.42	42.6	53.4	0.11
Current smokers, %	23.7	23.4	0.91	6.9	6.9	0.99
LVH at ECG, %	20.0	19.6	0.86	23.5	29.3	0.33
BMI, Kg/m^2	27.9 (4.1)	28.0 (4.1)	0.58	27.4 (3.4)	27.2 (5.0)	0.78
Waist circumference, cm	98.3 (12)	98.8 (12)	0.56	99.1 (11)	97.5 (12)	0.31
Systolic BP, mm Hg	158.4 (8)	157.8 (8)	0.31	159.4 (10)	158.2 (9)	0.37
Diastolic BP, mm Hg	87.9 (7)	87.6 (8)	0.46	85.5 (9)	84.3 (9)	0.34
Heart rate, beats/min	69.4 (10)	70.2 (10)	0.19	66.7 (10)	68.6 (9)	0.14

Tight Versus Standard Blood Pressure Control in Patients With Hypertension With and Without Cardiovascular Disease

Gianpaolo Reboldi, Fabio Angeli, Giovanni de Simone, Jan A. Staessen and Paolo Verdecchia

Hypertension. published online December 16, 2013;

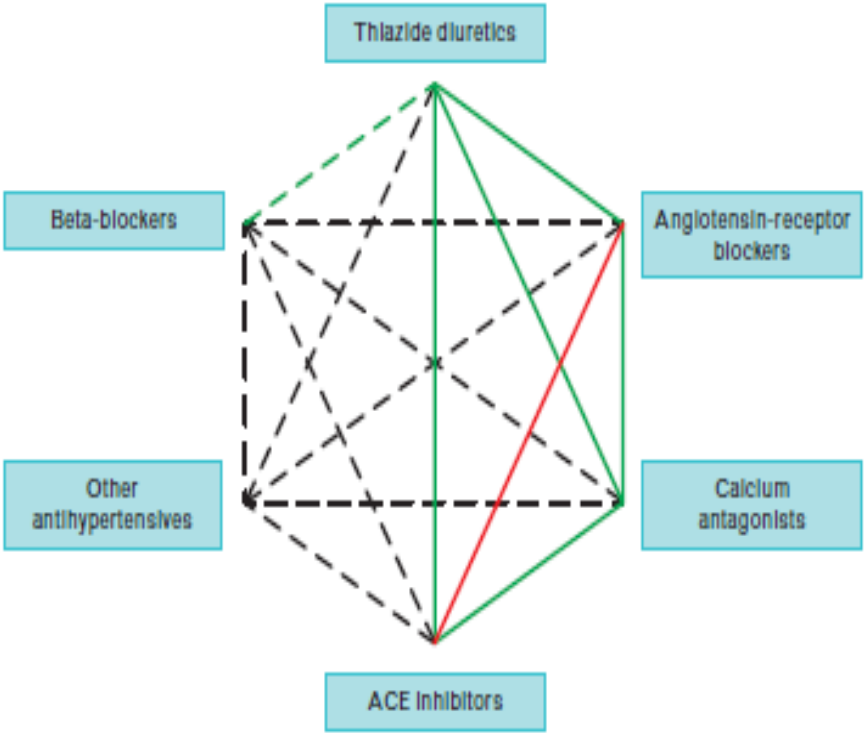



A = Established CV Disease/Standard BP control
B = Established CV Disease/Tight BP control
C = No Established CV Disease/Standard BP control
D = No Established CV Disease/Tight BP control
Cumulative Hazard of events
0.25
0.20
0.15
0.10
0.05
0.00
0
0.5
1
1.5
2
Follow-up (years)
(A)
(B)
(C)
(D)
p = 0.049
p = 0.016
11.2
7.9
3.7
1.5
Event rate (x 100 patients/year)
12
9
6
3
0
Established CV Disease
No Established CV Disease
Groups

2013 ESH/ESC Guidelines for the management of arterial hypertension

Treatment strategies and choice of drugs

Recommendations	Class[a]	Level[b]
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.	I	A



2013 ESH/ESC Guidelines for the management of arterial hypertension

Antihypertensive treatment strategies in the elderly

Recommendations	Class[a]	Level[b]
In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A
In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated.	IIb	C
In individuals older than 80 years with an initial SBP ≥160 mmHg it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B
In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment.	I	C
Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian.	IIa	C
All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension.	I	A

Treatment strategies in patients with diabetes

Recommendations	Class[a]	Level[b]
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.	I	A
A SBP goal <140 mmHg is recommended in patients with diabetes.	I	A
The DBP target in patients with diabetes is recommended to be <85 mmHg.	I	A
All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.	I	A
It is recommended that individual drug choice takes comorbidities into account.	I	C
Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.	III	B

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

This article was published on November 3, 2012, at NEJM.org.

CONCLUSIONS

The addition of aliskiren to standard therapy with renin–angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. (Funded by Novartis; ALTITUDE ClinicalTrials.gov number, NCT00549757.)

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

CONCLUSIONS

Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.)

This article was published on November 9, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1303154

2013 ESH/ESC Guidelines for the management of arterial hypertension

Therapeutic strategies in hypertensive patients with nephropathy

Recommendations	Class[a]	Level[b]
Lowering SBP to <140 mmHg should be considered.	IIa	B
When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored.	IIb	B
RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria.	I	A
Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents.	I	A
Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended.	III	A
Aldosterone antagonists cannot be recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia.	III	C

2013 ESH/ESC Guidelines for the management of arterial hypertension

Therapeutic strategies in patients with resistant hypertension

Recommendations	Class[a]	Level[b]
In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal.	I	C
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.	IIa	B
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	IIb	C
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.	I	C

2014 Evidence-Based Guideline for the Manage of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

JAMA. doi:10.1001/jama.2013.284427
Published online December 18, 2013.

- 9 recommendations

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Recommendation 1

In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.

Strong Recommendation – Grade A

Corollary Recommendation

In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

Expert Opinion – Grade E

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Recommendation 2

In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mm Hg or higher and treat to a goal DBP of lower than 90 mm Hg.

For ages 30 through 59 years, Strong Recommendation – Grade A

For ages 18 through 29 years, Expert Opinion – Grade E

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Table 6. Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB
	General <60 y	<140/90	Black: thiazide-type diuretic or CCB
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	β-Blocker, diuretic, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	

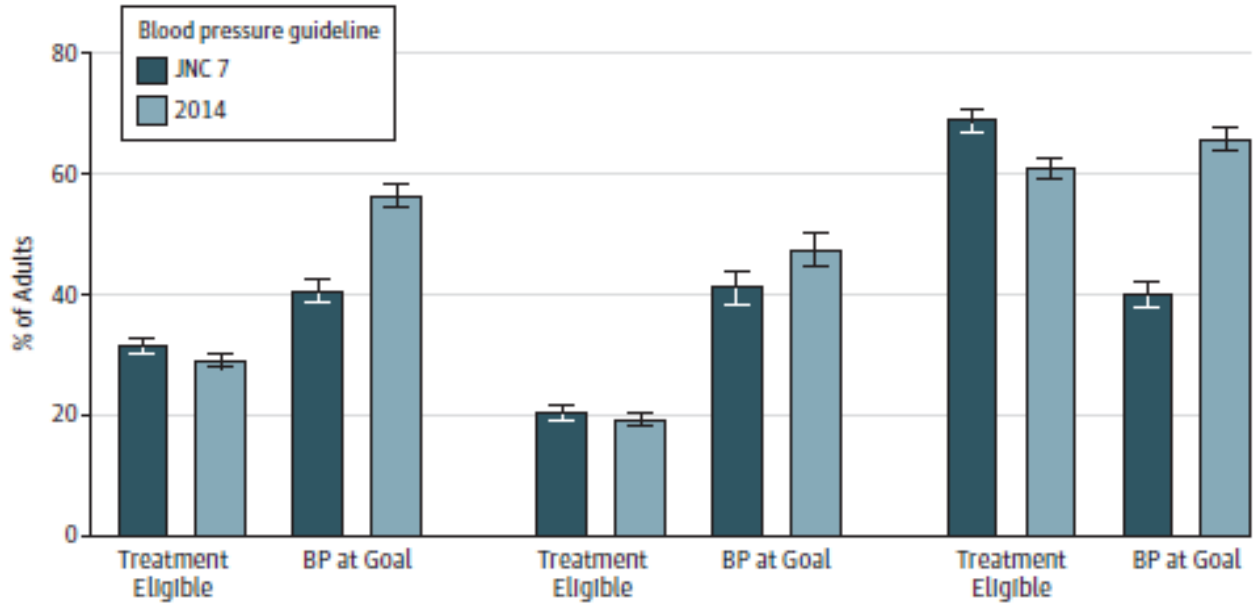
Proportion of US Adults Potentially Affected by the 2014 Hypertension Guideline

Ann Marie Navar-Boggan, MD, PhD; Michael J. Pencina, PhD; Ken Williams, MS; Allan D. Sniderman, MD; Eric D. Peterson, MD, MPH

JAMA. doi:10.1001/jama.2014.2531
Published online March 29, 2014.

CONCLUSIONS AND RELEVANCE Compared with the JNC 7 guideline, the 2014 BP guideline from the panel members appointed to the JNC 8 was associated with a reduction in the proportion of US adults recommended for hypertension treatment and a substantial increase in the proportion of adults considered to have achieved goal BP, primarily in older adults.

Figure. Treatment-Eligible Hypertension and Adults With Above-Goal BP According to JNC 7 and the 2014 Blood Pressure Guideline



NHANES participants												
No. in category	5982	5448	2292	3080	2218	2109	859	943	3764	3339	1433	2137
Total No.	16372	16372	5982	5448	11076	11076	2218	2109	5296	5296	3764	3339

Proportion of all adults aged 18-59 years and aged 60 years or older considered eligible for medication treatment, and the proportion of adults with treatment-eligible hypertension who met BP goals according to JNC 7 and the 2014 blood pressure guideline. Medication-eligible hypertension is defined as receiving therapy or above goal for each guideline. NHANES indicates National Health and Nutrition Examination Survey. Percentages and 95% CIs (error bars) are weighted.

BP measurement
What is new?

Ambulatory Blood Pressure Measurement: What Is the International Consensus?
Eoin O'Brien, Gianfranco Parati and George Stergiou

Hypertension. 2013;62:988-994; originally published online September 23, 2013;

Table 1. Thresholds for Hypertension Diagnosis Based on ABPM

24-h Average	≥130/80 mm Hg
Awake (daytime) average	≥135/85 mm Hg
Asleep (night-time) average	≥120/70 mm Hg

ABPM indicates ambulatory blood pressure monitoring.

Adapted with permission from O'Brien et al.[6] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Table 4. Definition of White-Coat and Masked Hypertension Phenomena*

White-coat hypertension
Untreated subjects with elevated office blood pressure ≥140/90 mm Hg† and
24-h ABPM <130/80 mm Hg and
Awake ABPM <135/85 mm Hg and
Sleep <120/70 mm Hg or
Home blood pressure <135/85 mm Hg
Masked hypertension
Untreated subjects with office blood pressure <140/90 mm Hg and
24-h ABPM ≥130/80 mm Hg and
Awake ABPM ≥135/85 mm Hg and
Sleep ≥120/70 mm Hg or
Home blood pressure ≥135/85 mm Hg
Masked uncontrolled hypertension
Treated subjects with office blood pressure <140/90 mm Hg and
24-h ABPM ≥130/80 mm Hg and/or
Awake ABPM ≥135/85 mm Hg and/or
Sleep ≥120/70 mm Hg or
Home blood pressure ≥135/85 mm Hg

Interpretation of Ambulatory Blood Pressure Profile for Risk Stratification: Keep It Simple

Gianpaolo Reboldi, Fabio Angeli and Paolo Verdecchia

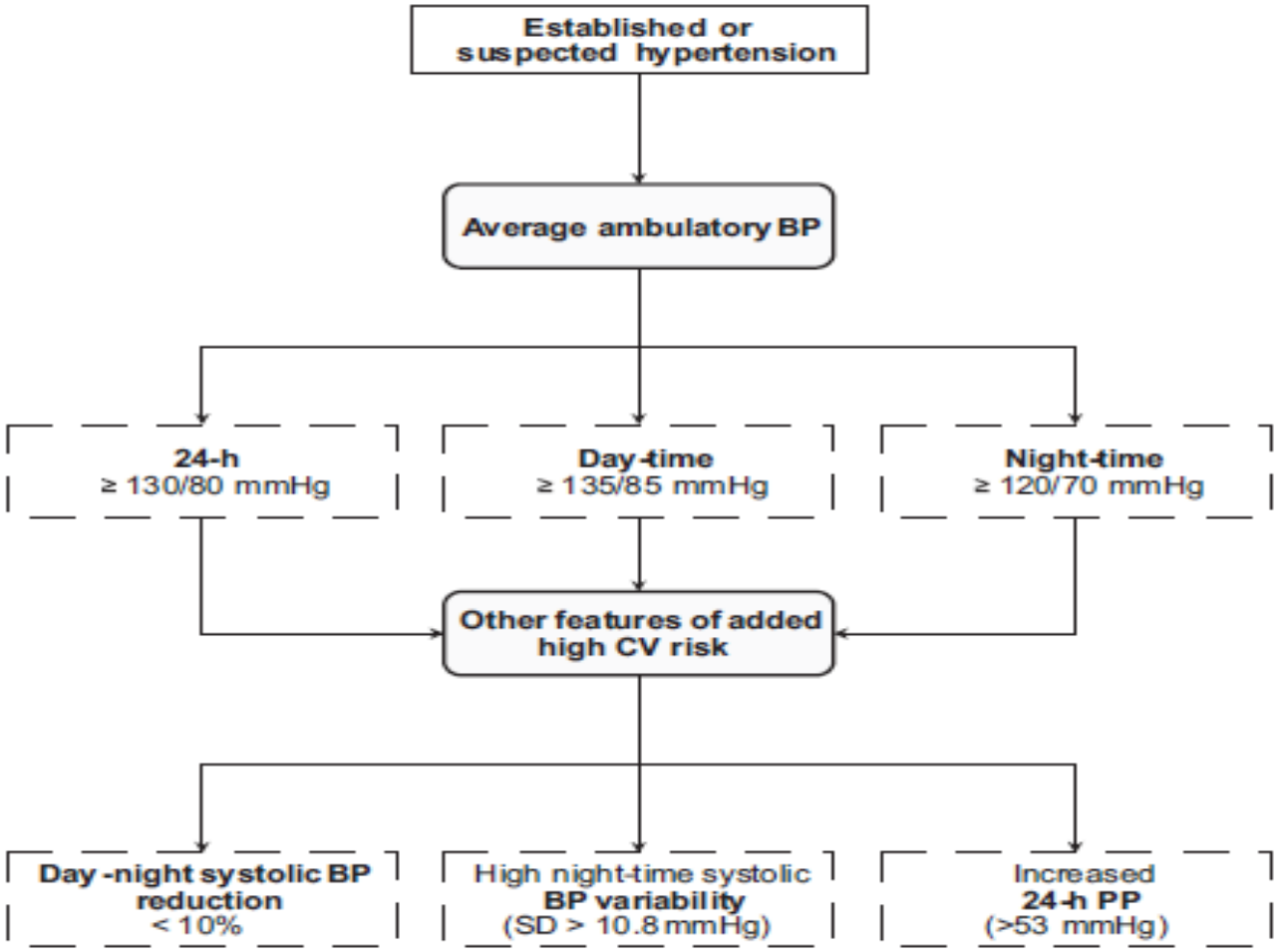


Figure. Components of ambulatory blood pressure (BP) monitoring that identify candidates for commencing antihypertensive drug treatment for increased cardiovascular (CV) risk. PP indicates pulse pressure.

Diet and lifestyle in HTA

Lower Levels of Sodium Intake and Reduced Cardiovascular Risk

(*Circulation*. 2014;129:981-989.

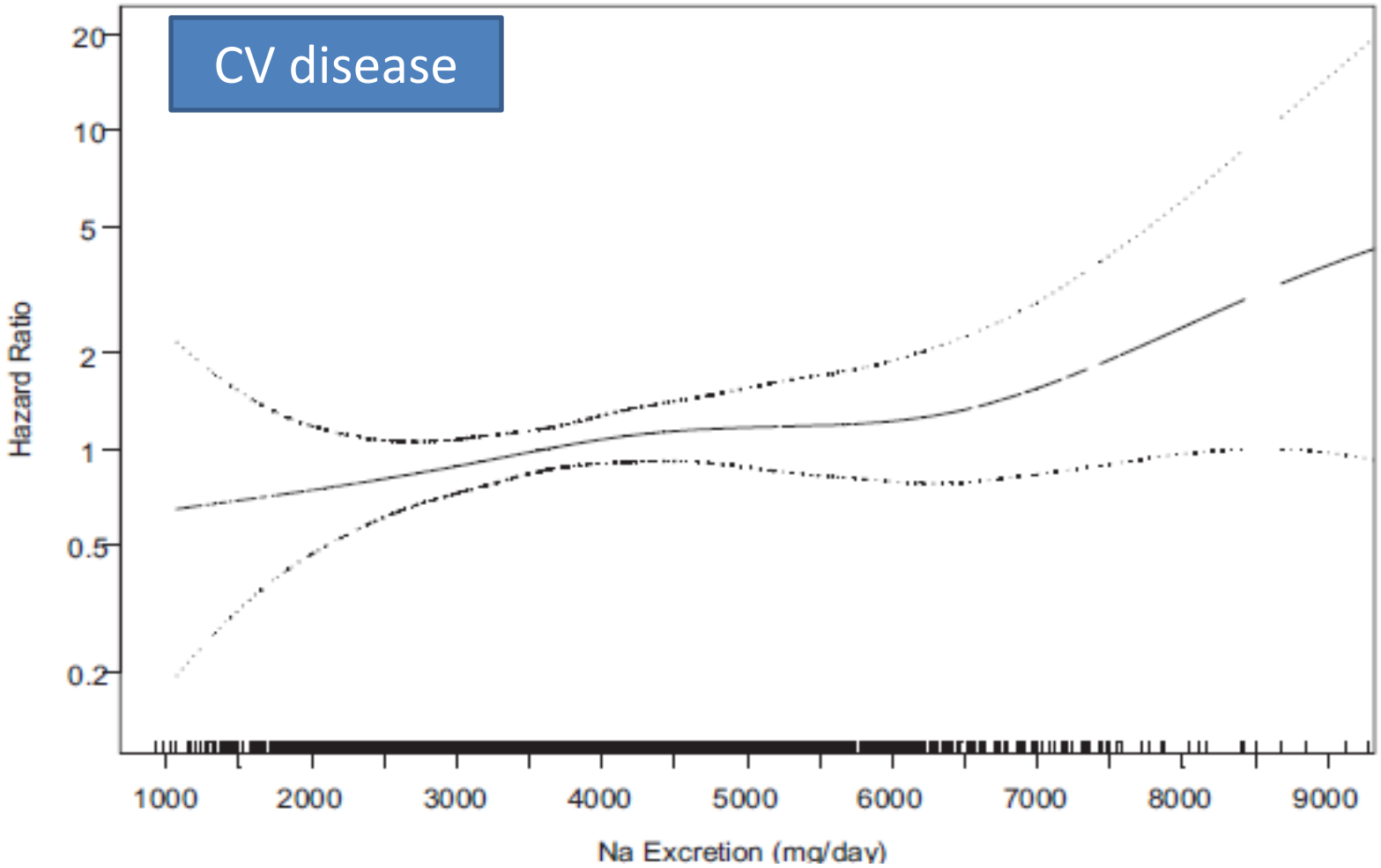
Nancy R. Cook, ScD; Lawrence J. Appel, MD, MPH; Paul K. Whelton, MB, MD, MSc

Methods and Results—Phases 1 and 2 of the Trials of Hypertension Prevention (TOHP) collected multiple 24-hour urine specimens among prehypertensive individuals. During extended posttrial surveillance, 193 cardiovascular events or cardiovascular disease deaths occurred among 2275 participants not in a sodium reduction intervention with 10 (TOHP II) or 15 (TOHP I) years of posttrial follow-up. Median sodium excretion was 3630 mg/d, with 1.4% of the participants having intake <1500 mg/d and 10% <2300 mg/d, consistent with national levels. Compared with those with sodium excretion of 3600 to <4800 mg/d, risk for those with sodium <2300 mg/d was 32% lower after multivariable adjustment (hazard ratio, 0.68; 95% confidence interval, 0.34–1.37; *P* for trend=0.13). There was a linear 17% increase in risk per 1000 mg/d increase in sodium (*P*=0.05). Spline curves supported a linear association of sodium with cardiovascular events, which continued to decrease from 3600 to 2300 and 1500 mg/d, although the data were sparse at the lowest levels.

Lower Levels of Sodium Intake and Reduced Cardiovascular Risk

(*Circulation*. 2014;129:981-989.

Nancy R. Cook, ScD; Lawrence J. Appel, MD, MPH; Paul K. Whelton, MB, MD, MSc



Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

N Engl J Med 2013;369:145-54.

In 16 study centers in the United States, we randomly assigned 5145 overweight or obese patients with type 2 diabetes to participate in an intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or to receive diabetes support and education (control group). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years.

The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in glycated hemoglobin and greater initial improvements in fitness and all cardiovascular risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the control group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51).

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

This article was published on June 24, 2013, at NEJM.org.

Table 1. Characteristics of the Patients at Baseline.*

Variable	Control Group (N= 2575)	Intervention Group (N= 2570)
Age — yr	58.9±6.9	58.6±6.8
Female sex — no. (%)	1537 (59.7)	1526 (59.4)
Race or ethnic group — no. (%)†		
Black	404 (15.7)	400 (15.6)
Native American	128 (5.0)	130 (5.1)
Asian or Pacific Islander	21 (0.8)	29 (1.1)
White	1631 (63.3)	1621 (63.1)
Hispanic	340 (13.2)	340 (13.2)
Other	51 (2.0)	50 (1.9)
History of cardiovascular disease — no. (%)‡	348 (13.5)	366 (14.2)
Use of insulin — no. (%)§	410 (16.5)	382 (15.4)
Current smoking — no. (%)	110 (4.3)	117 (4.6)
Median duration of diabetes (interquartile range) — yr	5.0 (2.0–10)	5.0 (2.0–10)
Weight — kg	101±19	101±20
Body-mass index¶	36.0±5.8	35.9±6.0
Waist circumference — cm	114±14	114±14
Glycated hemoglobin — %	7.3±1.2	7.2±1.1
Blood pressure — mm Hg		
Systolic	129±17	128±17
Diastolic	70.4±9.6	69.9±9.5
Cholesterol — mg/dl		
High-density lipoprotein	43.5±12	43.4±12
Low-density lipoprotein	112±32	112±32
Median triglycerides (interquartile range) — mg/dl	152 (107–218)	155 (110–221)

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

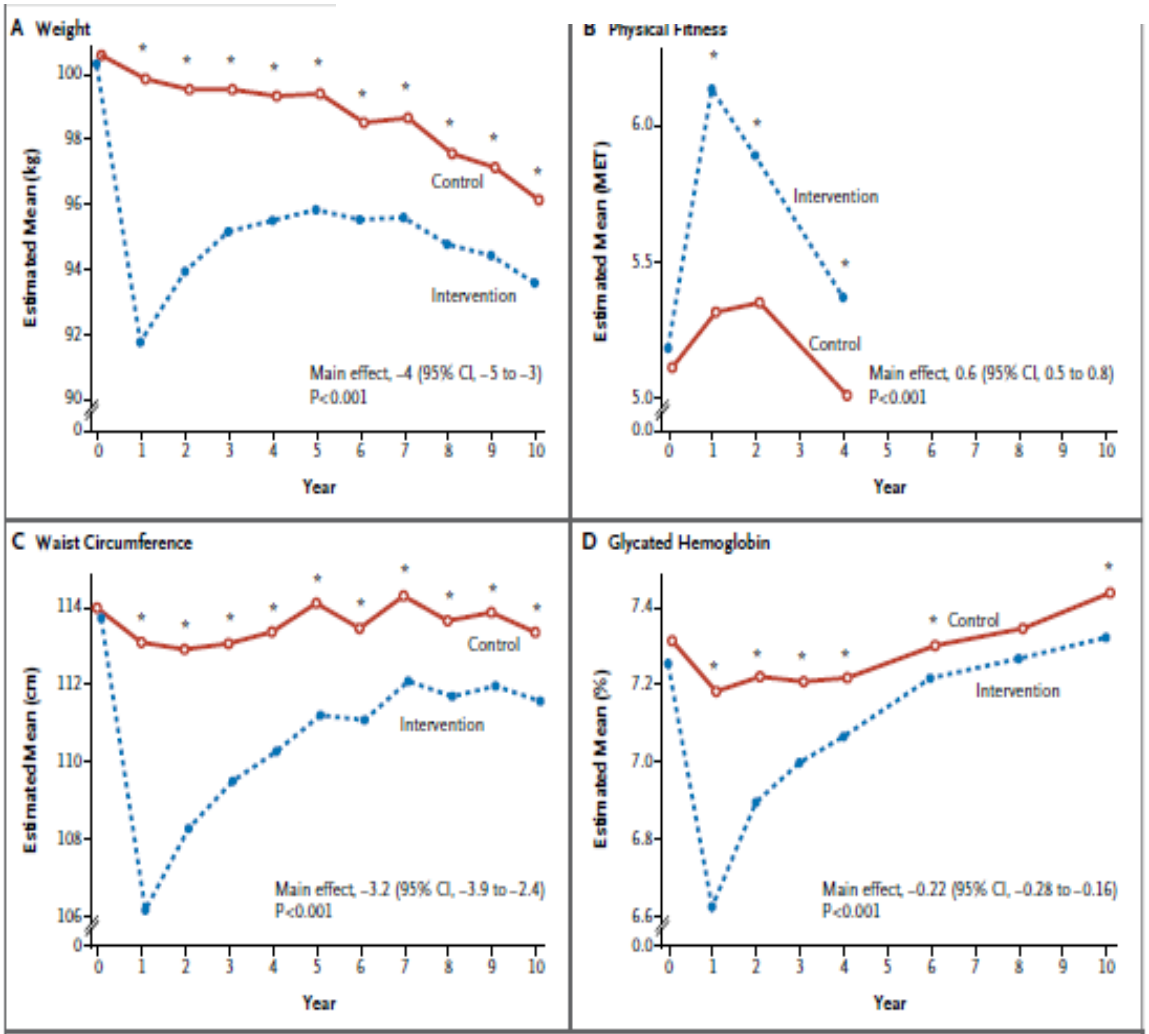


Figure 1. Changes in Weight, Physical Fitness, Waist Circumference, and Glycated Hemoglobin Levels during 10 Years of Follow-up.

Shown are the changes from baseline in overweight or obese patients with type 2 diabetes who participated in an intensive lifestyle intervention (intervention group) or who received diabetes support and education (control group). The reported main effect is the average of all between-group differences after baseline. Means were estimated with the use of generalized linear models for continuous measures. MET denotes metabolic equivalents; asterisks indicate P<0.05 for the between-group comparison. Data from 107 visits during year 11 were not included in the analyses.

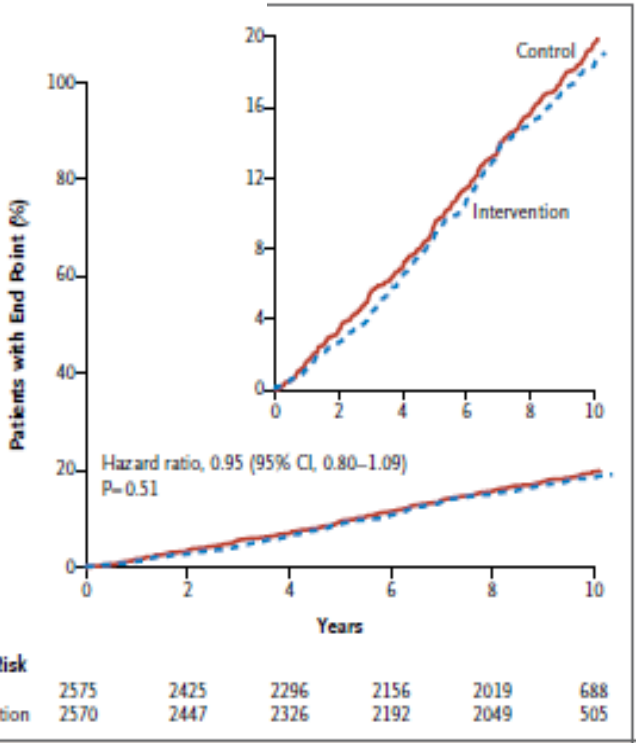


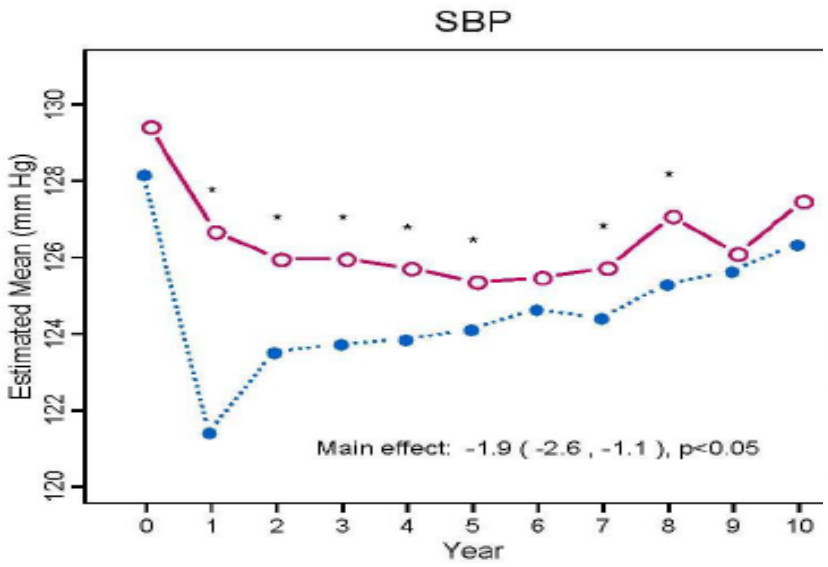
Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

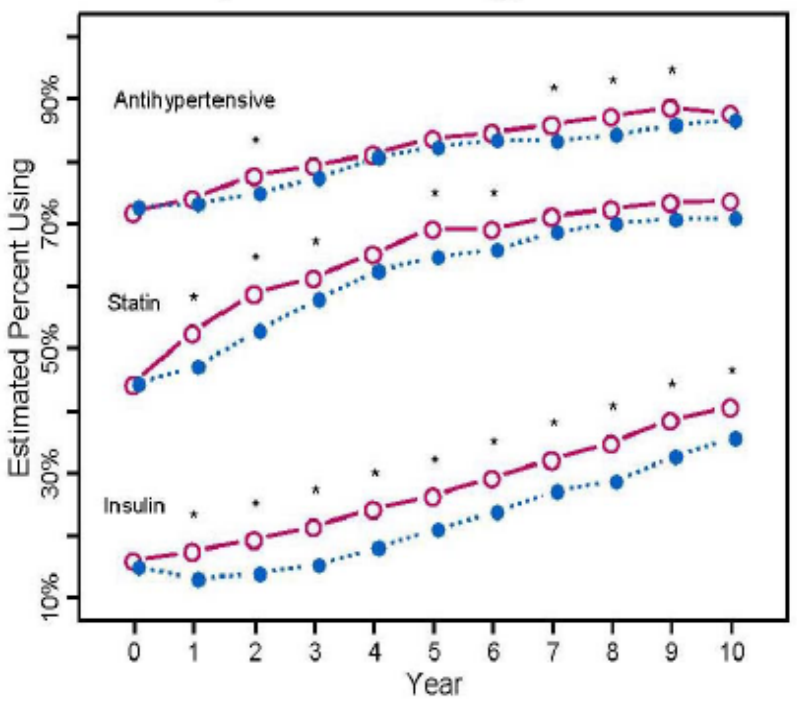
Shown are Kaplan–Meier estimates of the cumulative proportion of patients with a primary event. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. The numbers below the graph are the numbers of patients at risk in each study group at years 2, 4, 6, and 8 and at 10.4 years, when the last observed event occurred. The inset shows the same data on an expanded y axis.

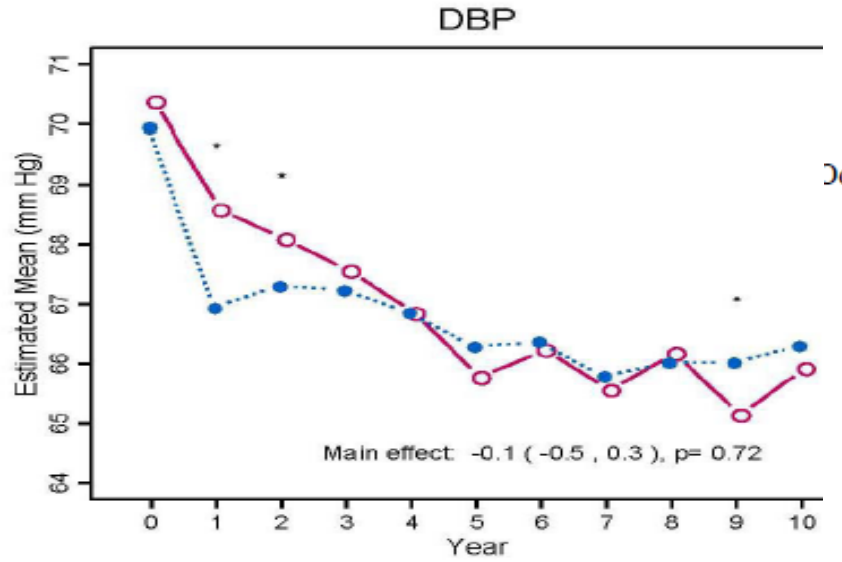
Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

N Engl J Med 2013;369:145-54.

The Look AHEAD Research Group*







Odds ratios for medication use are: antihypertensive 0.88, 95% CI 0.78 to 0.89, p=0.026;

Renal denervation in Resistant HTA

Refractory Hypertension

Determination of Prevalence, Risk Factors, and Comorbidities in a Large, Population-Based Cohort

David A. Calhoun, John N. Booth III, Suzanne Oparil, Marguerite R. Irvin, Daichi Shimbo, Daniel T. Lackland, George Howard, Monika M. Safford, Paul Muntner

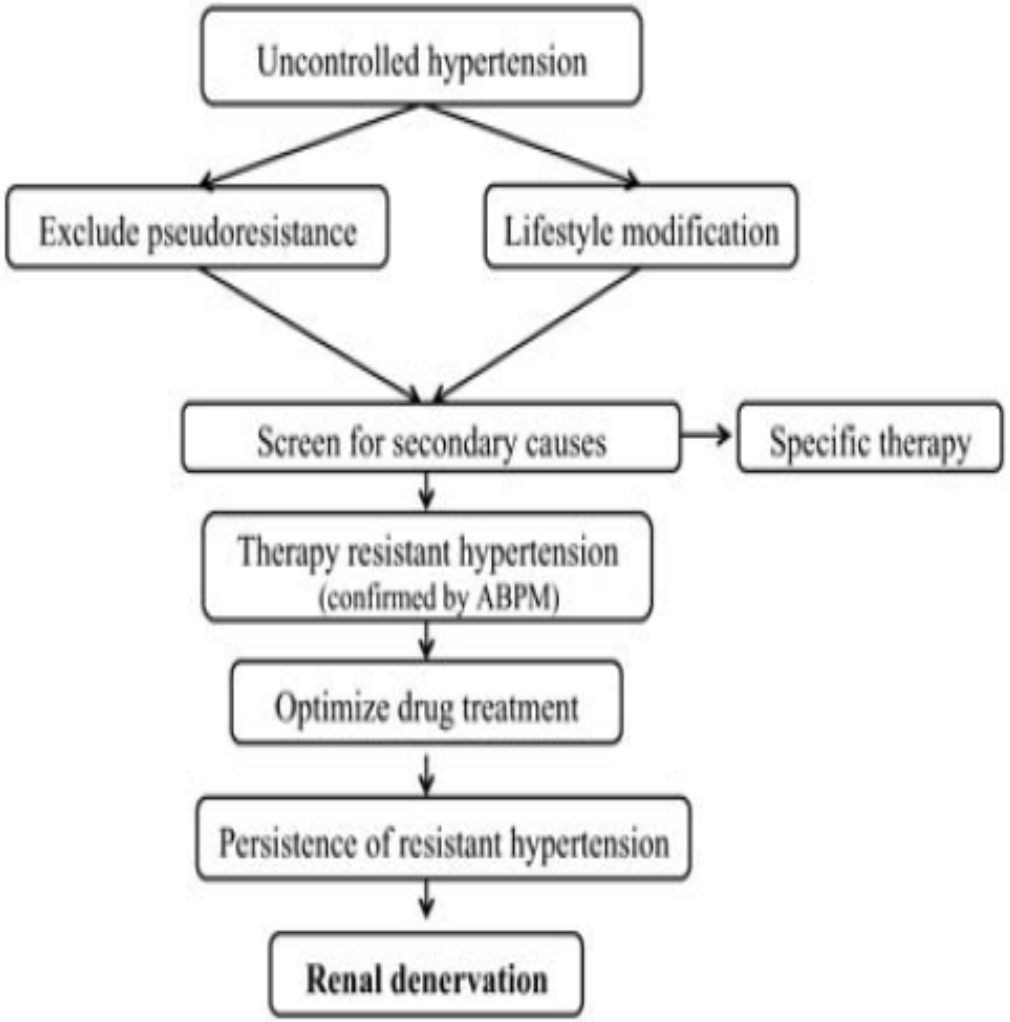
Hypertension. 2014;63:451-458.

- Among 30000 people followed in USA, 14800 are taking antiHTA drugs
- 78 (0.5%) are refractory to 5 or more antiHTA agents
- 2066 (14%) are considered resistant (normalisation of BP with more than 3 drugs)
- Refractory people are mainly men, black, obese, diabetic, suffering from proteinuria, CKD, or having an history of CVD: so with a very high CV risk!

Treating resistant hypertension: role of renal denervation

Table 1 Causes of resistant hypertension

Risk factors
Older age
High systolic blood pressure
Obesity
High salt consumption
Chronic renal disease
Diabetes mellitus
Left ventricular hypertrophy
Female sex
Interfering medications and substances
Nonsteroidal anti-inflammatory drugs
Corticosteroids
Sympathomimetics
Amphetamines
Oral contraceptives
Cyclosporines
Tacrolimus
Erythropoietin
Tricyclic antidepressants
Alcohol
Licorice
Secondary causes
Common
Obstructive sleep apnea
Chronic renal disease
Primary aldosteronism
Renal artery stenosis
Uncommon
Pheochromocytoma
Cushing's syndrome
Hyperparathyroidism
Aortic coarctation



European Heart Journal
doi:10.1093/eurheartj/eht154

Received 30 January 2013; revised 27 March 2013; accepted 8 April 2013

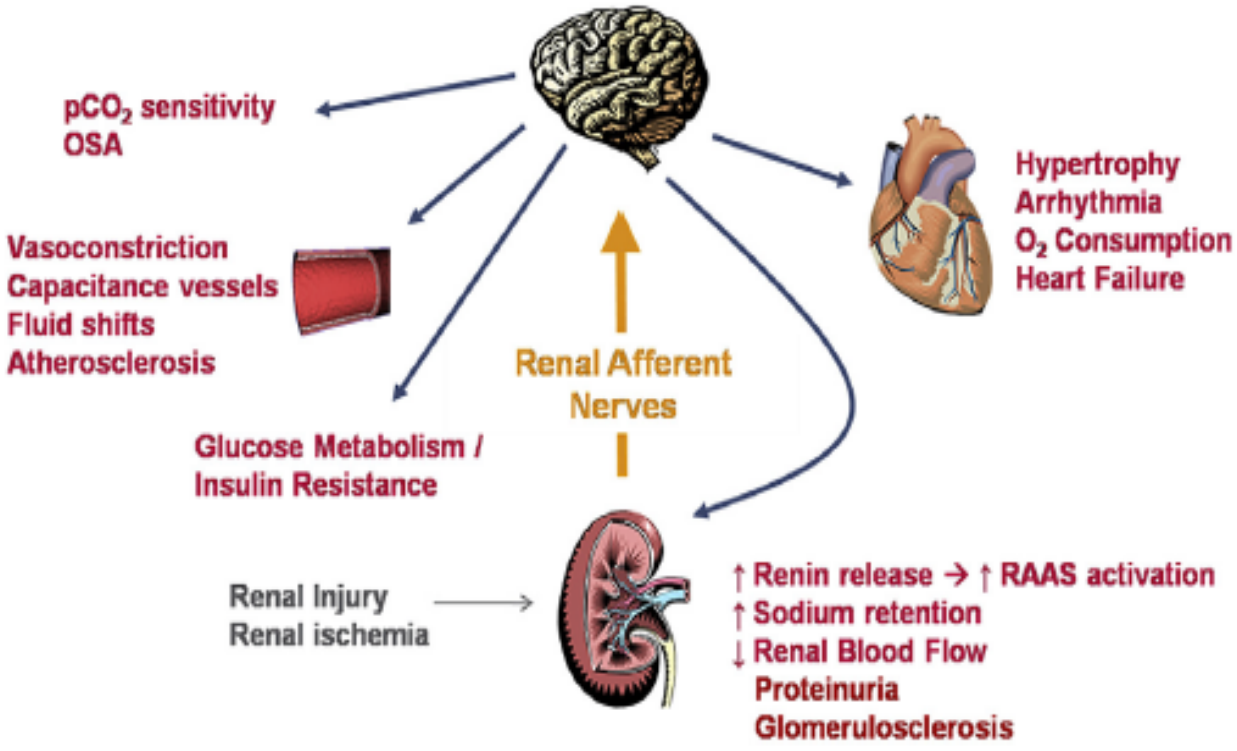
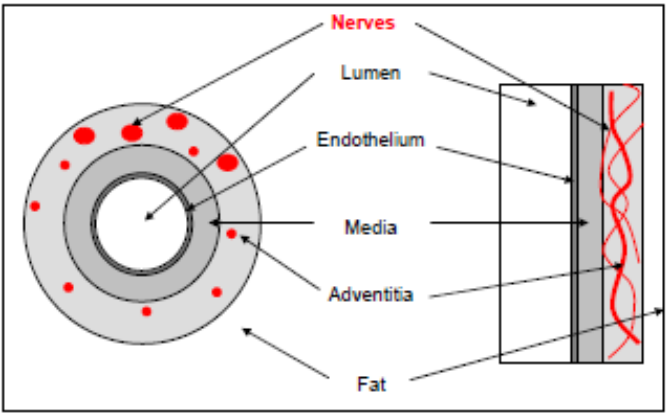


Figure 1 Effects of Afferent Renal Nerve Signaling

Various triggers, such as renal injury and ischemia, can stimulate afferent signaling from the kidney to central integrative nuclei, with the consequence of exaggerated efferent sympathetic outflow to target organs, including the heart, the vasculature, the kidneys, and other organs involved in both cardiovascular and metabolic control, as illustrated. Renal denervation, by targeting both efferent and afferent nerves as can be achieved by catheter-based application of radiofrequency energy, may be useful to effectively interrupt this vicious cycle. OSA = obstructive sleep apnea; pCO_2 = partial pressure of carbon dioxide; RAAS = renin-angiotensin-aldosterone system.



. Illustration of anatomy of renal artery and nerve distribution

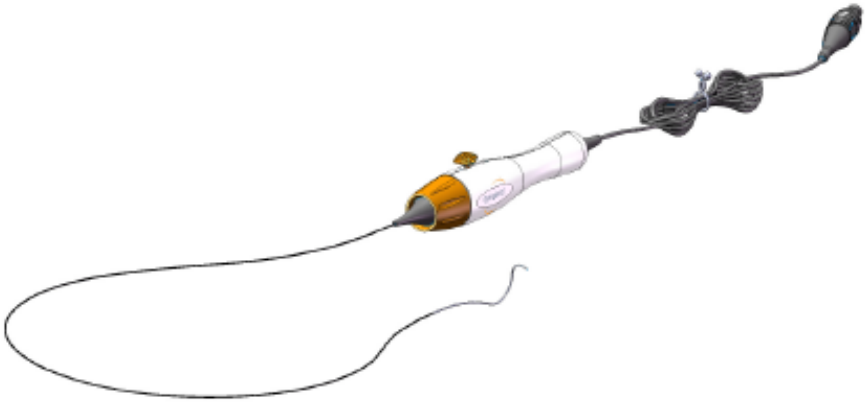


Figure 1. Symplicity Catheter (RDN006)

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ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.1616

STATE-OF-THE-ART PAPER

International Expert Consensus Statement

Percutaneous Transluminal Renal Denervation for the Treatment of Resistant Hypertension

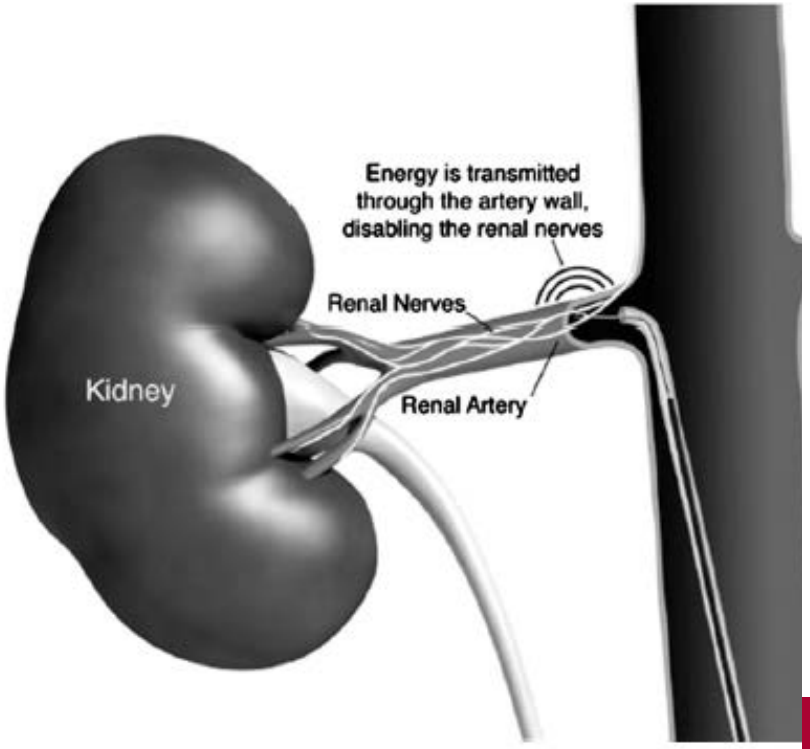


Figure 2 Schematic Illustration of the Percutaneous Catheter-Based Approach to Functionally Denervate the Human Kidney

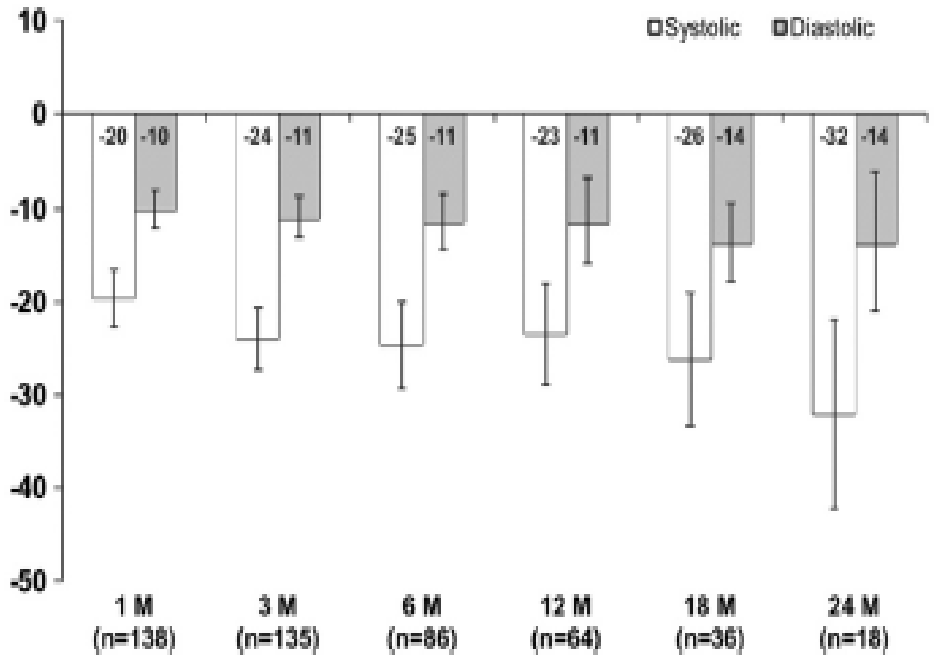
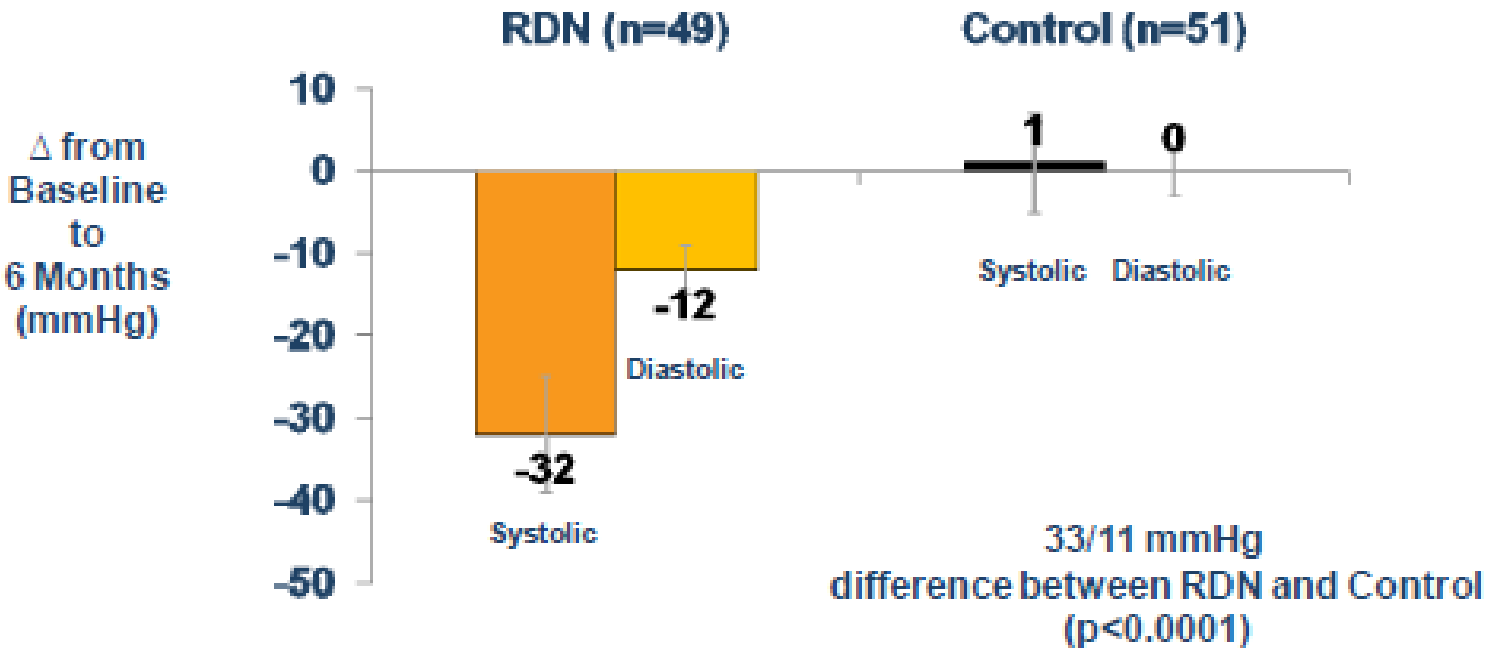


Figure 5 Mean Systolic and Diastolic BP Changes From Baseline After Renal Denervation With Up to 2 Years of Follow-Up in the Symplicity HTN-1 Trial

Hypertension. 2011;57:911-917;



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Figure 4. Change in Office Blood Pressure from Baseline, Treatment (RDN) vs. Control

[4] Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 Trial): A randomised controlled trial. Elser, *et. al. Lancet*. 2010;376:1903-1909

A Controlled Trial of Renal Denervation for Resistant Hypertension

This article was published on March 29, 2014, at NEJM.org.

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D.,

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4

RENAL DENERVATION FOR RESISTANT HYPERTENSION

SYMPLICITY HTN-3

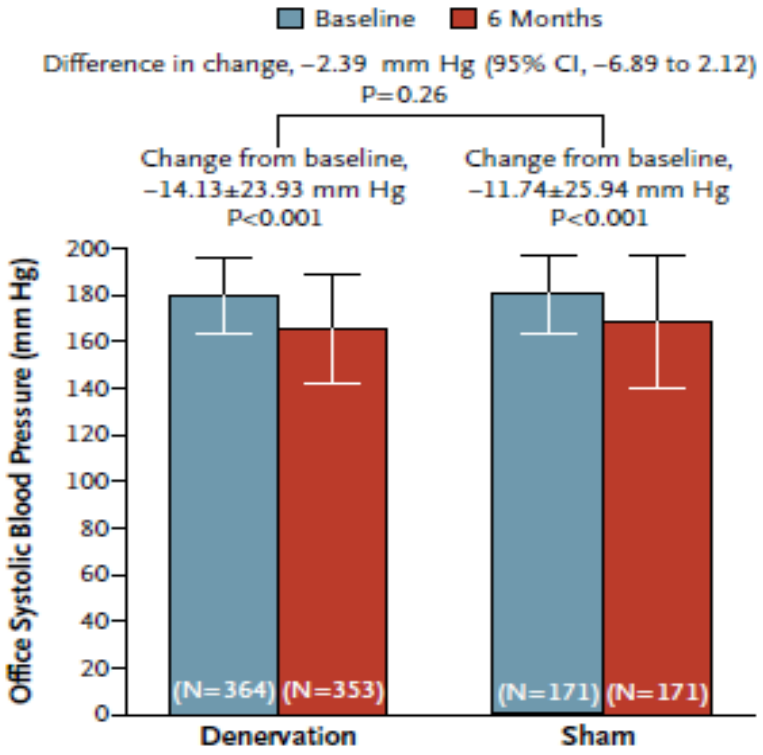


Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

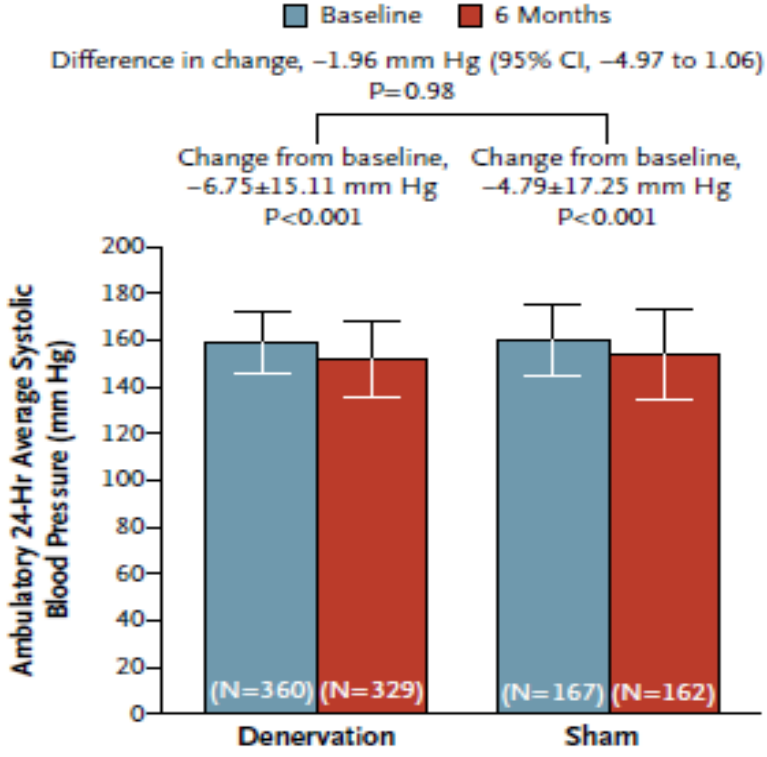


Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

SYMPLICITY HTN-3

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (–0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	–1.9 (–6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (–1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (–2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (–0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	–2.7 (–6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (–2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (–1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (–0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (–0.3 to 0.9)

* CI denotes confidence interval.

† The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criterion for the primary safety end point was a rate of major adverse events of 9.8%, which was derived from historical data. The rate in the renal-denervation group was 1.4% with an upper boundary of the one-sided 95% CI of 2.9%; therefore, the performance criterion was met with a P value of <0.001.

‡ This end point was a composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis of more than 70% within 6 months.

Should we still consider renal denervation for Resistant HTA?

- Interests in glucose metabolism, LVH, CHF, AF, CKD, Sleep apnea syndrome but ..

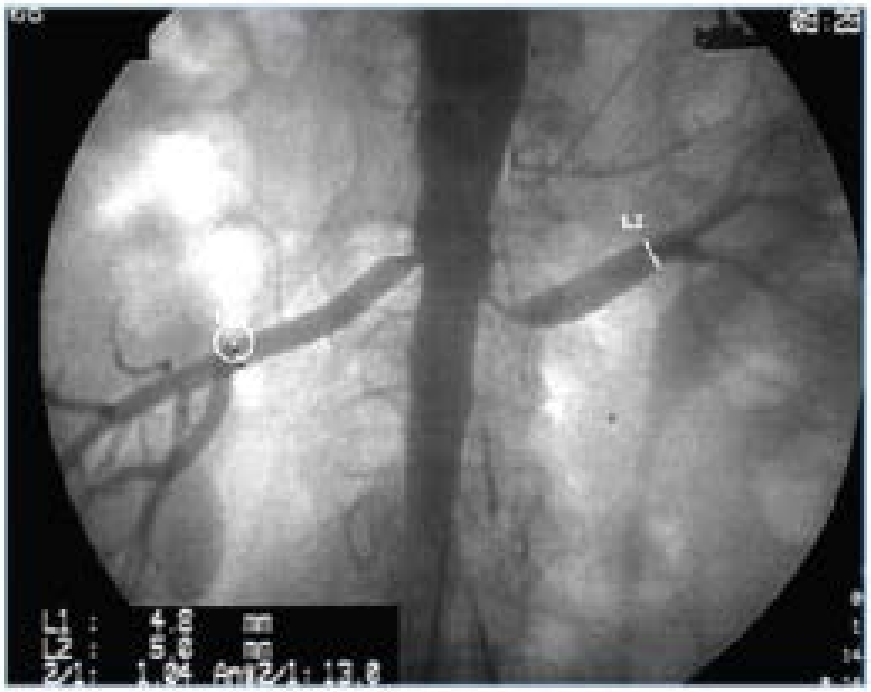
Renal denervation: still more questions than answers

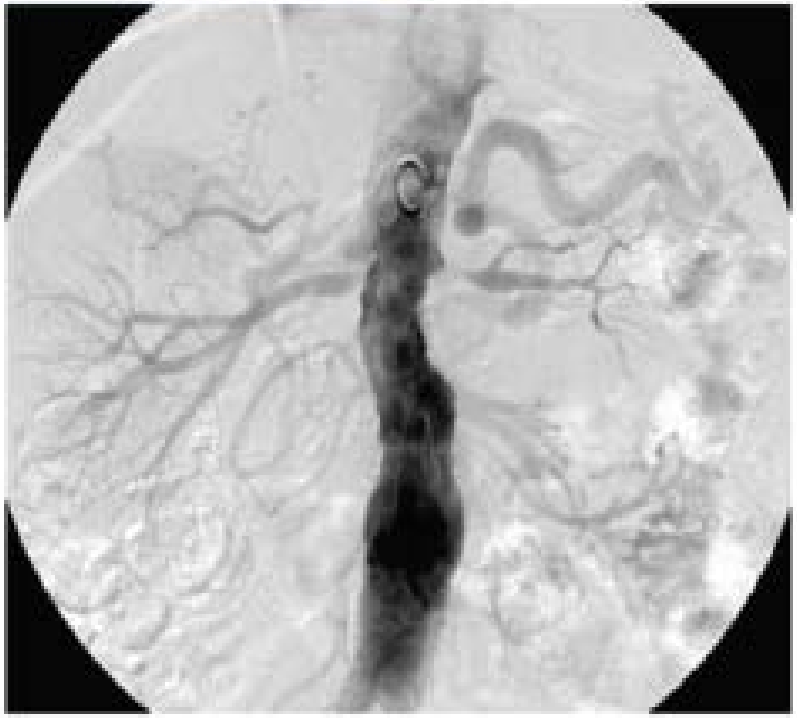
Stefano Taddei[a] and Rosa Maria Bruno[a,b]

Journal of Hypertension 2014, 32:28–29

Atherosclerotic Renal Artery stenosis

Spectrum of Renovascular Disease Manifestations





Asymptomatic "Incidental RAS"

Renovascular Hypertension

Accelerated CV Disease
Congestive Heart failure
Stroke

Ischemic Nephropathy

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

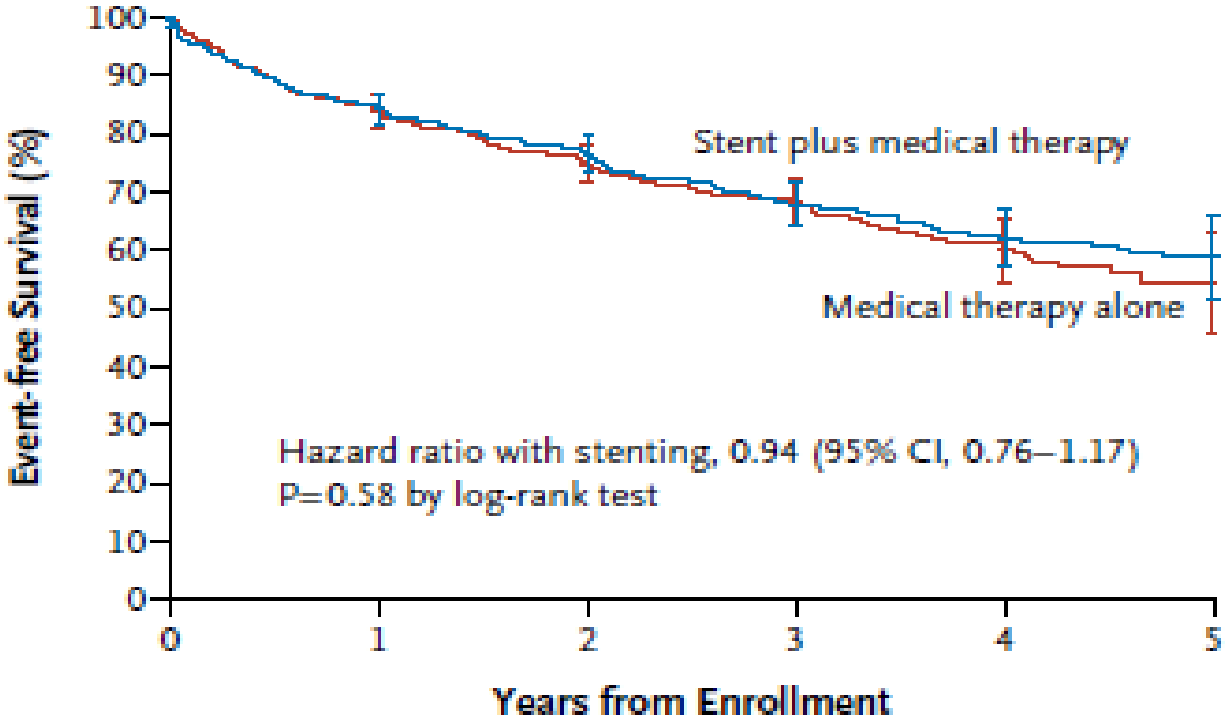
Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

This article was published on November 18, 2013, at NEJM.org.

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Table 1. Baseline Characteristics of the Study Population, According to Treatment Group.*

Characteristic	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)
Age (yr)	69.3±9.4	69.0±9.0
Male sex (%)	51.0	48.9
Race (%)†		
Black	7.0	7.0
Other	93.0	93.0
Body-mass index‡	28.2±5.3	28.7±5.7
Systolic blood pressure (mm Hg)	149.9±23.2	150.4±23.0
Blood pressure at target level (%)§	29.2	25.3
Estimated GFR (ml/min/1.73 m²)¶	58.0±23.4	57.4±21.7
Stage ≥3 chronic kidney disease (%)	49.6	50.4
Method of identification of stenosis (%)		
Angiography	68.4	68.6
Duplex ultrasonography	25.5	24.2
Computed tomographic angiography	4.4	5.3
Magnetic resonance angiography	1.7	1.9
Medical history and risk factors (%)		
Diabetes	32.4	34.3
Prior myocardial infarction	26.5	30.2
History of heart failure	12.0	15.1
Smoking in past yr	28.0	32.2
Hyperlipidemia	89.4	90.0
Angiographic findings		
% Stenosis, as assessed by core laboratory	67.3±11.4	66.9±11.9
% Stenosis, as assessed by investigator	72.5±14.6	74.3±13.1
Global ischemia (%)**	20.0	16.2
Bilateral disease (%)††	22.0	18.1



No. at Risk

Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

Figure 2. Kaplan–Meier Curves for the Primary Outcome.

Survival curves are truncated at 5 years owing to instability of the curves because few participants remained in the study after 5 years.

Table 2. Clinical End Points.*

End Point	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or permanent renal-replacement therapy†	161 (35.1)	169 (35.8)	0.94 (0.76–1.17)	0.58
Components of primary end point‡				
Death from cardiovascular or renal causes	20 (4.4)	20 (4.2)		
Stroke	12 (2.6)	16 (3.4)		
Myocardial infarction	30 (6.5)	27 (5.7)		
Hospitalization for congestive heart failure	27 (5.9)	26 (5.5)		
Progressive renal insufficiency	68 (14.8)	77 (16.3)		
Permanent renal-replacement therapy	4 (0.9)	3 (0.6)		
Secondary clinical end points§				
Death from any cause	63 (13.7)	76 (16.1)	0.80 (0.58–1.12)	0.20
Death from cardiovascular causes	41 (8.9)	45 (9.5)	0.89 (0.58–1.36)	0.60
Death from renal causes	2 (0.4)	1 (0.2)	1.89 (0.17–20.85)	0.60
Stroke	16 (3.5)	23 (4.9)	0.68 (0.36–1.28)	0.23
Myocardial infarction	40 (8.7)	37 (7.8)	1.09 (0.70–1.71)	0.70
Hospitalization for congestive heart failure	39 (8.5)	39 (8.3)	1.00 (0.64–1.56)	0.99
Progressive renal insufficiency	77 (16.8)	89 (18.9)	0.86 (0.64–1.17)	0.34
Permanent renal-replacement therapy	16 (3.5)	8 (1.7)	1.98 (0.85–4.62)	0.11

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

In summary, renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease.

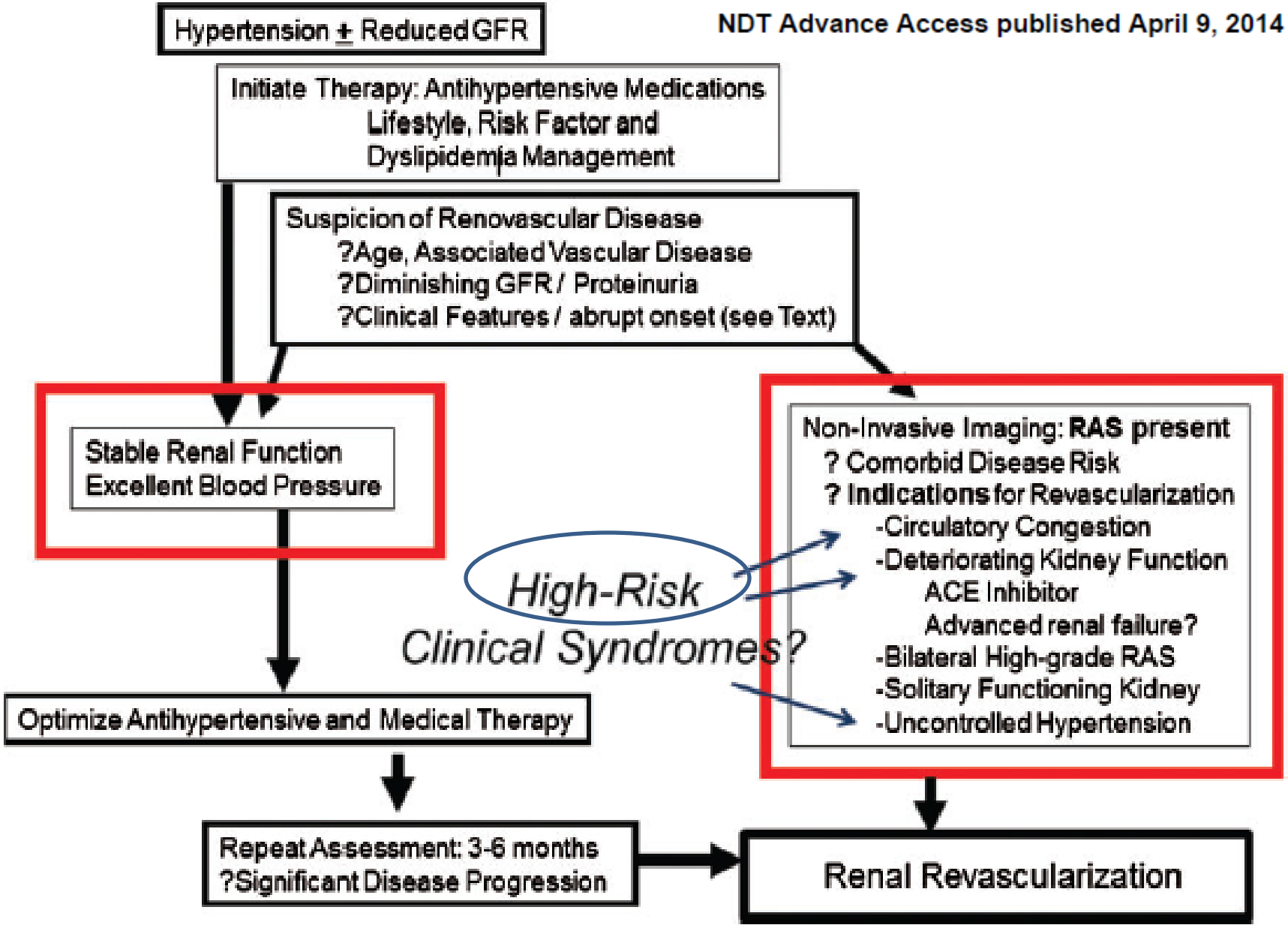
Treatment of atherosclerotic renovascular hypertension: review of observational studies and a meta-analysis of randomized clinical trials

NDT Advance Access published April 16, 2014

- Small decrease in DBP and number of antiHTA agents in the stenting group according to 7 RCT studies (2155 patients at baseline and 1741 available at FU)
- No difference in SBP, serum creatinine, incident CV event rates
- However, the patients included are those whose the baseline therapeutic decision was uncertain (low risk group)
- What about high risk patients?

Management of Renovascular Hypertension and Ischemic Nephropathy

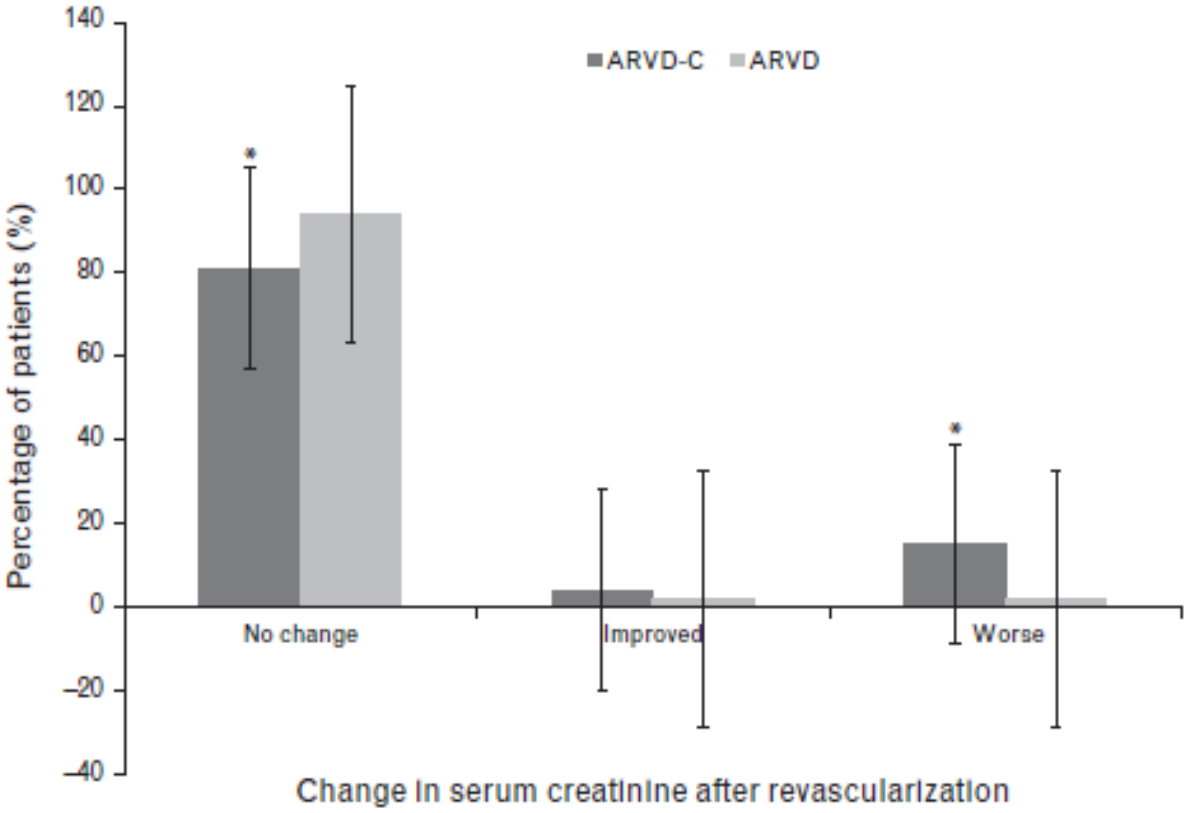
NDT Advance Access published April 9, 2014



Extrarenal atherosclerotic disease blunts renal recovery in patients with renovascular hypertension

Journal of Hypertension 2014, 32:1300–1306

Khangura *et al.*



Distribution of changes in serum creatinine after revascularization in ARVD and ARVD-C,

Extrarenal atherosclerotic disease blunts renal recovery in patients with renovascular hypertension

Journal of Hypertension 2014, 32:1300–1306

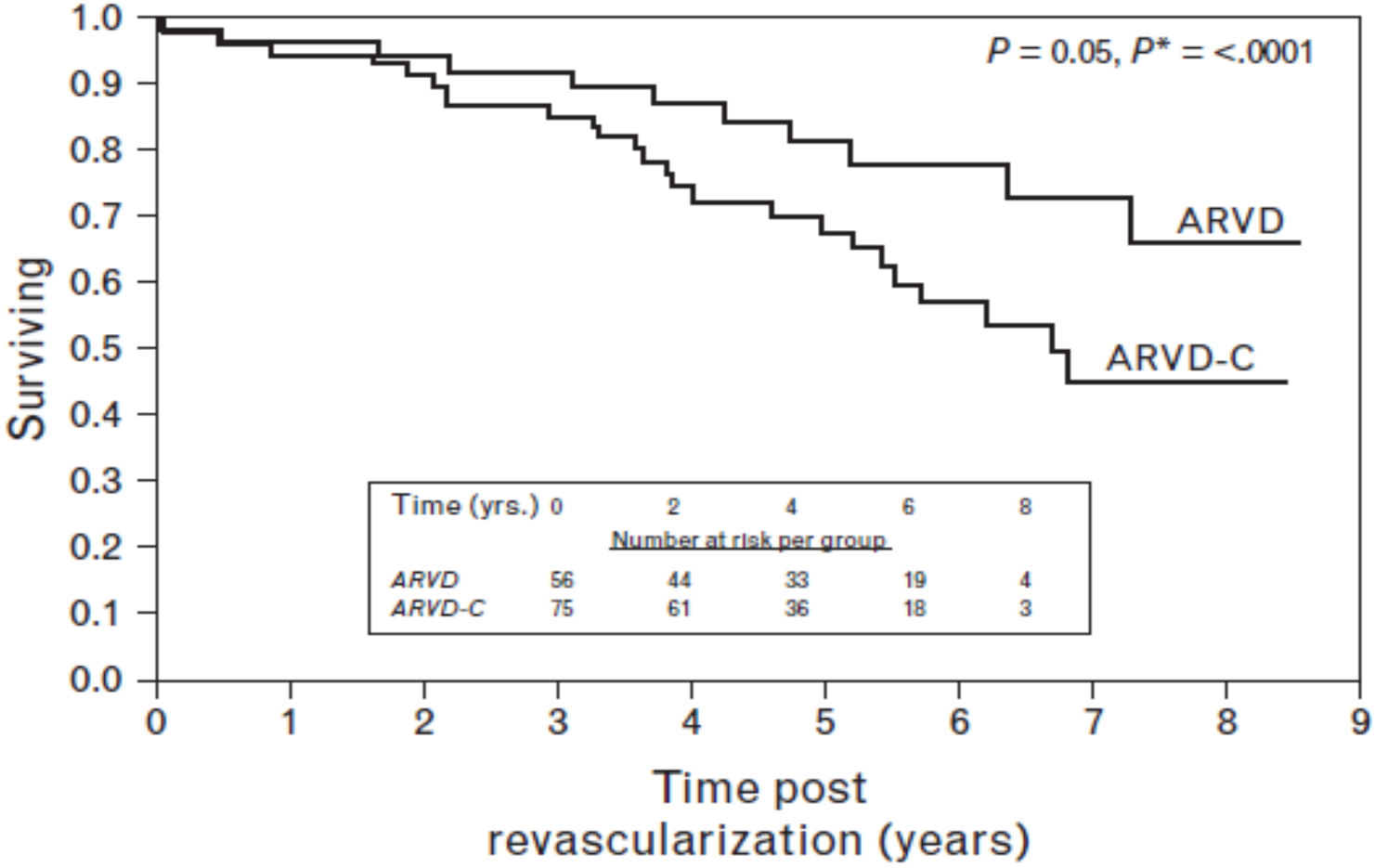


FIGURE 2 Survival plots of atherosclerotic renal artery disease patients with (ARVD-C) or without (ARVD) coronary artery disease. Events were recorded in 27 and 12 patients in the ARVD-C and ARVD groups, respectively, Log-Rank test,

Dialysis and HTA

Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial

Nephrol Dial Transplant (2014) 29: 672–

Rajiv Agarwal, Arjun D. Sinha, Maria K. Pappas, Terri N. Abraham and Getachew G. Tegegne

Background. The purpose of this study was to determine among maintenance hemodialysis patients with echocardiographic left ventricular hypertrophy and hypertension whether in comparison with a β-blocker-based antihypertensive therapy, an angiotensin converting enzyme-inhibitor-based antihypertensive therapy causes a greater regression of left ventricular hypertrophy.

Methods. Subjects were randomly assigned to either open-label lisinopril ($n = 100$) or atenolol ($n = 100$) each administered three times per week after dialysis. Monthly monitored home blood pressure (BP) was controlled to <140/90 mmHg with medications, dry weight adjustment and sodium restriction. The primary outcome was the change in left ventricular mass index (LVMI) from baseline to 12 months.

FIGURE 1: BP profiles at baseline and over time. BP obtained in the interdialytic period (Left panel) and self-measured by the patients at home (right panel) are shown. Ambulatory BP monitoring was performed in the interdialytic period over 44 h at baseline, 3, 6 and 12 months. Solid line shows the atenolol group and the dotted line the lisinopril group; vertical bars represent standard error of mean

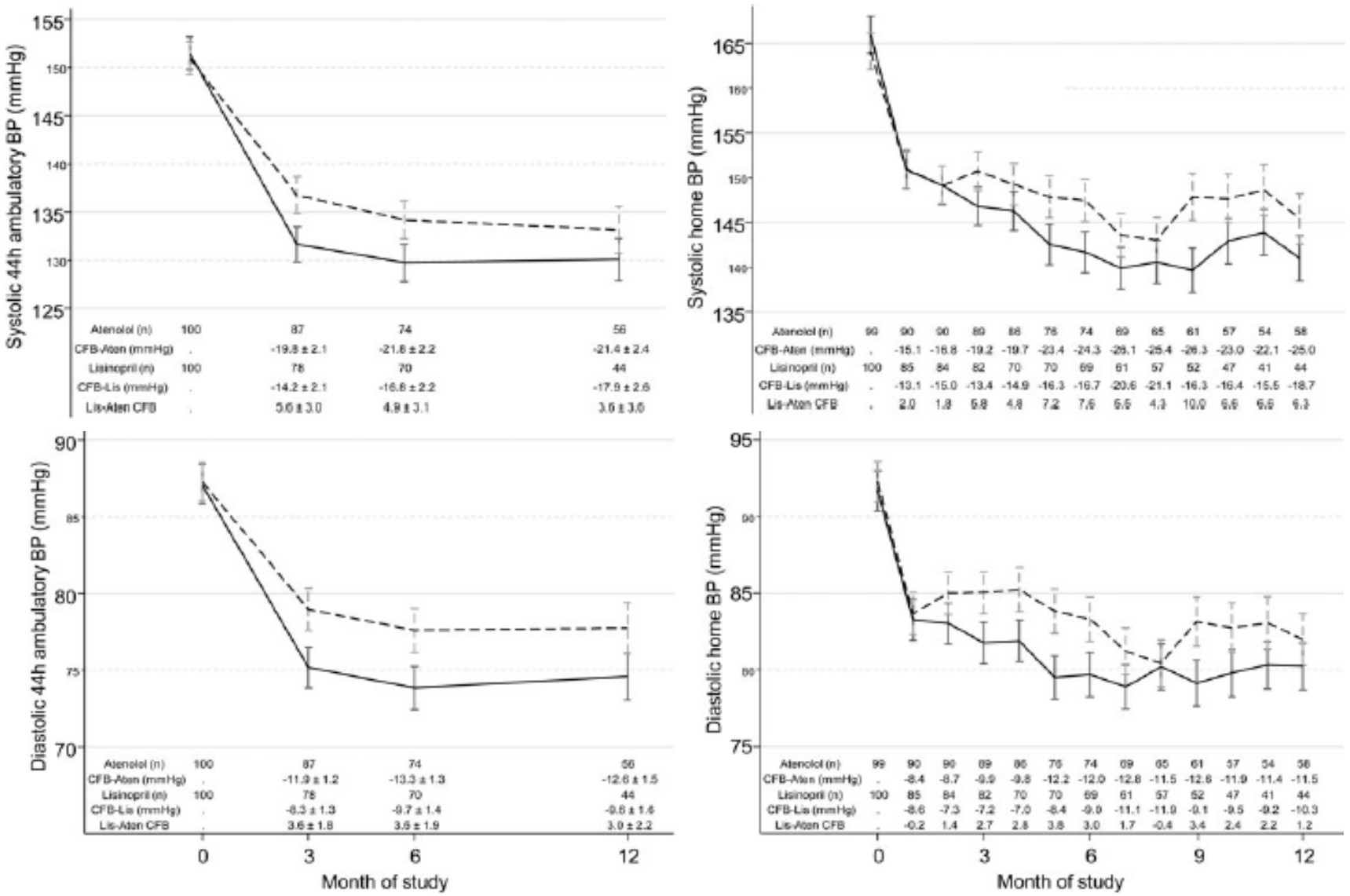


Table 3. Serious adverse events reported following randomization

Event type	Atenolol			Lisinopril				
	Subjects (*n*)	Events (*n*)	Incidence rate(events/ 100patient-years)	Subjects (*n*)	Events (*n*)	Incidence rate(events/ 100patient-years)	IRR Lisinopril/atenolol (95% CI)	P
Overall serious adverse events	58	140	172.4	70	188	253.6	1.47 (1.18–1.84)	<0.001
All-cause hospitalization rate	37	73	89.9	59	107	144.3	1.61 (1.18–2.19)	0.002
Cardiovascular events	16	20	24.6	28	43	58	2.36 (1.36–4.23)	0.001
Combined MI, Stroke, CHF;	10	11	13.5	17	23	31	2.29 (1.07–5.21)	0.02

serious adverse events of myocardial infarction, stroke and hospitalization for heart failure or cardiovascular death in the atenolol group occurred in 10 subjects, who had 11 events and in the lisinopril group in 17 subjects, who had 23 events (IRR 2.29, P = 0.021). Hospitalizations for heart failure were worse in the lisinopril group (IRR 3.13, P = 0.021). All-cause hospitalizations were higher in the lisinopril group [IRR 1.61 (95% CI 1.18–2.19, P = 0.002)]. LVMI improved with time; no difference between drugs was noted.

Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial

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Conclusions. Among maintenance dialysis patients with hypertension and left ventricular hypertrophy, atenolol-based antihypertensive therapy may be superior to lisinopril-based therapy in preventing cardiovascular morbidity and all-cause hospitalizations. (Funded by the National Institute of Diabetes

Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients

Objectives This study sought to assess whether spironolactone treatment reduces the high incidence of cardiovascular and cerebrovascular (CCV) morbidity and mortality in hemodialysis (HD) patients.

Background Aldosterone receptor blockers reduce cardiac-related events, but the efficacy of the agents in HD patients is unclear.

Methods A 3-year randomized trial involving 5 clinics was performed. Of the 309 oligoanuric HD patients enrolled in the study, 157 patients were randomly assigned to receive 25 mg/day of spironolactone without any restriction on dietary potassium intake (treatment group), and 152 patients were assigned to a control group. The primary outcome was a composite of death from CCV events or hospitalization for CCV events, and the secondary outcome was death from all causes.

Results During the 3-year follow-up, the primary outcome occurred in 5.7% of patients in the treatment group and in 12.5% of patients in the control group. Hazard ratios (HRs) for the primary outcome for treatment were 0.404 (95% confidence interval [CI]: 0.202 to 0.809; $p = 0.017$) and 0.379 (95% CI: 0.173 to 0.832; $p = 0.016$) before and after adjustment, respectively. The secondary outcome was significantly reduced in the treatment group compared with the control group (6.4% vs. 19.7%; HRs: 0.355 [95% CI: 0.191 to 0.662; $p = 0.002$] and 0.335 [95% CI: 0.162 to 0.693; $p = 0.003$] before and after adjustment, respectively). Gynecomastia or breast pain was reported in 16 patients (10.2%) in the treatment group. Serious hyperkalemia led to treatment discontinuation in 3 patients (1.9%).

Conclusions Aldosterone receptor blockade using spironolactone may substantially reduce the risk of both CCV morbidity and death among HD patients; however, larger-scale studies are recommended to further confirm its efficacy. (Effects of Spironolactone on Cardio- and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients; NCT01687699) (J Am Coll Cardiol 2014;63:528–36) © 2014 by the American College of Cardiology Foundation

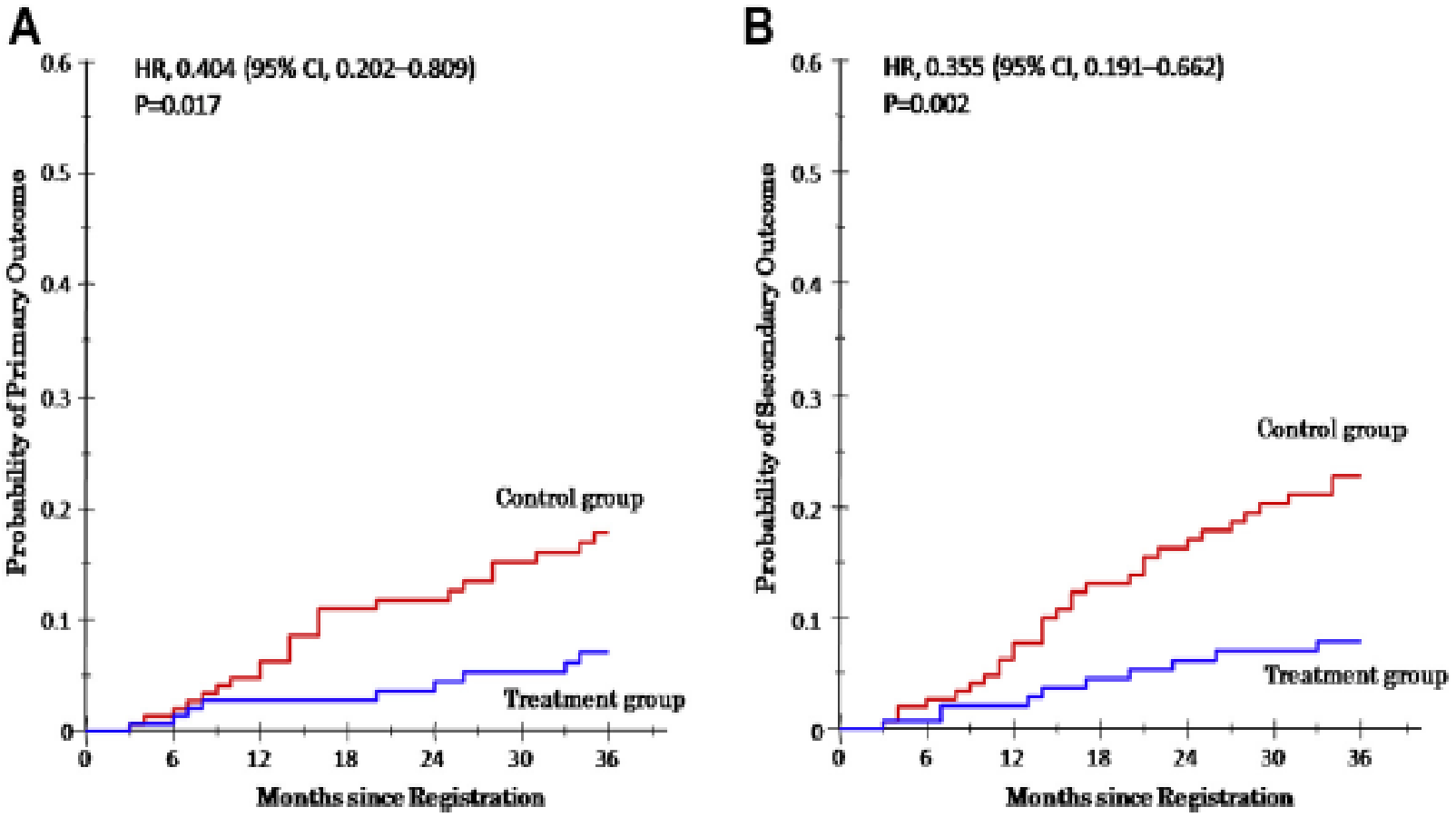

Figure 2 Cumulative Kaplan-Meier Outcomes Estimates

The Kaplan-Meier curve depicts the rates of primary (**A**) and secondary (**B**) outcomes in the control and treatment groups. HR = hazard ratio.

Thank you

Any questions?