Уроци от негативни клинични проучвания

Интензивна антихипертензивна терапия

Доц. Борислав Георгиев

Национална кардиологична болница

Епидемиология на артериалната хипертония

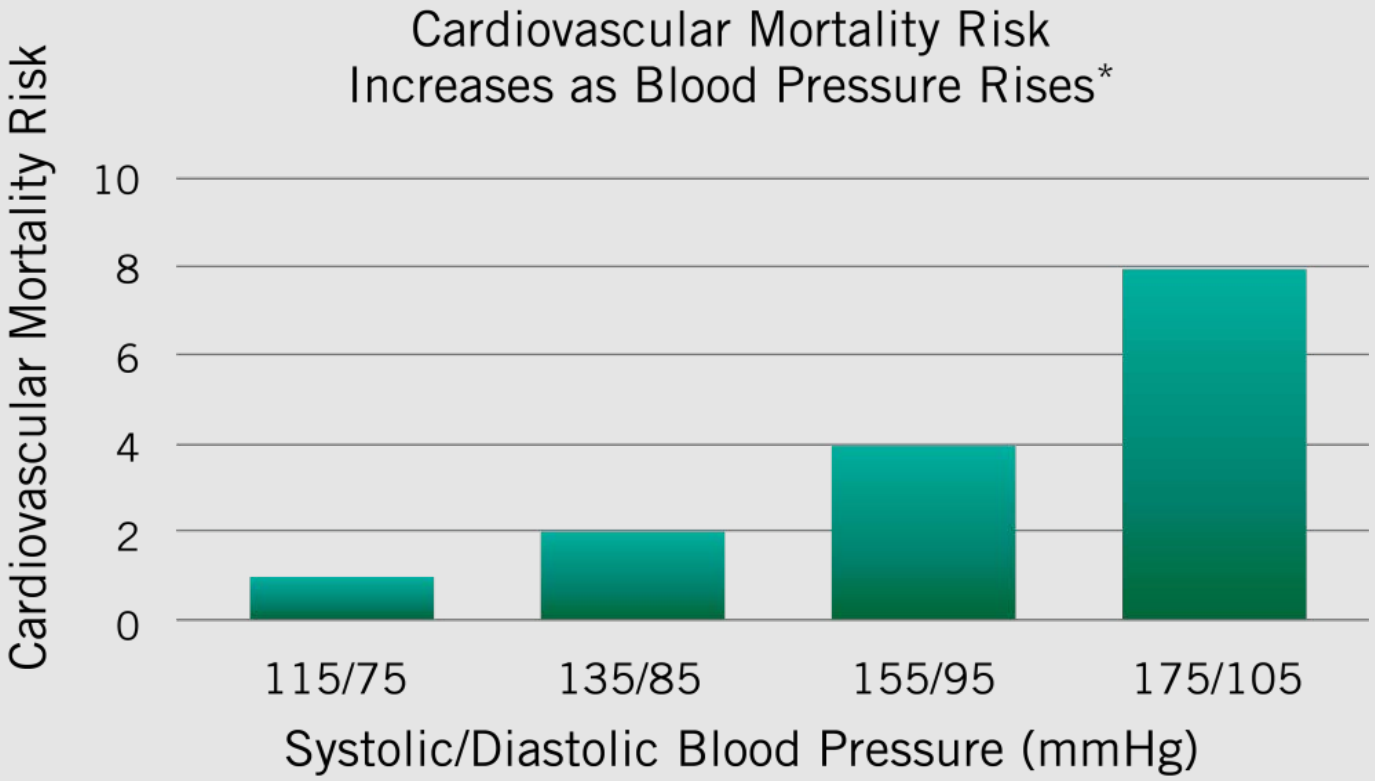
- Самостоятелна причина за смъртността по света
- Всяко повишаване с 20/10 mmHg на АН корелира с двойно увеличаване на 10-год. СС смъртност
- Значимо повишава риска от инсулт, коронарна болест, сърдечна недостатъчност & бъбречна недостатъчност
- Само половината от лекуваните хипертоници са контролирани под прицелните стойности
- Висока честота:
  - засяга 1 от 3 възрастни
  - 1 милиард по света → 1.6 милиарда до 2025

Chobanian et al. Hypertension. 2003;42(6):1206–1252.

Повишен риск от болестност и смъртност

Неконтролирана АХ е рисков фактор за СС болестност и смъртност

- Хроничната неконтролирана АХ е свързана с инсулт и СН[1]
- Рискът от СС смърт се увеличава с всяко увеличение на САН с 20 mmHg и се удвоява риска[2-4]



*Measurements taken in individuals aged 40-69 years, beginning with a blood pressure of 115/75 mmHg, the data in this graph is from Lewington et al. 2002[2]

1. Roger VL, et al. Heart disease and stroke statistics–2011 update: A report from the American Heart Association. *Circulation.* 2011;123(4):e18-e209.
2. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903-13.
3. Chobanian AV, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA.* 2003;289:2560-2572.
4. The graph on this page includes data from sources 2 and 3 and was adapted from www.hypertensiononline.org.

ПРОУЧВАНИЯ НА КОМБИНИРАНА РААС БЛОКАДА

Доц. Б Георгиев, НКБ

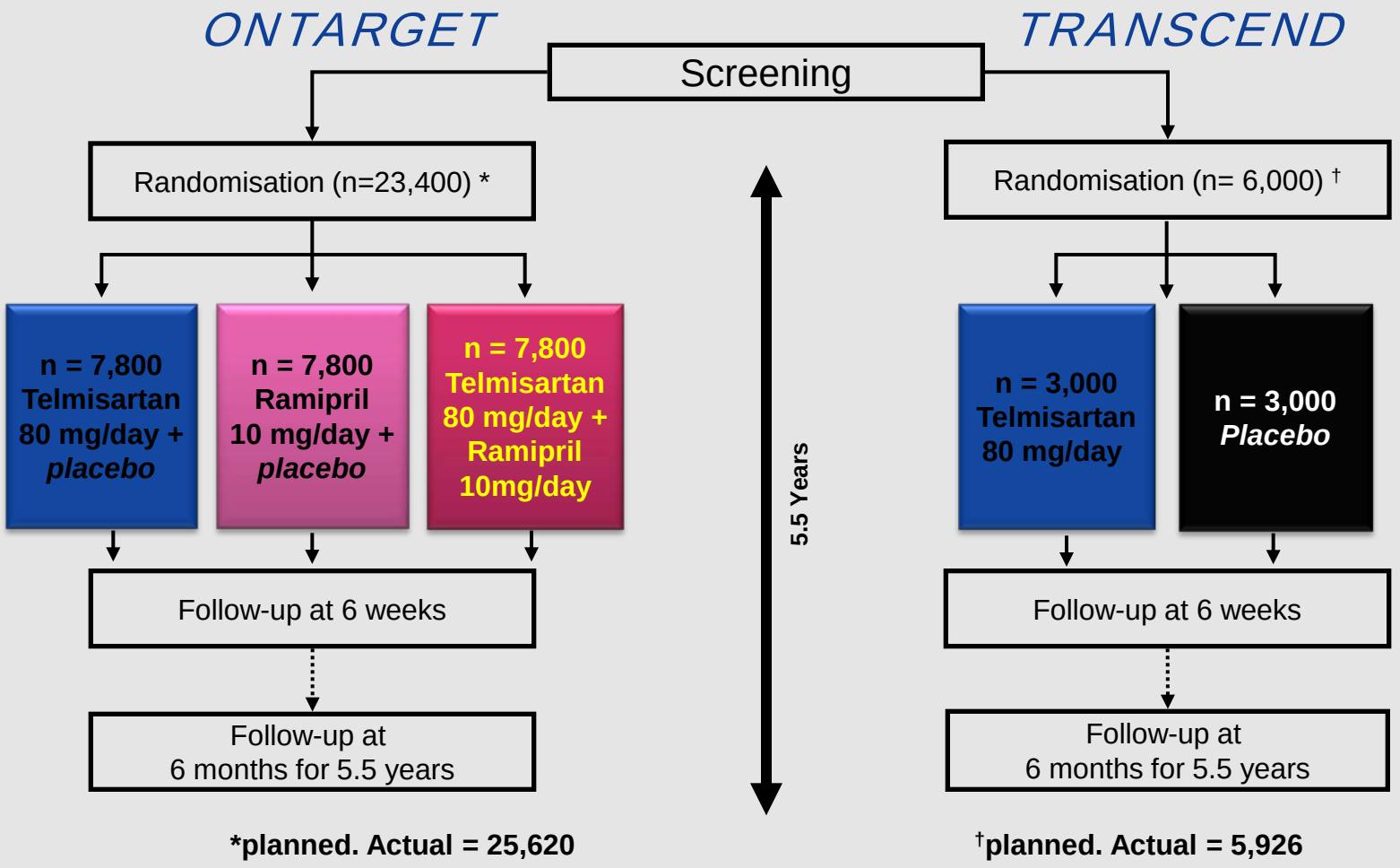
ACE-инхибитор+АРБ

ONTARGET

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial

ONTARGET: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial

Дизайн



***planned. Actual = 25,620**

†planned. Actual = 5,926

Teo K, et al. *Am Heart J* 2004;148:52–61.

ONTARGET

Въпроси:

- Дали telmisartan е “не по-лош” от ramipril?
- Дали комбинацията е по-добра от ramipril?

Оценка:

- Първични крайни точки: СС смърт, МИ, инсулт, хоспитализация за ЗСН

Yusuf S, et al. *American College of Cardiology* 2008. Late-breaking Clinical Trials;Chicago, Il, USA.

Медикация

- Run-in (единично сляп)
  - ден1-3 Ram 2.5 mg + Tel Placebo
  - ден 4-10 Ram 2.5 mg + Tel 40 mg
  - ден 11-18 Ram 5.0 mg + Tel 40 mg
- Рандомизация (двойно сляп)
  - 2 седм Ram Placebo + Tel 80 mg
    Ram 5 mg + Tel Placebo
    Ram 5 mg + Tel 80 mg
  - после пълна доза (Tel 80 mg ден,
    Ram 10 mg ден) за 3-те рамена

Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

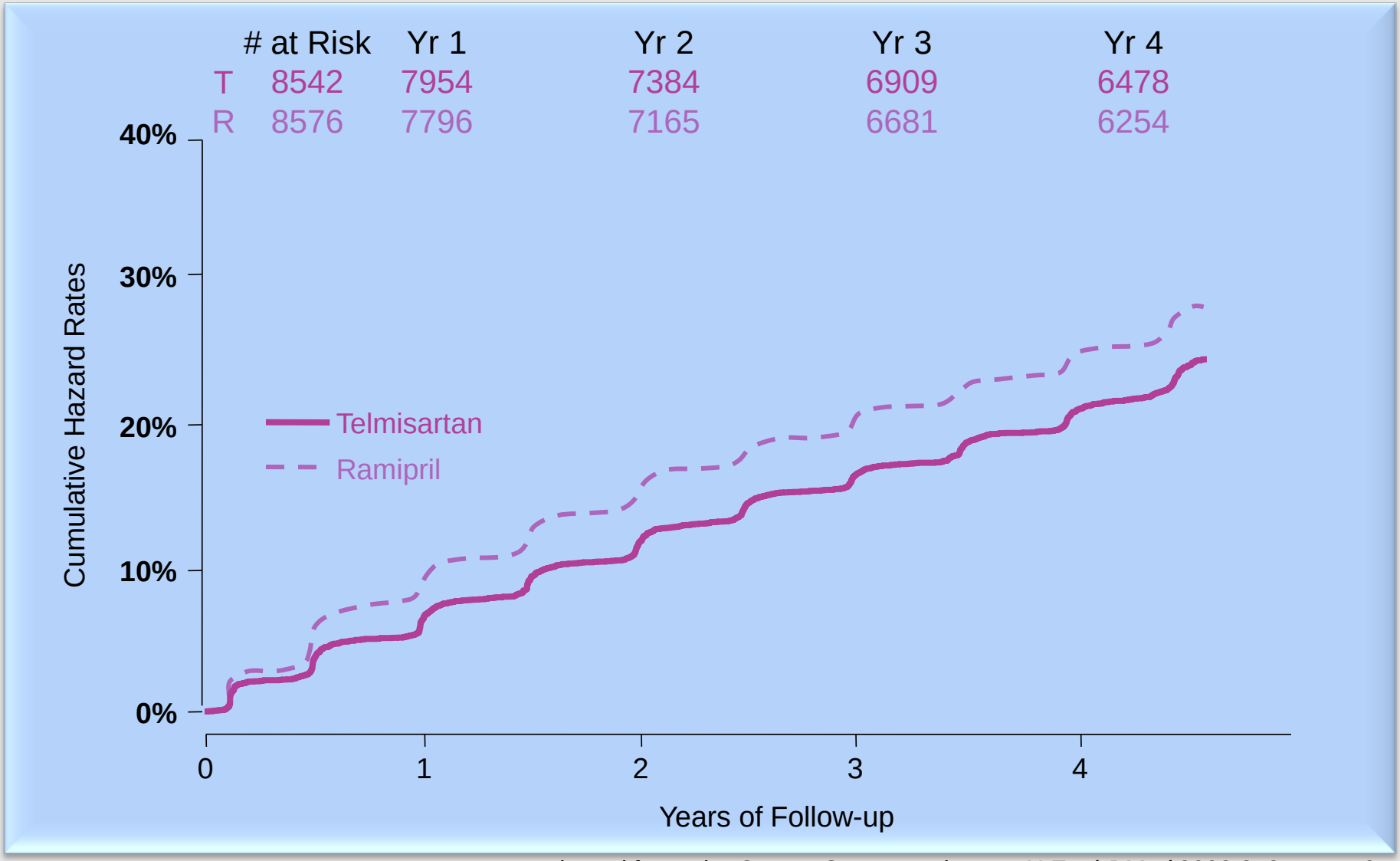
Telmisartan *vs* Ramipril

Промени в АН (mmHg)

	Ramipril	Telmisartan
САН	-6.0	-6.9
ДАН	-4.6	-5.2

Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Време до постоянно преустановяване на терапията



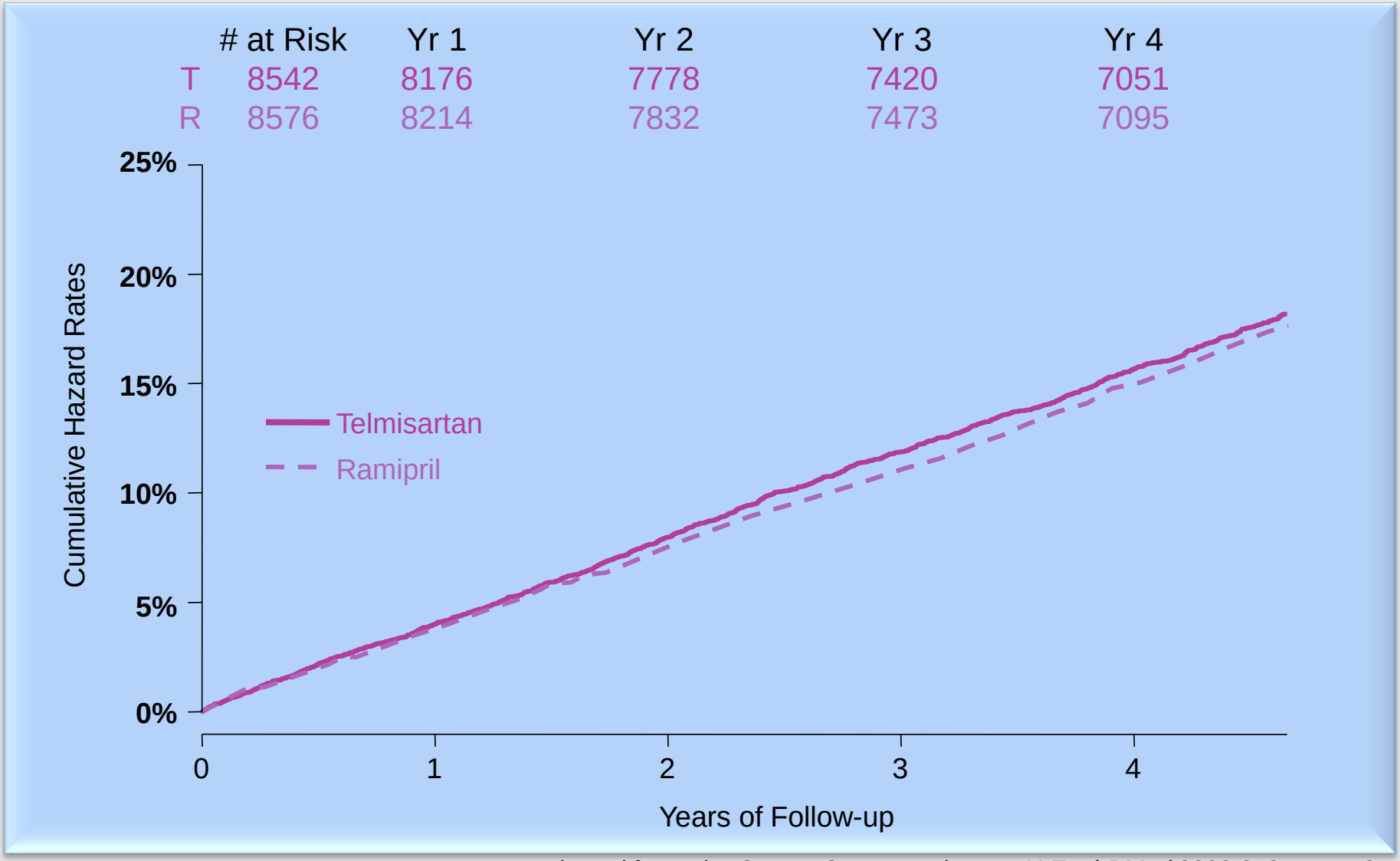
Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Причини за постоянно преустановяване на терапията

	Ram N=8576	Tel N=8542	Tel vs. Ram RR	Tel vs. Ram P
хипотония	149	229	1.54	0.0001
синкоп	15	19	1.27	0.4850
кашлица	360	93	0.26	<0.0001
диария	12	19	1.59	0.20
ангиоедем	25	10	0.40	0.0115
Бъбречна дисфункция	60	68	1.14	0.46
Всички прекъсвания	2099	1962	0.94	0.02

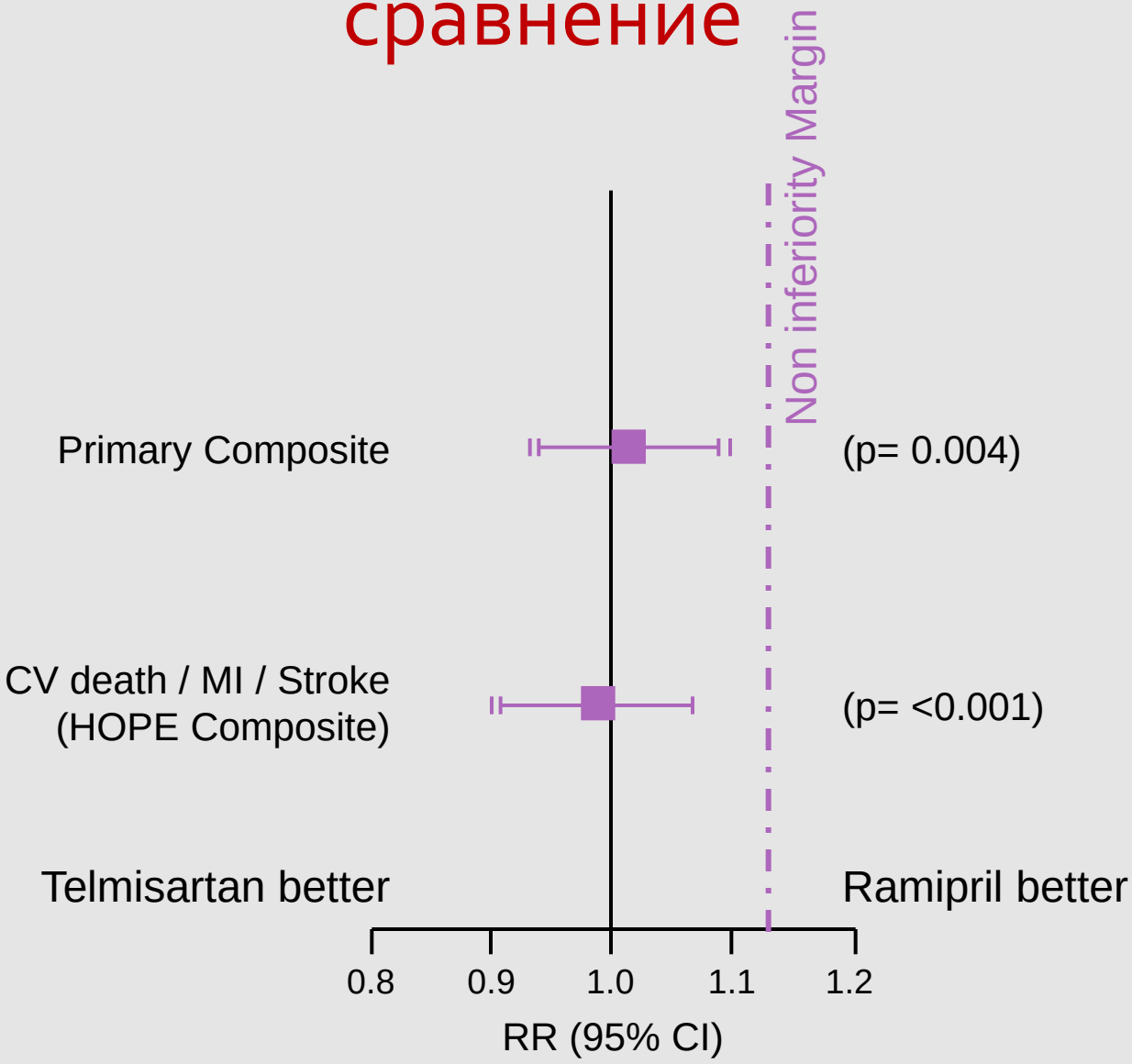
The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Време до първична крайна цел



Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

ONTARGET *Non-Inferiority* сравнение



Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

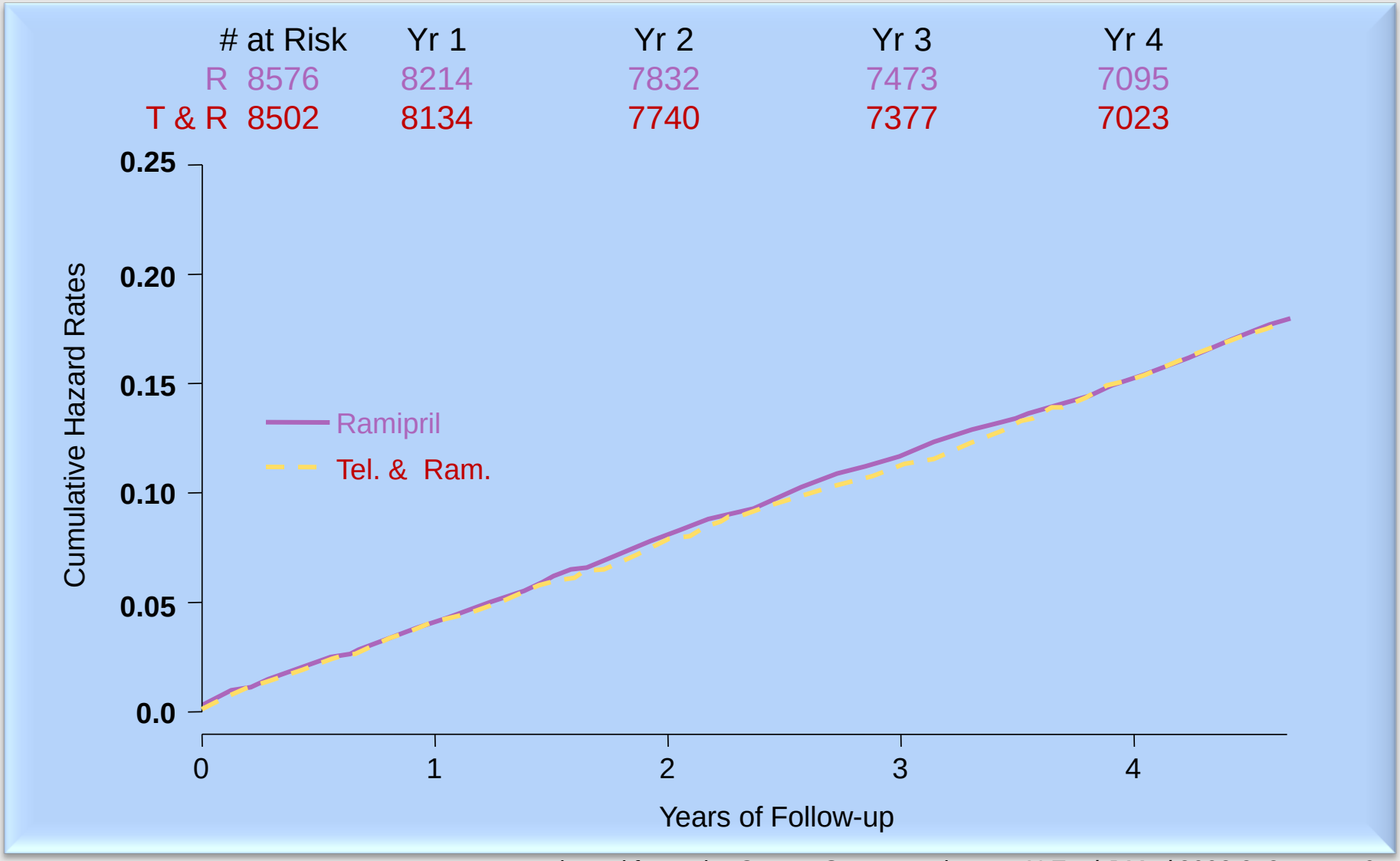
Комбинирана терапия *vs* Ramipril

Промени в АН (mmHg)

	Ramipril	Combination
САН	-6.0	-8.4
ДАН	-4.6	-6.0

Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Време до първична крайна цел



Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Причини за постоянно преустановяване на терапията

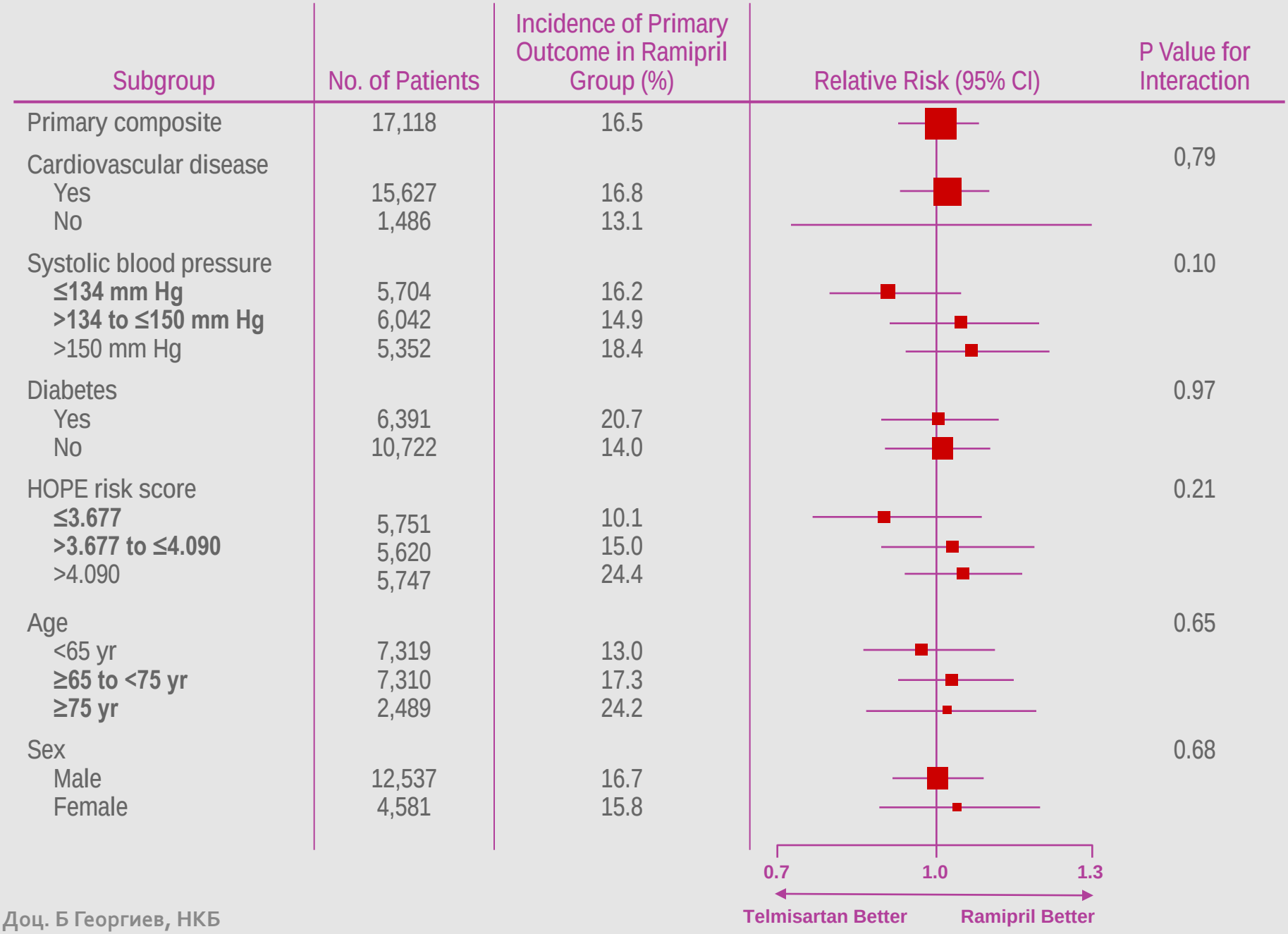
	Ram N=8576	Ram + Tel N=8502	Ram + Tel vs. Ram RR	P
хипотония	149	406	2.75	<0.0001
синкоп	15	29	1.95	0.032
кашлица	360	392	1.10	0.1885
диария	12	39	3.28	0.0001
ангиоедем	25	18	0.73	0.30
Бъбречна дисфункция	60	94	1.58	0.0050
Всички прекъсвания	2099	2495	1.20	<0.0001

Adapted from The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Изводи:
Telmisartan *vs.* Ramipril (1)

1. **Telmisartan е “не по-лош” от ramipril**
   - Първична комозитна крайна цел (p=0.0038)
   - HOPE – първични крайни цели (p=0.001)

2. **Стабилност на резултатите при:**
   - Вторичните цели
   - Подгрупите



The ONTARGET Investigators *N Engl J Med* 2008;358:1547-59.

Изводи:
Telmisartan *vs.* Ramipril (2)

3. Telmisartan е с по-добра поносимост

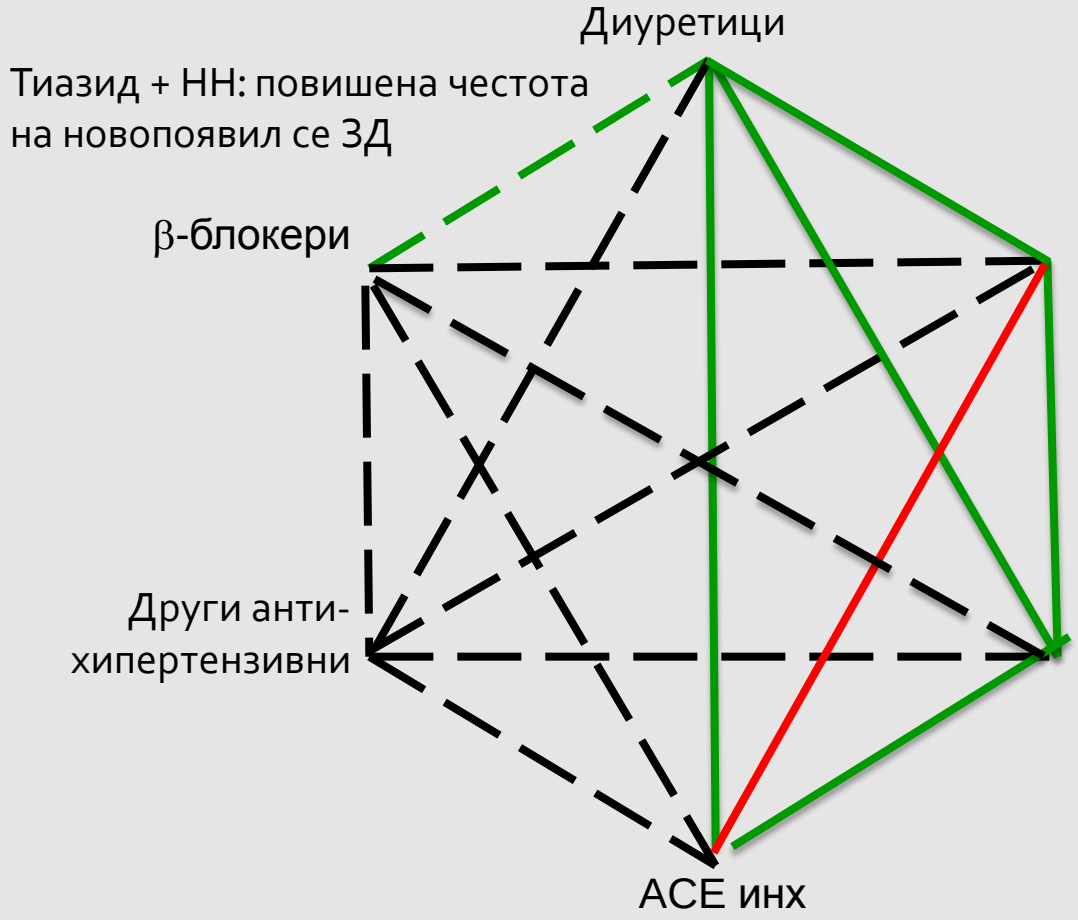
- По-малко кашлица и ангиоедем
- Повече лека хипотензивна симптоматика, но без разлика при тежката хипотония, като синкопи

Изводи:
Telmisartan+Ramipril *vs.* Ramipril

- Комбинираната терапия не намалява повече първичните крайни точки в сравнение само с ramipril

- Висока честота на странични ефекти:
  - Свързани с хипотония, вкл. синкоп
  - Бъбречна дисфункция

Възможни комбинации, ESH 2013



Само DHP-КА могат да се комбинират с ББ

Комбинации с алискирен

Aliskiren and Valsartan for Antihypertensive Therapy Trial

Aliskiren and Valsartan for
Antihypertensive Therapy Trial

Presented at the American College of Cardiology
Annual Scientific Session

March 2007

Presented by Dr. Suzanne Oparil

Aliskiren and Valsartan for Antihypertensive Therapy Trial: Study Design

1797 patients of mean age 52 years with mild to moderate hypertension (diastolic blood pressure (DBP) > 95 and < 220 mm Hg) prior to randomization

Placebo-controlled. Randomized. Blinded. Mean follow-up 8 weeks. 39% female.

R

1-2 week period of washout from prior therapy and a 3-4 week run-in period

Aliskiren	Valsartan	Aliskiren + Valsartan	Placebo
150 mg n=437	160 mg n=455	150 mg + 160 mg n=446	n=459

4 weeks, double dosages

Aliskiren	Valsartan	Aliskiren + Valsartan	Placebo
300 mg n=437	320 mg n=455	300 mg + 320 mg n=446	n=459

4 more weeks

- Primary Endpoint: Reduction in mean sitting DBP
- Secondary Endpoint: Reduction in mean sitting SBP, response rate, achievement of blood pressure control (<140/90 mm Hg)

Aliskiren and Valsartan for Antihypertensive Therapy: резултати на 4-седмица

Седм 4	Aliskiren 150 mg n=437	Valsartan 160 mg n=455	Aliskiren + Valsartan 150/160 mg n=446	Placebo n=459
Промяна в ДАН (mm Hg)	-7.5*	-8.7*†	-10.5*	-4.8
Промяна в САН (mm Hg)	-10.7*	-10.9*†	-15.3*	-5.2

*p<0.0001 vs. placebo
†p<0.001 vs. aliskiren/valsartan

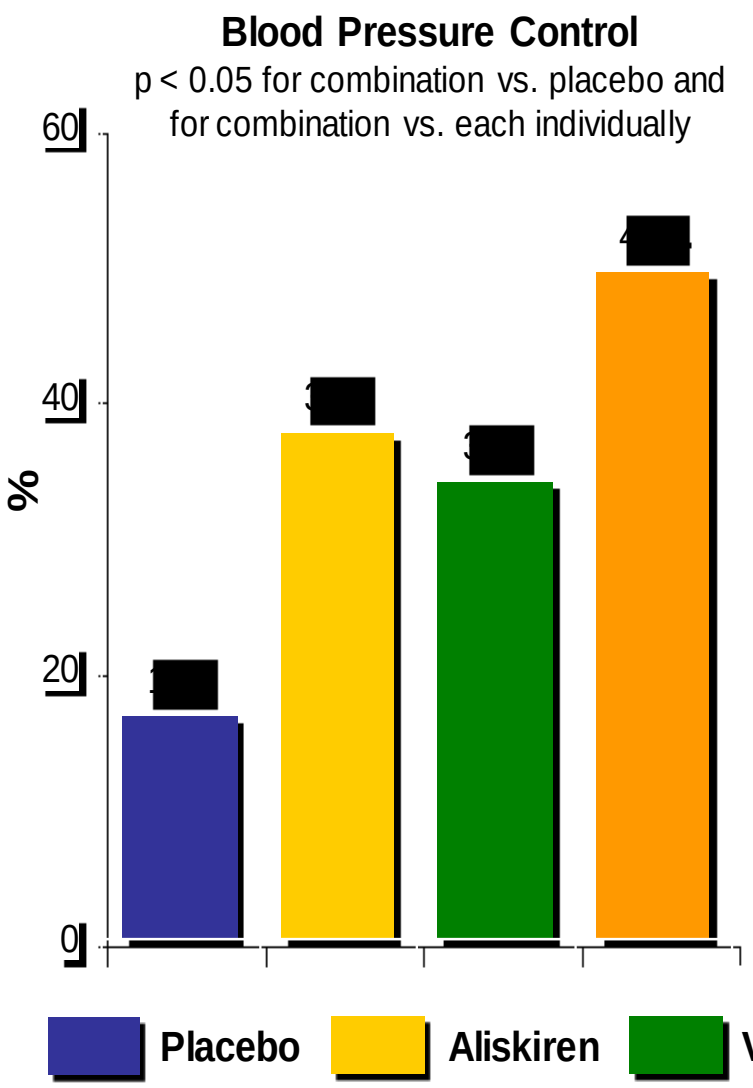
Aliskiren and Valsartan for Antihypertensive Therapy: резултати на 8-седмица

Седм 8	Aliskiren 300 mg n=437	Valsartan 320 mg n=455	Aliskiren + Valsartan 300/320 mg n=446	Placebo n=459
Промяна в ДАН (mm Hg)	-9.0*†	-9.7*†	-12.2*	-4.1
Промяна в САН (mm Hg)	-13.0*†	-12.8*†	-17.2*	-4.6
Контролирано АН (%)	37.4 *†	33.8 *†	49.3*	16.5

*p<0.0001 vs. placebo
†p<0.001 vs. aliskiren/valsartan

Aliskiren and Valsartan for Antihypertensive Therapy

Trial Design: The study was a randomized, double-blind trial of aliskiren (150 mg; n = 437), valsartan (160 mg; n = 455), the combination of the two (n = 446), or placebo (n = 459) in patients with mild to moderate hypertension. Primary endpoint was reduction in mean sitting DBP at 8 weeks.



Results

- Mean baseline blood pressure 154/100 mm Hg
- At follow-up, blood pressure (SBP/DBP) ↓ by 4.6/4.1 mm Hg in placebo group, 13.0/9.0 mm Hg in aliskiren group, 12.8/9.7 mm Hg in valsartan group, and 17.2/12.2 mm Hg in combination group ($p < 0.001$ for combination vs. placebo and for combination vs. each individually)
- Blood pressure control highest in combination group (Figure)
- Adverse event rate similar between groups

Conclusions

- Among patients with mild to moderate hypertension, aliskiren, valsartan, and the combination were associated with greater reductions in blood pressure compared with placebo at 8 weeks, with largest reductions seen in combination group
- Both aliskiren and valsartan inhibit renin-angiotensin-aldosterone system, but act at different points in system, with aliskiren acting at point of activation
- Both agents were effective in ↓ blood pressure, but combination of two agents appeared to be additive

Presented at ACC/i2 Summit 2007

Original Article

Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

Hans-Henrik Parving, M.D., D.M.Sc., Frederik Persson, M.D., Julia B. Lewis, M.D., Edmund J. Lewis, M.D., Norman K. Hollenberg, M.D., Ph.D., for the AVOID Study Investigators

N Engl J Med
Volume 358(23):2433-2446
June 5, 2008

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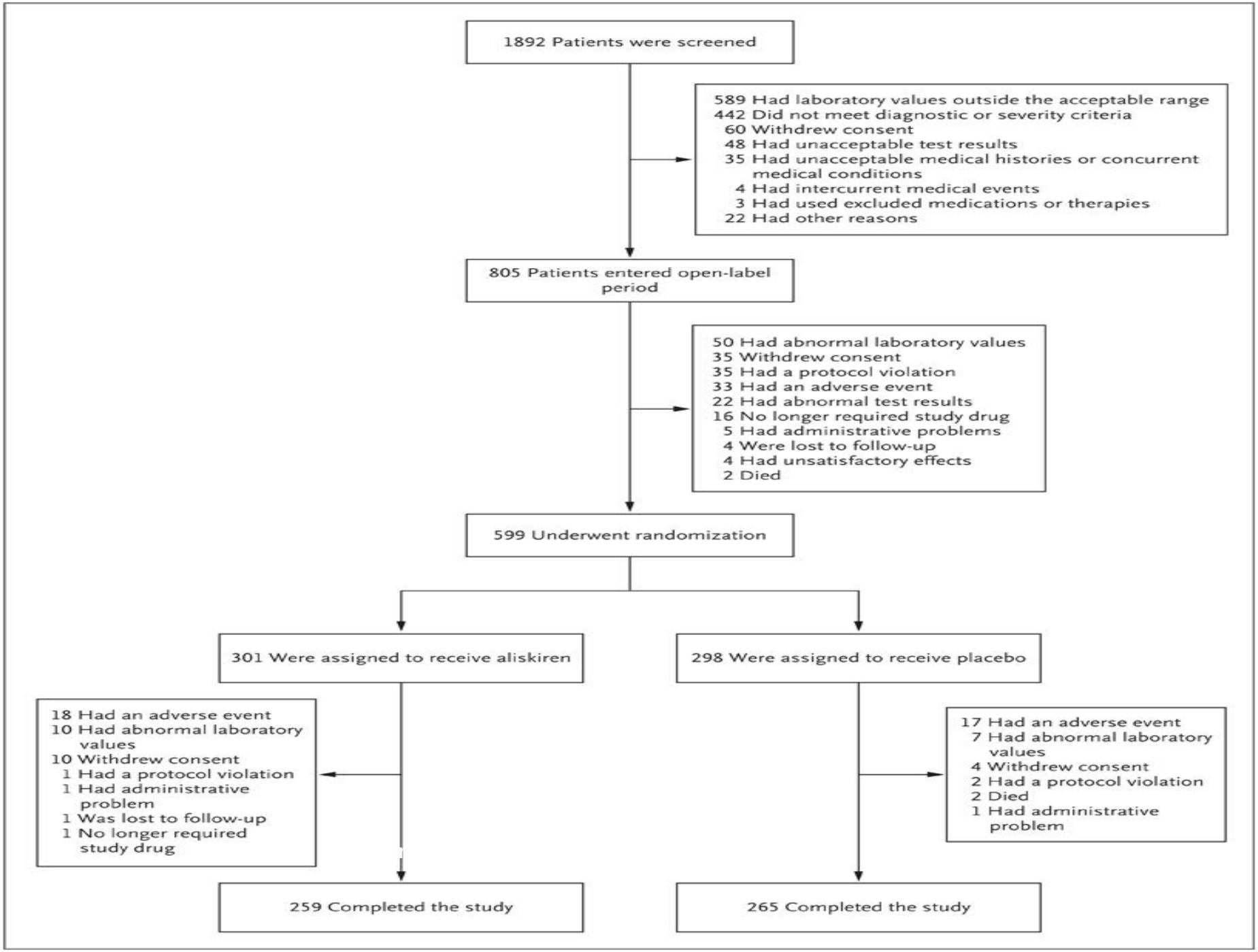
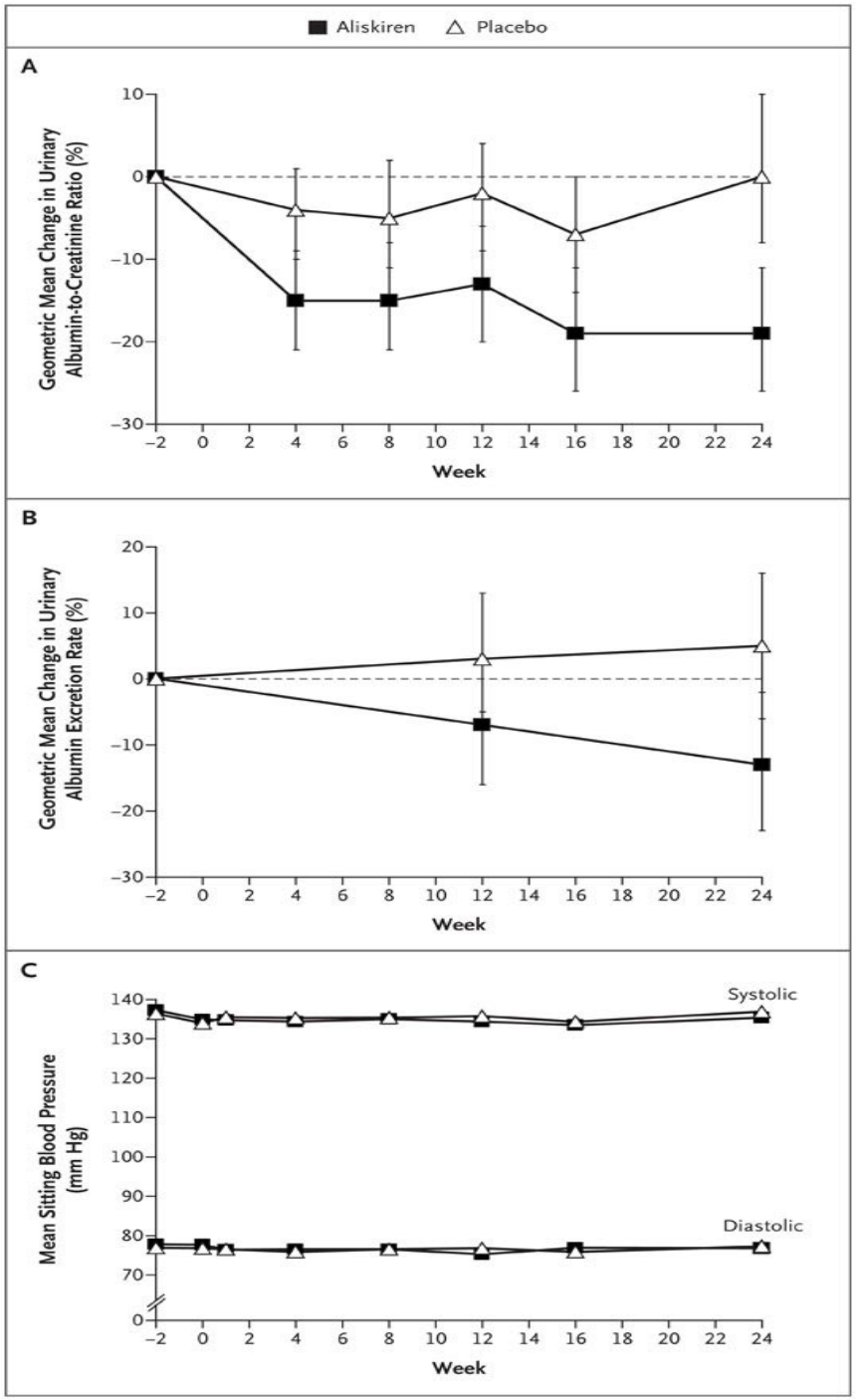

1892 Patients were screened
589 Had laboratory values outside the acceptable range
442 Did not meet diagnostic or severity criteria
60 Withdrew consent
48 Had unacceptable test results
35 Had unacceptable medical histories or concurrent medical conditions
4 Had intercurrent medical events
3 Had used excluded medications or therapies
22 Had other reasons
805 Patients entered open-label period
50 Had abnormal laboratory values
35 Withdrew consent
35 Had a protocol violation
33 Had an adverse event
22 Had abnormal test results
16 No longer required study drug
5 Had administrative problems
4 Were lost to follow-up
4 Had unsatisfactory effects
2 Died
599 Underwent randomization
301 Were assigned to receive aliskiren
298 Were assigned to receive placebo
18 Had an adverse event
10 Had abnormal laboratory values
10 Withdrew consent
1 Had a protocol violation
1 Had administrative problem
1 Was lost to follow-up
1 No longer required study drug
17 Had an adverse event
7 Had abnormal laboratory values
4 Withdrew consent
2 Had a protocol violation
2 Died
1 Had administrative problem
259 Completed the study
265 Completed the study

Table 1. Baseline Characteristics of the Randomized Population.*

Characteristic	Aliskiren Group (N = 301)	Placebo Group (N = 298)	P Value
Demographic			
Age — yr	59.8±9.6	61.8±9.6	0.009
Male sex — no. (%)	206 (68.4)	221 (74.2)	0.11
Race — no. (%)†			0.39
White	259 (86.0)	261 (87.6)	
Black	24 (8.0)	26 (8.7)	
Asian	5 (1.7)	6 (2.0)	
Other	13 (4.3)	5 (1.7)	
Clinical			
Body-mass index‡	33±7	32±6	0.08
Known duration of diabetes — yr	13.2±8.4	14.9±8.7	0.02
Mean sitting blood pressure — mm Hg			
Systolic	135±12	134±12	0.38
Diastolic	78±8	77±9	0.18
Medical history — no. (%)			
Angina pectoris	24 (8.0)	20 (6.7)	0.55
Coronary artery disease	24 (8.0)	25 (8.4)	0.85
Myocardial infarction	19 (6.3)	15 (5.0)	0.50
Stroke	9 (3.0)	12 (4.0)	0.49
Diabetic neuropathy	55 (18.3)	49 (16.4)	0.56
Diabetic retinopathy	65 (21.6)	82 (27.5)	0.09
Dyslipidemia	74 (24.6)	72 (24.2)	0.90
Current smoking	61 (20.3)	53 (17.8)	0.48
Urinary albumin-to-creatinine ratio§	513 (463–569)	553 (502–609)	0.29
Urinary albumin excretion rate — μg/min§	495 (440–557)	520 (469–576)	0.52
Serum creatinine — mg/dl¶			
Men	1.3±0.5	1.3±0.4	0.62
Women	1.1±0.4	1.1±0.4	0.28
Estimated glomerular filtration rate — ml/min/1.73 m²‖	68.5±25.7	66.8±24.5	0.41
Hemoglobin — g/liter	135.4±17.8	133.6±15.8	0.55
Glycated hemoglobin — %	8.0±1.4	7.9±1.4	0.16
Triglycerides — mg/dl	203.5±156.6	177.0±144.2	0.42
Cholesterol — mg/dl			
Total	181.5±43.6	177.6±44.8	0.88
Low-density lipoprotein	104.2±36.3	104.2±36.7	0.77
High-density lipoprotein	42.5±11.6	42.5±12.4	0.60
Serum potassium — mmol/liter	4.5±0.5	4.5±0.5	0.88
Glucose-lowering therapies — no. (%)			
Insulin and insulin analogues	162 (53.8)	158 (53.0)	0.84
Biguanides	145 (48.2)	141 (47.3)	0.83
Sulfonylureas	113 (37.5)	119 (39.9)	0.55
Thiazolidinediones	33 (11.0)	38 (12.8)	0.50
Lipid-lowering therapies — no. (%)			
Statins	169 (56.1)	169 (56.7)	0.89
Fibrates	24 (8.0)	22 (7.4)	0.79
Aspirin — no. (%)	122 (40.5)	123 (41.3)	0.85

* Plus–minus values are means ±SD. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.
† Race was determined by investigator report.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Values are geometric means, with 95% confidence intervals in parentheses.
¶ Data are for 205 men in the aliskiren group and 221 men in the placebo group and for 95 women in the aliskiren group and 77 women in the placebo group.
‖ The glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease (MDRD) formula.



Changes from Baseline in the Urinary Albumin-to-Creatinine Ratio, Urinary Albumin Excretion Rate, and Blood Pressure According to Study Group

Parving HH et al. N Engl J Med 2008;358:2433-2446

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Table 3. Serious Adverse Events, Adverse Events, and Prespecified Abnormal Laboratory Values during Double-Blind Treatment (Safety Population).

Adverse Event or Abnormal Laboratory Value	Aliskiren Group (N=301)	Placebo Group (N=298)
	number (percent)	
Any adverse event	201 (66.8)	200 (67.1)
Any serious adverse event	27 (9.0)	28 (9.4)
Death	0	2 (0.7)
Discontinuation of study medication due to adverse event	17 (5.6)	19 (6.4)
Discontinuation of study medication due to serious adverse event	9 (3.0)	8 (2.7)
Serious adverse events occurring in more than one patient		
Pneumonia	2 (0.7)	3 (1.0)
Peripheral edema	2 (0.7)	1 (0.3)
Congestive cardiac failure	2 (0.7)	1 (0.3)
Limb abscess	2 (0.7)	0
Gastroenteritis	2 (0.7)	0
Acute renal failure	2 (0.7)	0
Angina pectoris	1 (0.3)	2 (0.7)
Cellulitis	1 (0.3)	2 (0.7)
Adverse events in ≥2% of either group		
Headache	18 (6.0)	11 (3.7)
Nasopharyngitis	18 (6.0)	15 (5.0)
Dizziness	15 (5.0)	10 (3.4)
Hyperkalemia	15 (5.0)	17 (5.7)
Edema, peripheral	13 (4.3)	23 (7.7)
Back pain	13 (4.3)	12 (4.0)
Anemia	12 (4.0)	5 (1.7)
Hypotension	12 (4.0)	3 (1.0)
Diarrhea	9 (3.0)	8 (2.7)
Influenza	9 (3.0)	7 (2.3)
Nausea	8 (2.7)	5 (1.7)
Upper respiratory tract infection	8 (2.7)	4 (1.3)
Urinary tract infection	8 (2.7)	11 (3.7)
Gastroenteritis	7 (2.3)	1 (0.3)
Pain in extremity	7 (2.3)	7 (2.3)
Asthenia	6 (2.0)	3 (1.0)
Cough	5 (1.7)	7 (2.3)
Dyspnea	5 (1.7)	6 (2.0)
Fatigue	5 (1.7)	6 (2.0)
Angina pectoris	4 (1.3)	6 (2.0)
Arthralgia	4 (1.3)	7 (2.3)
Abdominal pain, upper	3 (1.0)	6 (2.0)
Myalgia	3 (1.0)	7 (2.3)
Laboratory abnormalities*		
Serum potassium		
<3.5 mmol/liter	15 (5.0)	11 (3.7)
>5.5 mmol/liter	41 (13.7)	32 (10.8)
≥6.0 mmol/liter	14 (4.7)	5 (1.7)
Creatinine >2.0 mg/dl (176.8 μmol/liter)	37 (12.4)	54 (18.2)
Blood urea nitrogen >40.0 mg/dl (14.28 mmol/liter)	65 (21.7)	66 (22.2)

* Data were available for 299 patients in the aliskiren group and 297 patients in the placebo group.

Parving HH et al. N Engl J Med 2008;358:2433-2446

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Conclusion

- Aliskiren може да има ренопротективен ефект независим от понижаването на АН при болни с АХ и ЗДТ2 и нефропатия, когато получават препоръчителната ренопротективна терапия

The NEW ENGLAND JOURNAL of MEDICINE

ALTITUDE trial

- Patients with type 2 DM with renal disease (either proteinuria or reduced eGFR)
- Randomized to aliskiren or placebo
- ACE inhibitor or ARB use required
- Primary endpoint
  - Composite of CV and renal endpoints
- DMC stopped study early because of futility for demonstrating benefit and evidence of potential harm

Parving H, et al. Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes, NEJM 2012; 367: 2204.

ALTITUDE terminated early (12/2011)

Variable	Treatment A (N=4283)	Treatment B (N=4296)	Total (N=8579)	HR	95% CI	P-value
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)	0.1663
Secondary composite outcome - CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)	0.0664
Secondary composite outcome - renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)	0.5178
Component event:						
CV death	179 (4.2%)	162 (3.8%)	341 (4.0%)	1.12	(0.90, 1.38)	0.3110
Resuscitated sudden death	13 (0.3%)	8 (0.2%)	21 (0.2%)	1.64	(0.68, 3.95)	0.2737
Non-fatal MI	90 (2.1%)	88 (2.0%)	178 (2.1%)	1.03	(0.77, 1.39)	0.8302
Non-fatal stroke	112 (2.6%)	85 (2.0%)	197 (2.3%)	1.34	(1.01, 1.77)	0.0439
Unplanned hospitalization for heart failure	150 (3.5%)	155 (3.6%)	305 (3.6%)	0.98	(0.78, 1.23)	0.8716
Onset of ESRD/renal death	72 (1.7%)	60 (1.4%)	132 (1.5%)	1.22	(0.87, 1.72)	0.2518
Doubling of baseline serum creatinine	141 (3.3%)	159 (3.7%)	300 (3.5%)	0.90	(0.71, 1.12)	0.3431
Death from any cause	297 (6.9%)	277 (6.4%)	574 (6.7%)	1.08	(0.92, 1.27)	0.3661

Treatment A= Aliskiren; Treatment B=placebo

Top-Line Safety Signals from ALTITUDE

- ↑ risk ESRD/renal death
- ↑ risk of non-fatal stroke, death
- Hyperkalemia
- Hypotension
- *Lack of efficacy for CV or renal protection*

Why was a CV outcome trial not required?

- Sponsor agreed to labeling changes
  - Addition of aliskiren to ACE/ARB in patients with diabetes contraindicated
  - Avoid combo therapy in patients with ↓ eGFR
- Sponsor agreed to discontinue marketing of Valturna (valsartan + aliskiren)
- FDA believed these restrictions would markedly reduce overall use of aliskiren

ПРОУЧВАНИЯ ЗА БЪБРЕЧНА ДЕНЕРВАЦИЯ

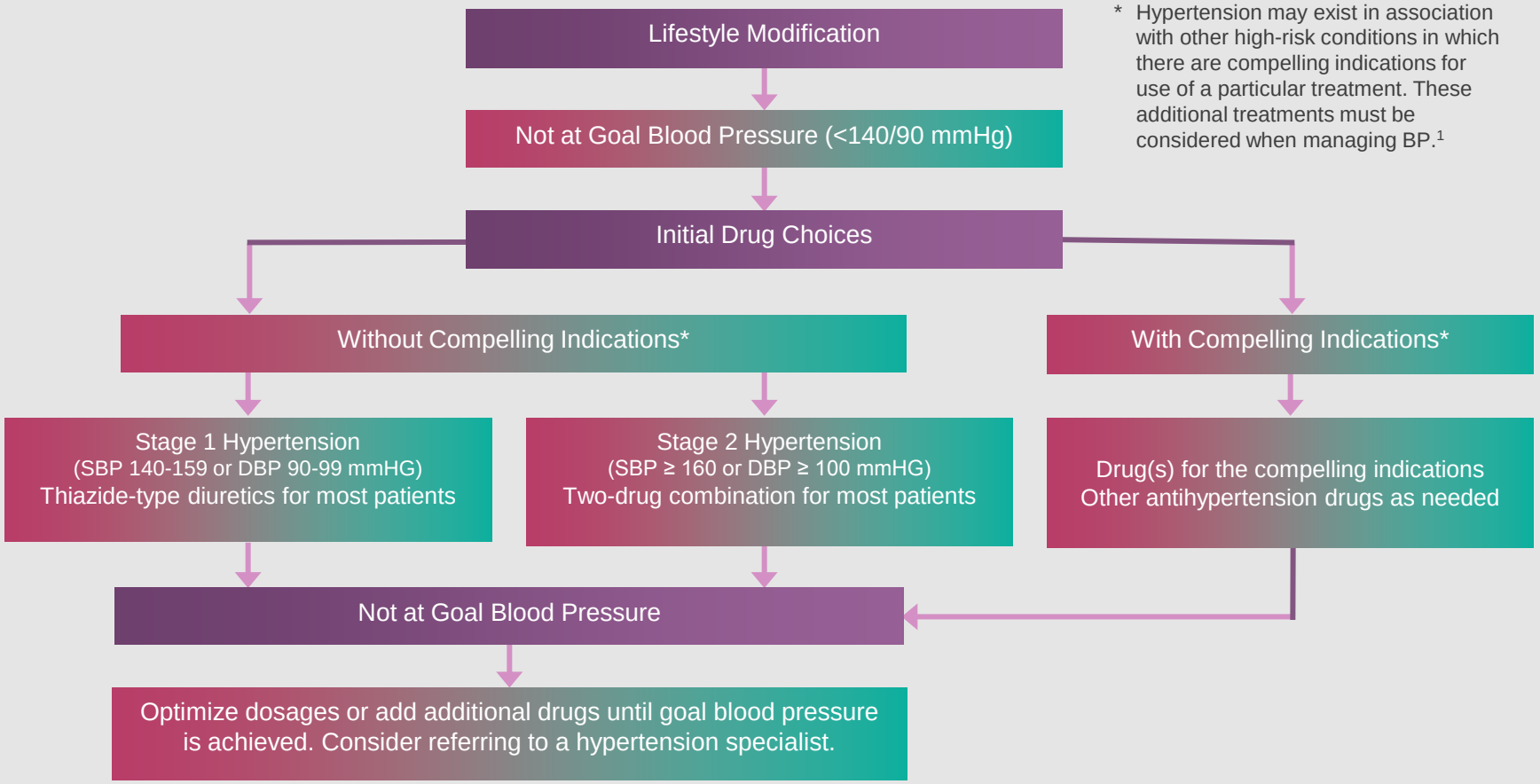
Доц. Б Георгиев, НКБ

Pharmacological Path

Traditional Treatment of Hypertension Follows a Progressively More Aggressive Pharmacological Regimen

The goal of pharmacotherapy is to reach a blood pressure of < 140/90 mmHg
(goal pressure for diabetic and chronic kidney disease patients is < 130/80 mmHg) (See Figure).[1]

- Patients with stage 1 hypertension are generally initiated on at least one antihypertension drug
- Patients with stage 2 hypertension are generally initiated on a combination drug therapy comprised of two or more antihypertension drugs

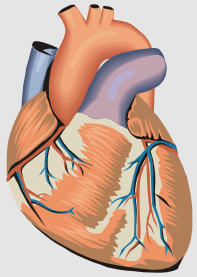


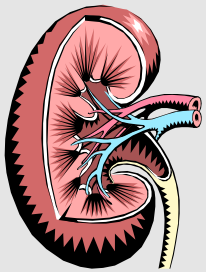
* Hypertension may exist in association with other high-risk conditions in which there are compelling indications for use of a particular treatment. These additional treatments must be considered when managing BP.[1]

1. Chobanian AV, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003;42(6):1206-52.

Бъбречна симпатикусова активация

Бъбрекът като инициатор на симпатикусова активност





Vasoconstriction
Atherosclerosis

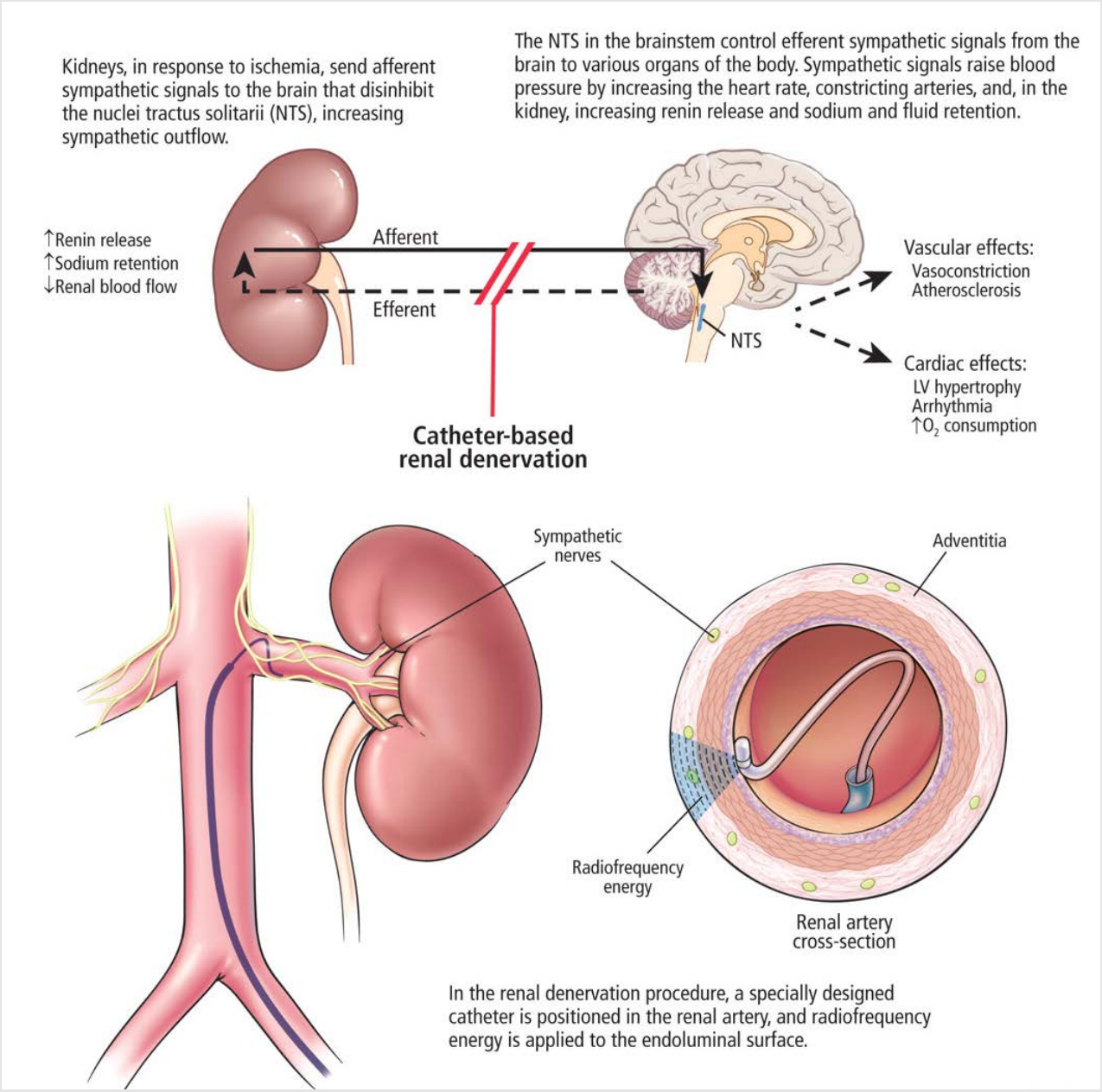
Insulin Resistance

Sleep Disturbances

Renal Afferent Nerves

Hypertrophy
Arrhythmia
Oxygen Consumption

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow


Kidneys, in response to ischemia, send afferent sympathetic signals to the brain that disinhibit the nuclei tractus solitarii (NTS), increasing sympathetic outflow.
The NTS in the brainstem control efferent sympathetic signals from the brain to various organs of the body. Sympathetic signals raise blood pressure by increasing the heart rate, constricting arteries, and, in the kidney, increasing renin release and sodium and fluid retention.
↑Renin release
↑Sodium retention
↓Renal blood flow
Afferent
Efferent
NTS
Vascular effects:
Vasoconstriction
Atherosclerosis
Cardiac effects:
LV hypertrophy
Arrhythmia
↑O_2 consumption
Catheter-based renal denervation
Sympathetic nerves
Adventitia
Radiofrequency energy
Renal artery cross-section
In the renal denervation procedure, a specially designed catheter is positioned in the renal artery, and radiofrequency energy is applied to the endoluminal surface.

История - хирургия

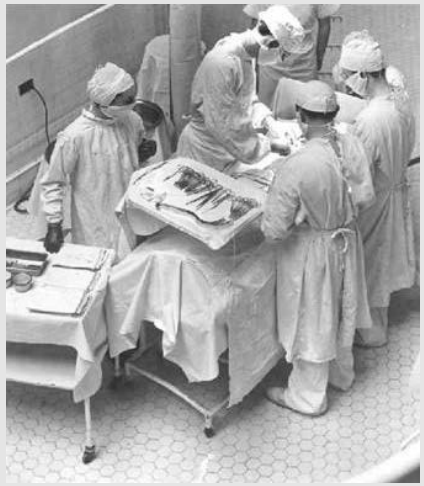
THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

Dr. Reginald H. Smithwick



THE EFFECT OF RENAL DENERVATION ON THE LEVEL OF ARTERIAL BLOOD PRESSURE AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

By IRVINE H. PAGE and GEORGE J. HEUER

(*From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Department of Surgery, New York Hospital, New York*)

(Received for publication September 12, 1934)

THE JOURNAL

of the American Medical Association

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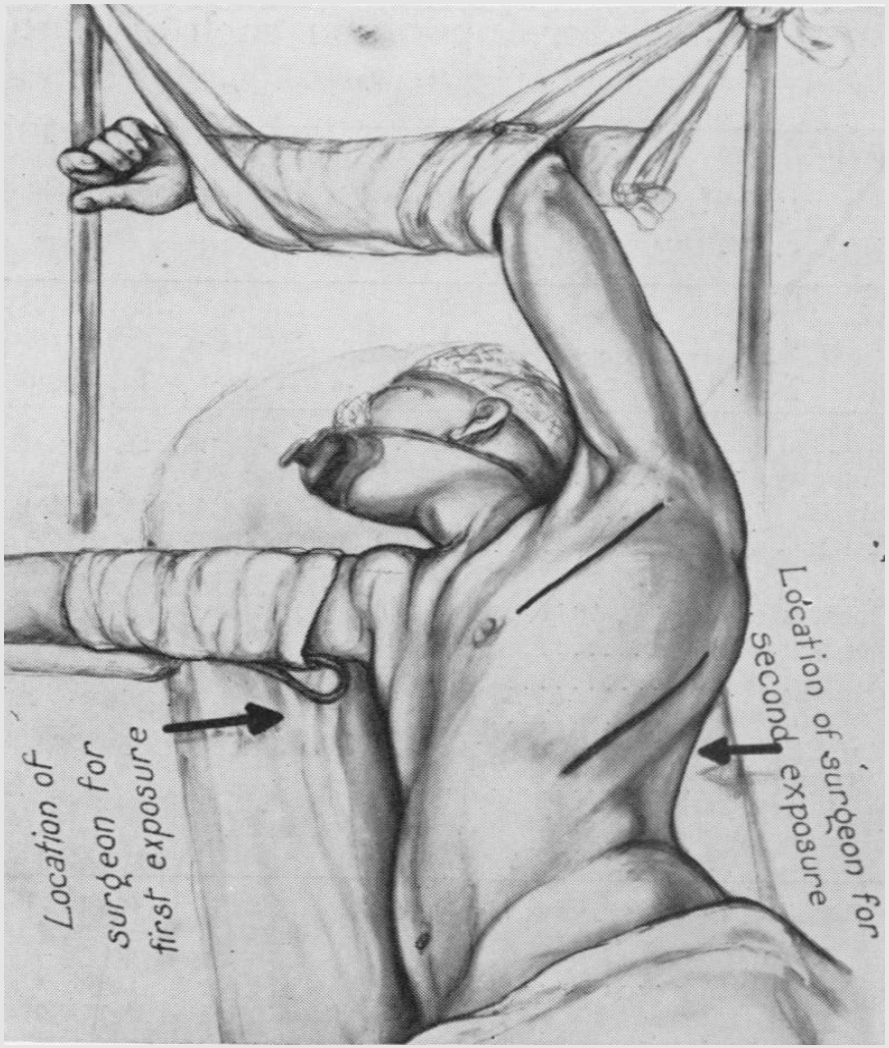
VOL. 152, NO. 16 — CHICAGO, ILLINOIS — AUGUST 15, 1953

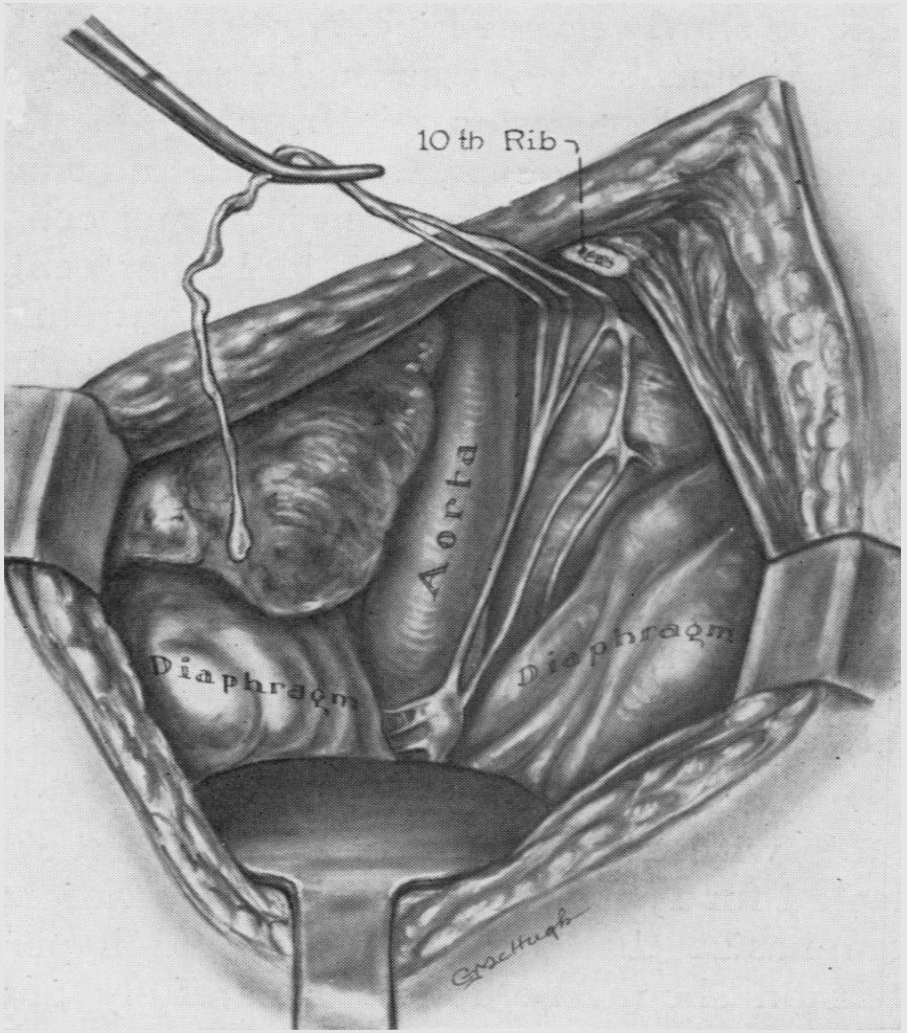
SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

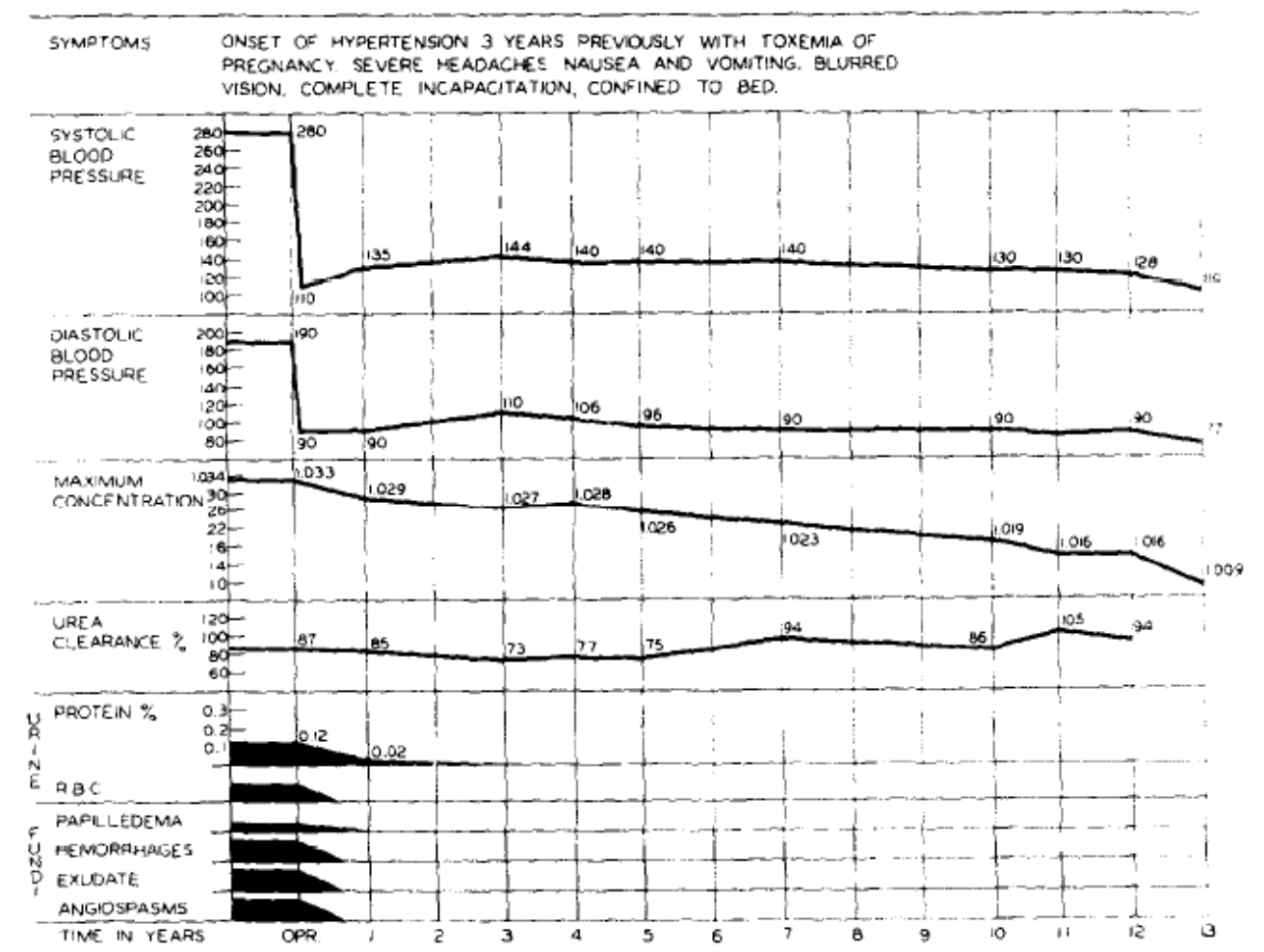
Хирургична симпатектомия





Grimson, Ann Surg 1941

Дългосрочен контрол на АН



Peet, Am J Surg 1948

Symplicity HTN-1


THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281


Hypertension

Celebrating 30 Years: 1979 to 2009

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Hypertension. 2011;57:911-917.

Initial Cohort – Reported in the *Lancet*, 2009:

-First-in-man, non-randomized

-Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)

- 12-month data

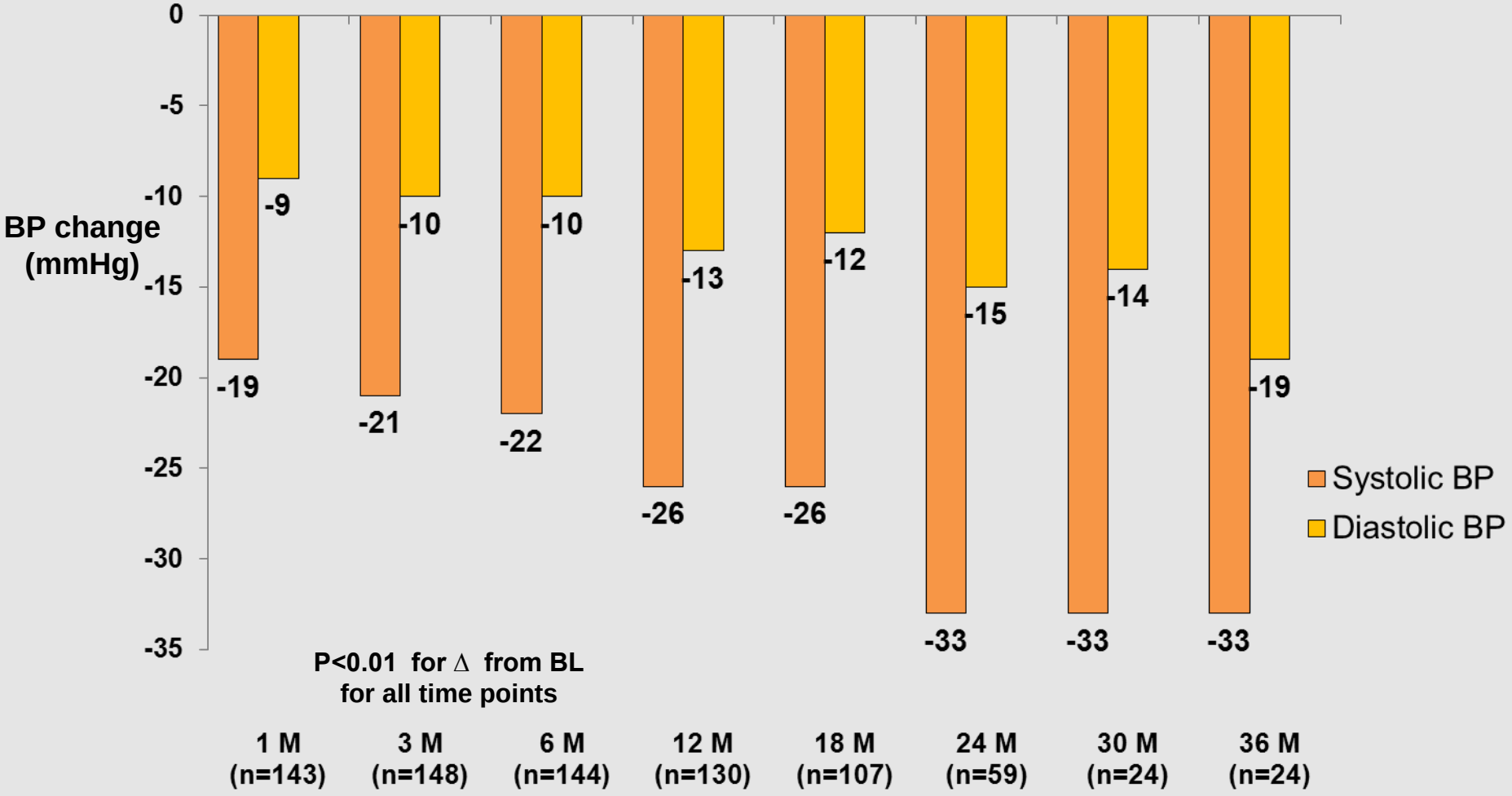
Expanded Cohort* – This Report (Symplicity HTN-1):

-Expanded cohort of patients (n=153)

-36-month follow-up

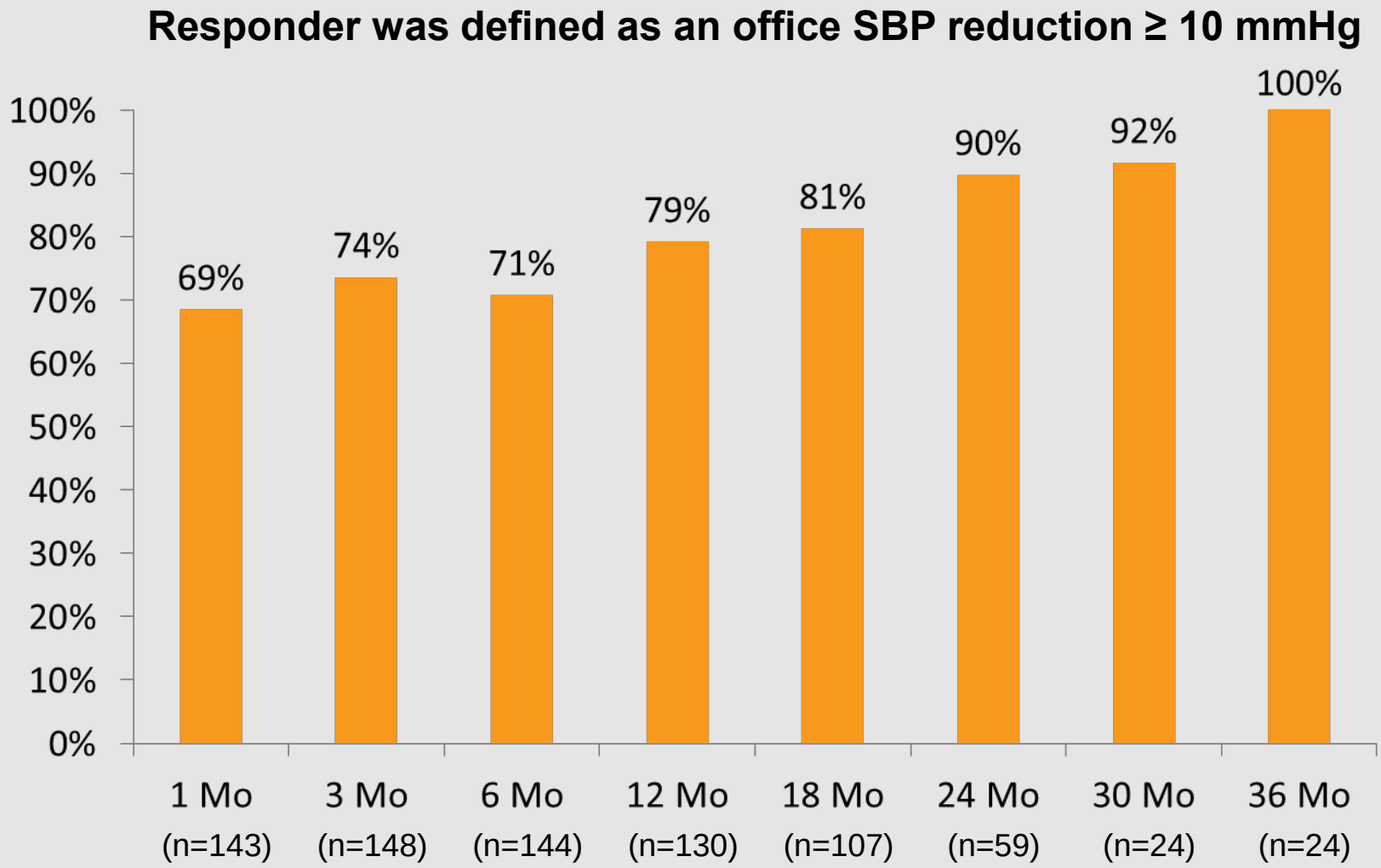
*Expanded results presented at the *American College of Cardiology Annual Meeting* 2012 (Krum, H.)

Symplicity HTN-1: понижение на АН за 3 години



*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Symplicity HTN-1: процент отговорили пациенти



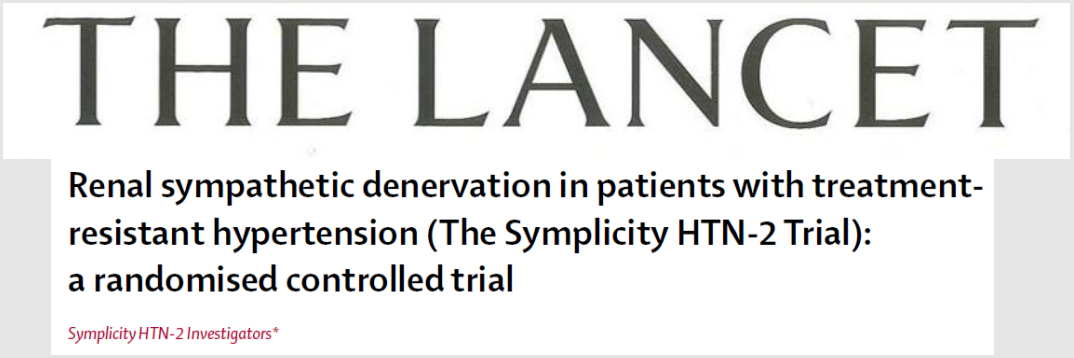
*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Изводи от Symplicity HTN-1

- Клиничният отговор е значителен и се запазва през 3-год период
- Повишаването на отговора сочи, че
  - Не се губи лечебният ефект до 36-ти месец
  - Не-отговорилите на терапия на 6-ти месец не предиктират неуспех в отговора на 12-ти месец или по-късно
- Лечебният ефект е постоянен във всички групи (възраст, диабет, изходна бъбречна недостатъчност)
- Не се установяват късни странични ефекти

*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Symplicity HTN-2


THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

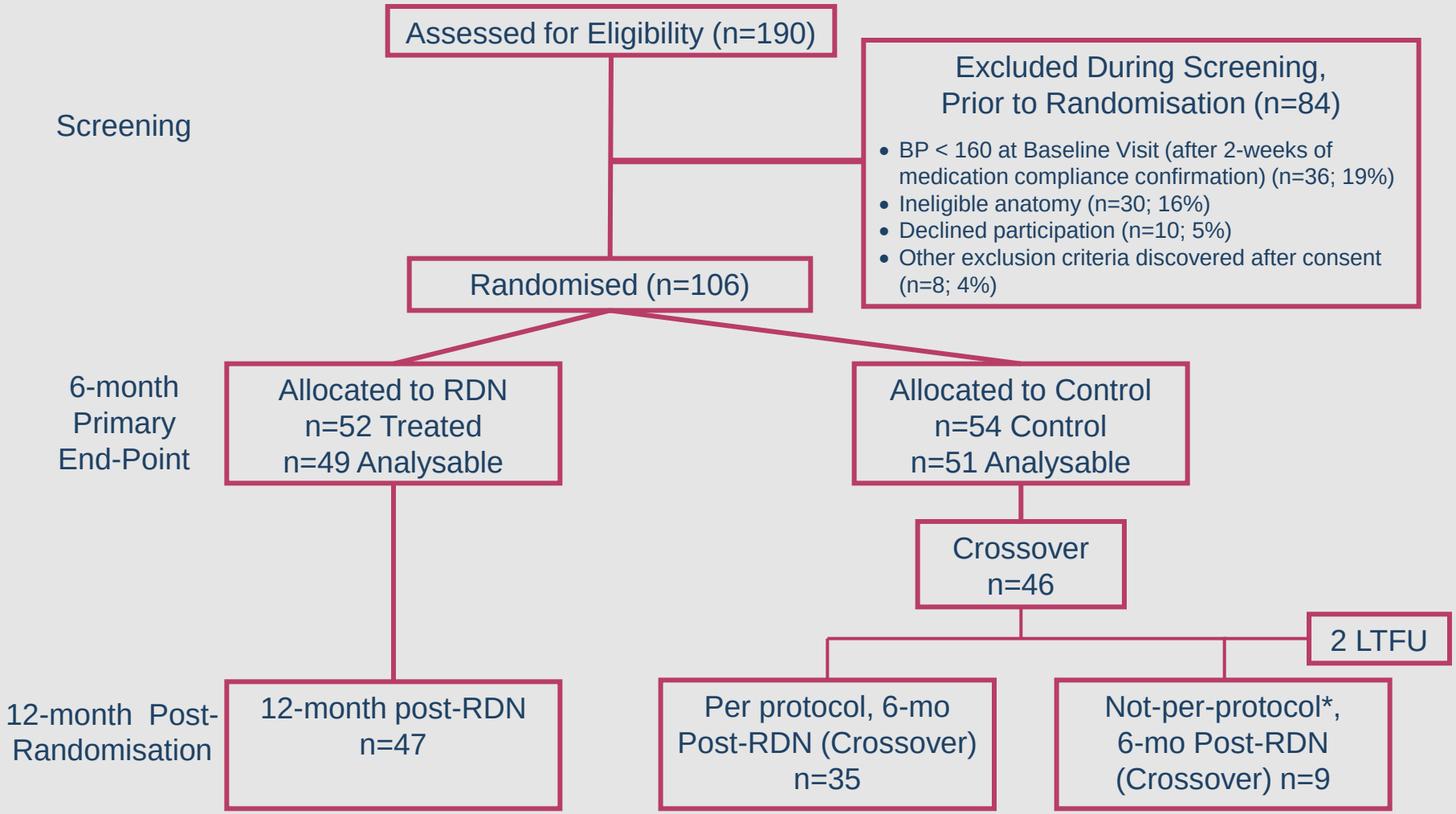
Symplicity HTN-2 Investigators*

Lancet. 2010;376:1903-1909.

- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

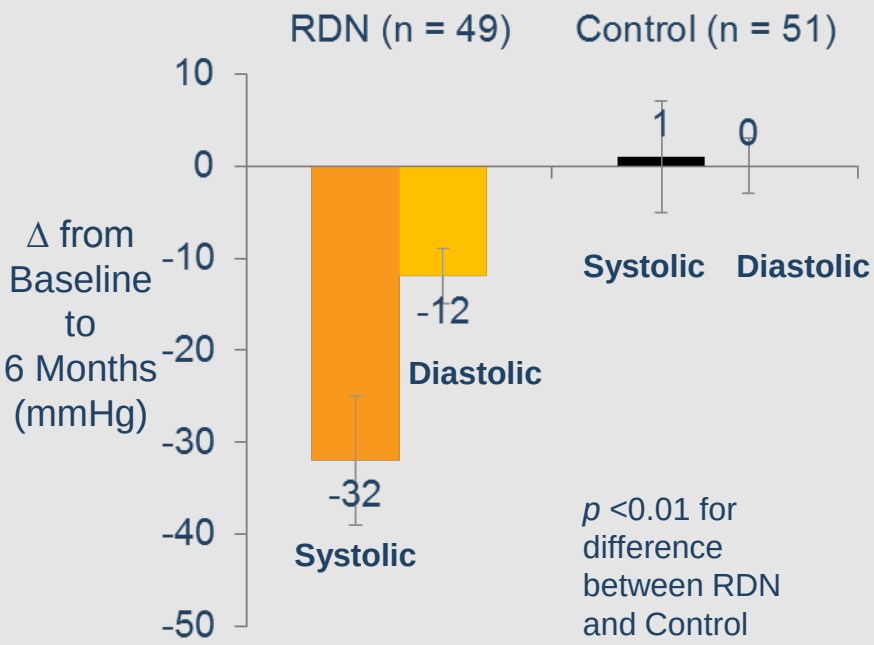
Symplicity HTN-2



* Crossed-over with ineligible BP (<160 mmHg)

Symplicity HTN-2: първични крайни цели и проследяване

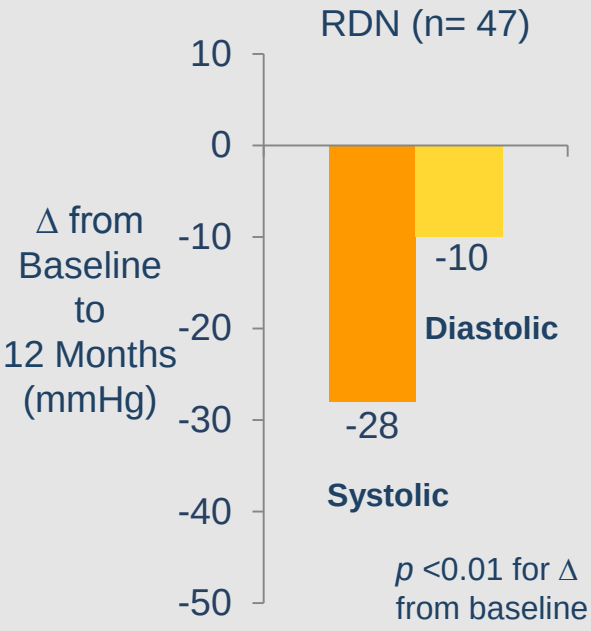
Primary Endpoint (6M post Randomisation)



Primary Endpoint:

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

Latest Follow-up (12M post Randomisation)



Latest Follow-up:

- Control crossover (n = 35): -24/-8 mmHg (Analysis on patients with SBP ≥ 160 mmHg at 6 M)

Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Esler, M.)

Symplicity HTN-2: Изводи

- Катетър-базираната терапия води до значимо понижение на АН.
- Степента на редукцията на АН може да предскаже повлияване на свързаната с АХ болестност и смъртност
- Техниката е без големи усложнения.
- Катетър-базираната бъбречна денервация е полезна за болни с резистентна на лечение АХ.

Symplicity HTN-2 Investigators. *Lancet.* 2010;376:1903-1909.

Renal Denervation in Patients with Uncontrolled Hypertension: Results of the SYMPLICITY HTN 3 Trial

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., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., M.Sc., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators

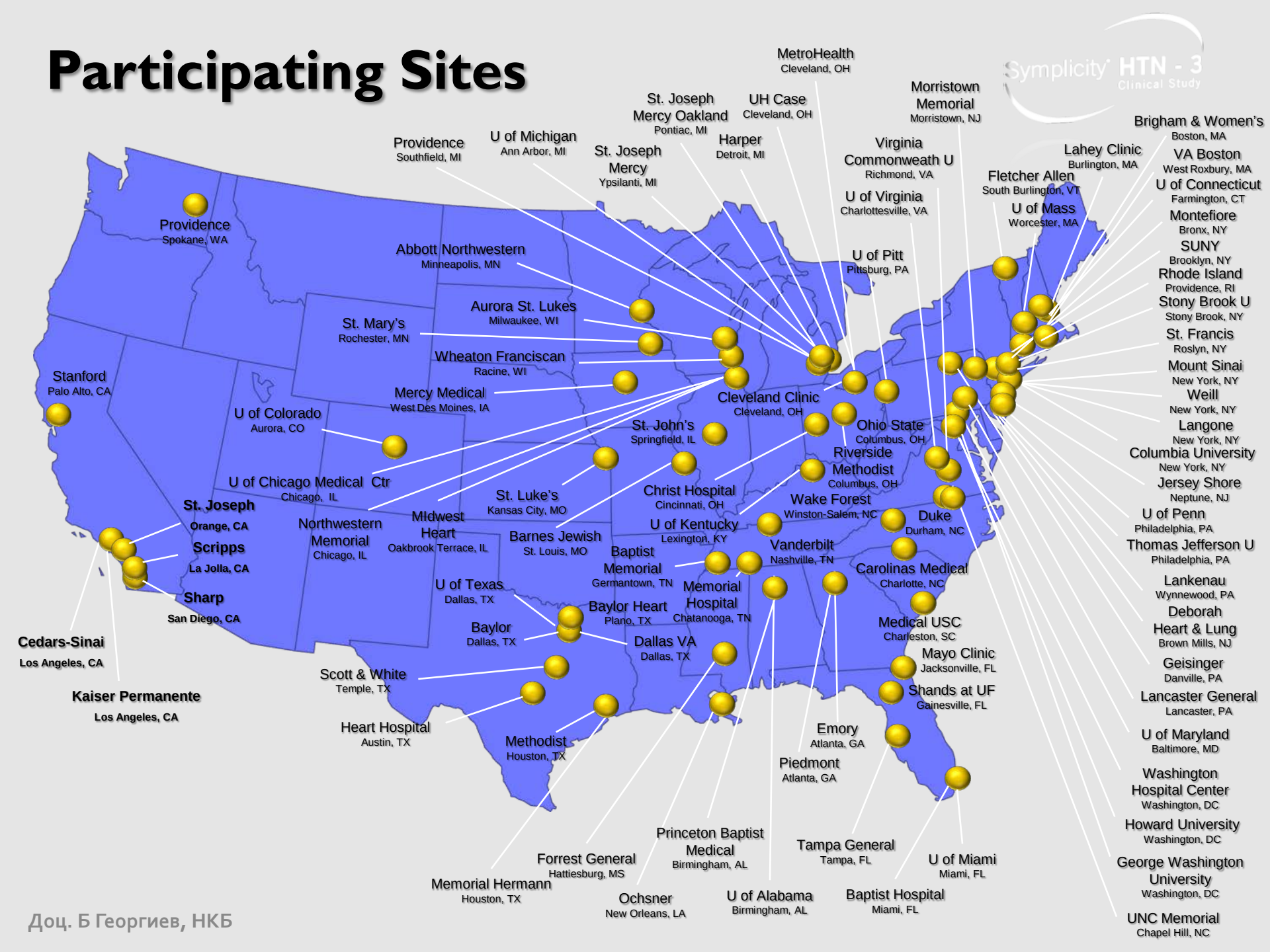
Trial Objectives

- SYMPLICITY HTN-3 е първото проспективно мултицентрово рандомизирано контролирано проучване, което оценява безопасност и ефикасност на бъбречната денервация при болни с тежка резистентна на лечение АХ.

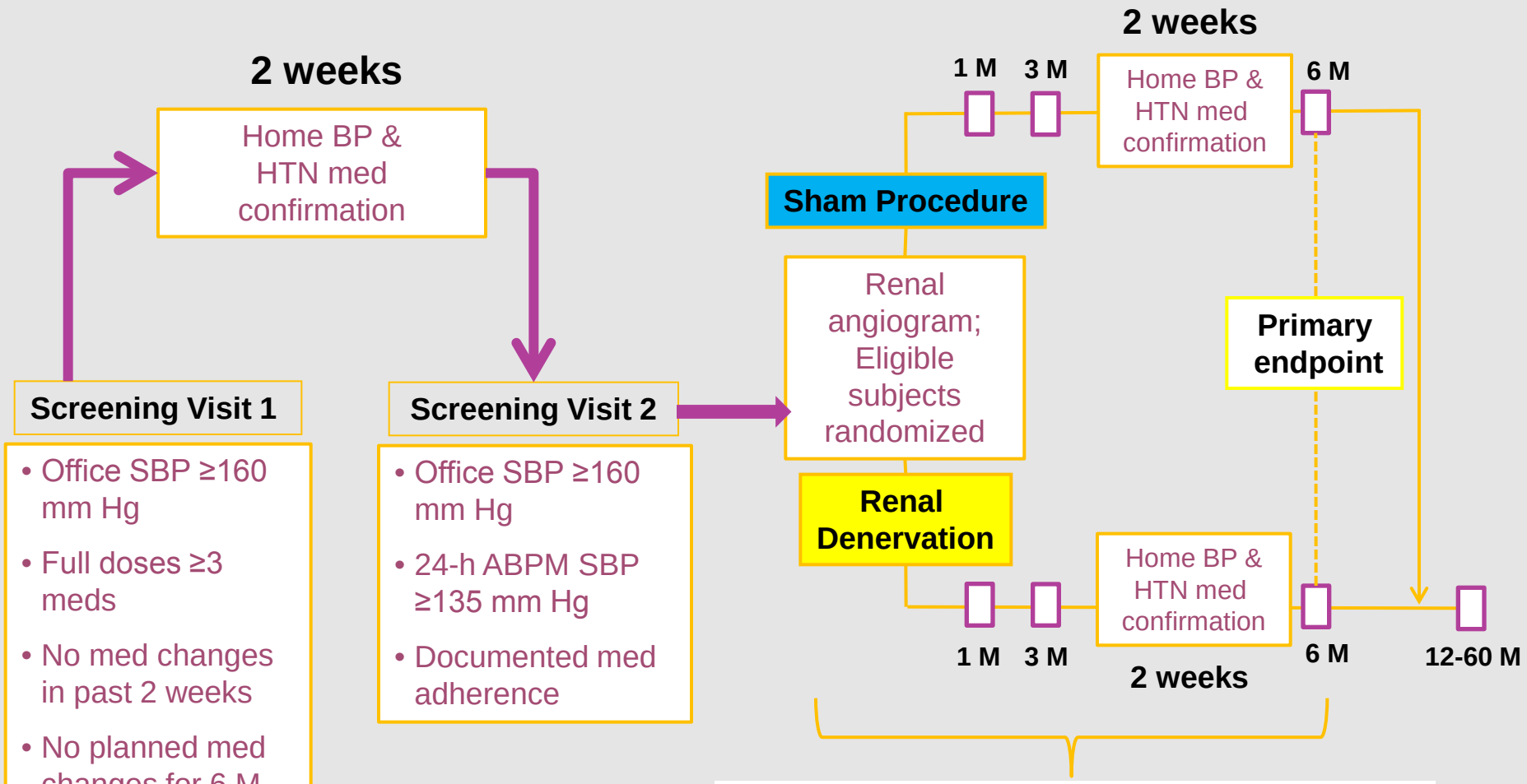
- Включени са 535 болни от 88 центъра в САЩ.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Participating Sites

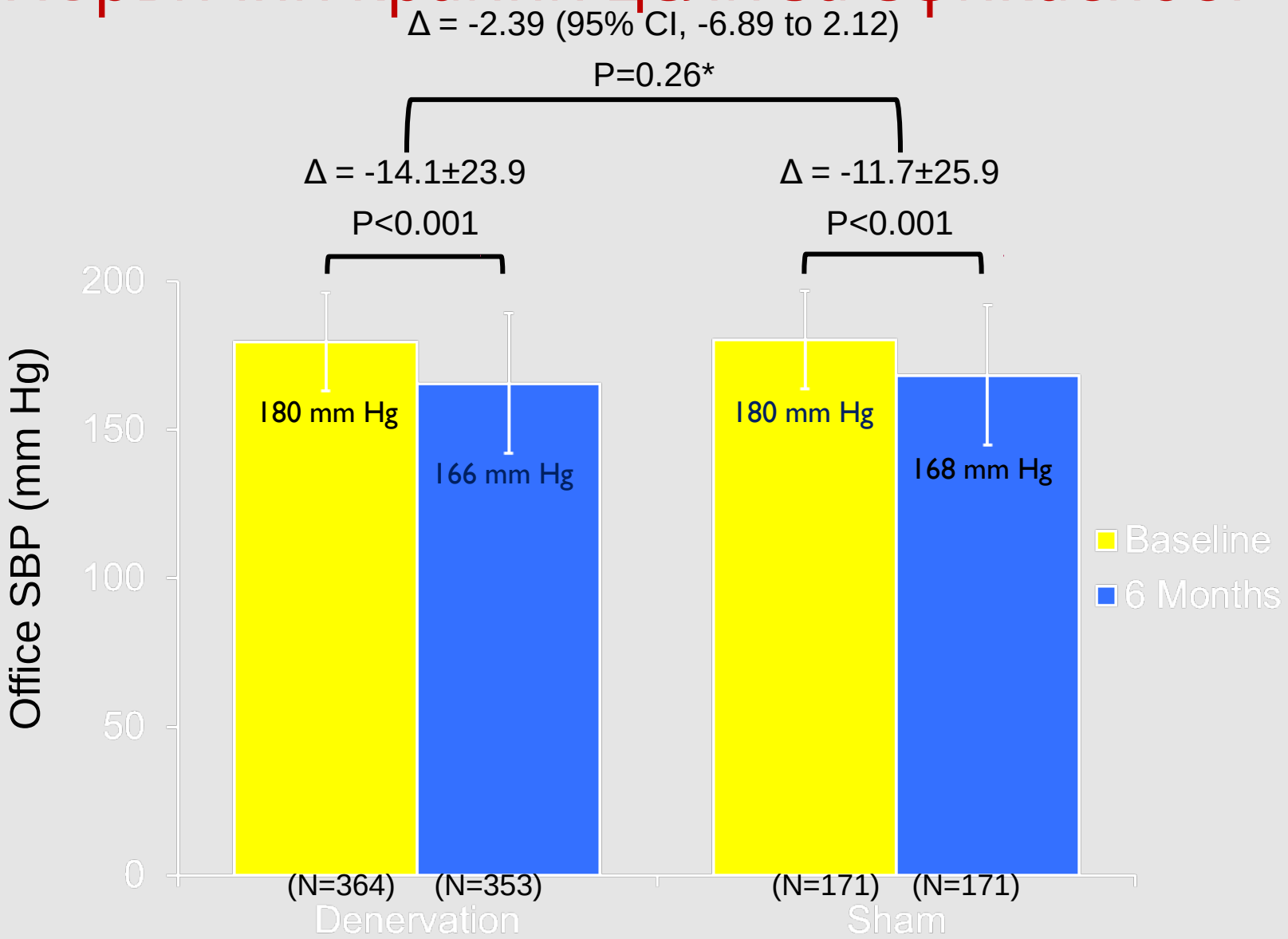


SYMPLICITY HTN-3 Дизайн



Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

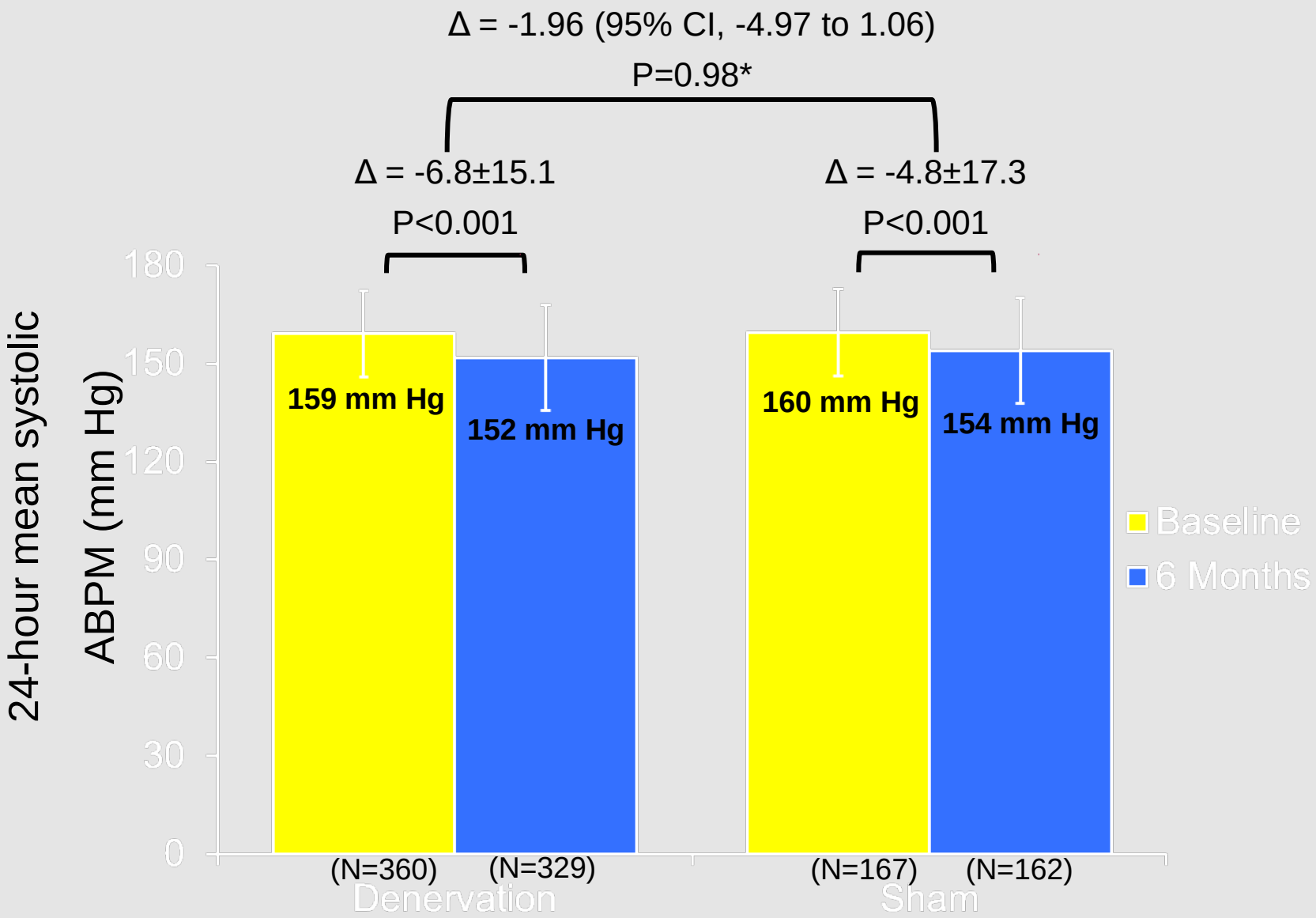
Първични крайни цели за ефикасност



P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

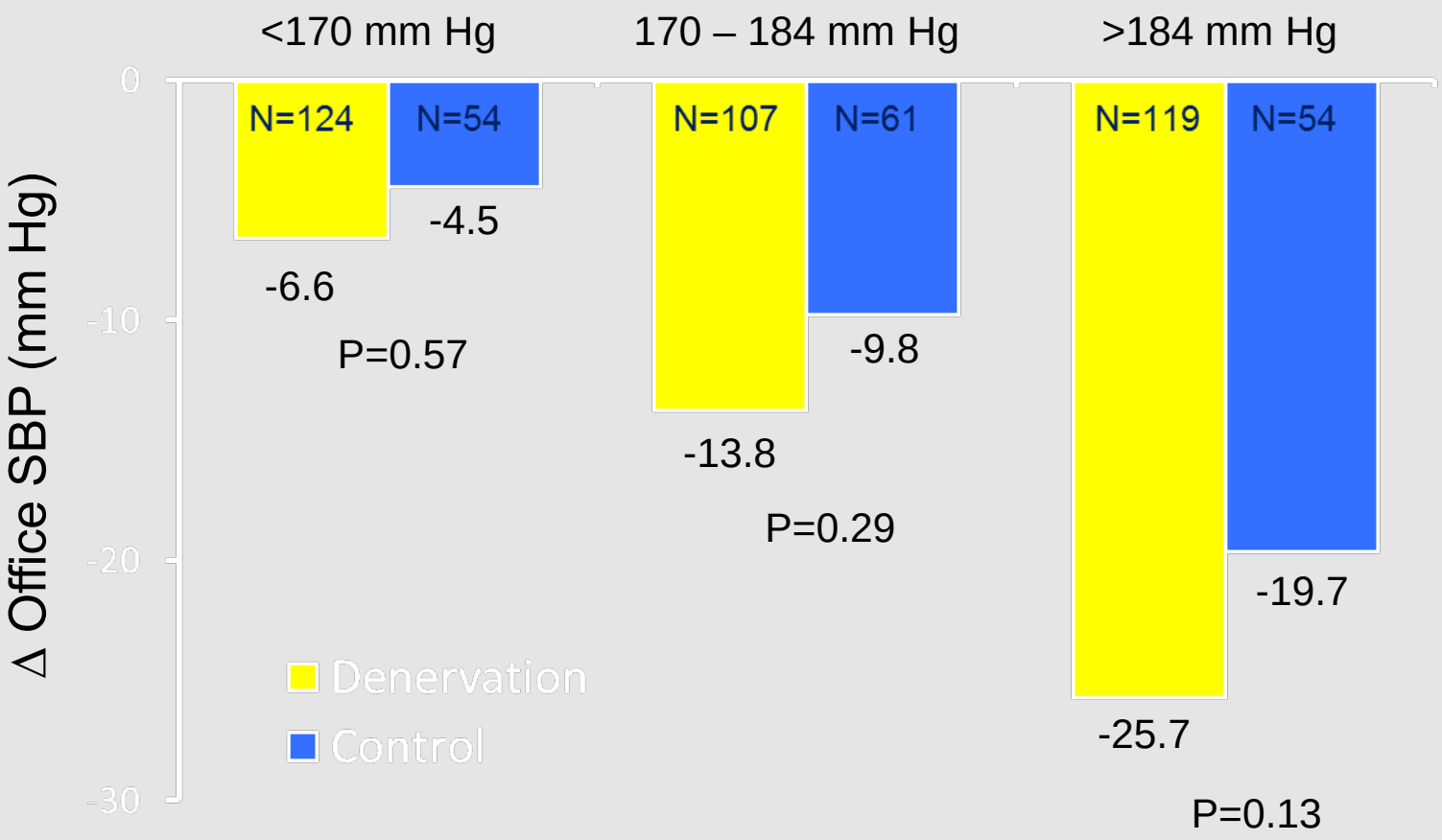
Вторични крайни цели



**P value for superiority with a 2 mm Hg margin; bars denote standard deviations*

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Промени в офисно АН според изходно САН



Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Изводи

- Перкутанната денервация е безопасна, но не е свързана със значимо намаление на офисното или амбулаторно АН.

- Тези резултати подчертават ролята на заслепените опити при оценка на нови устройства.

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

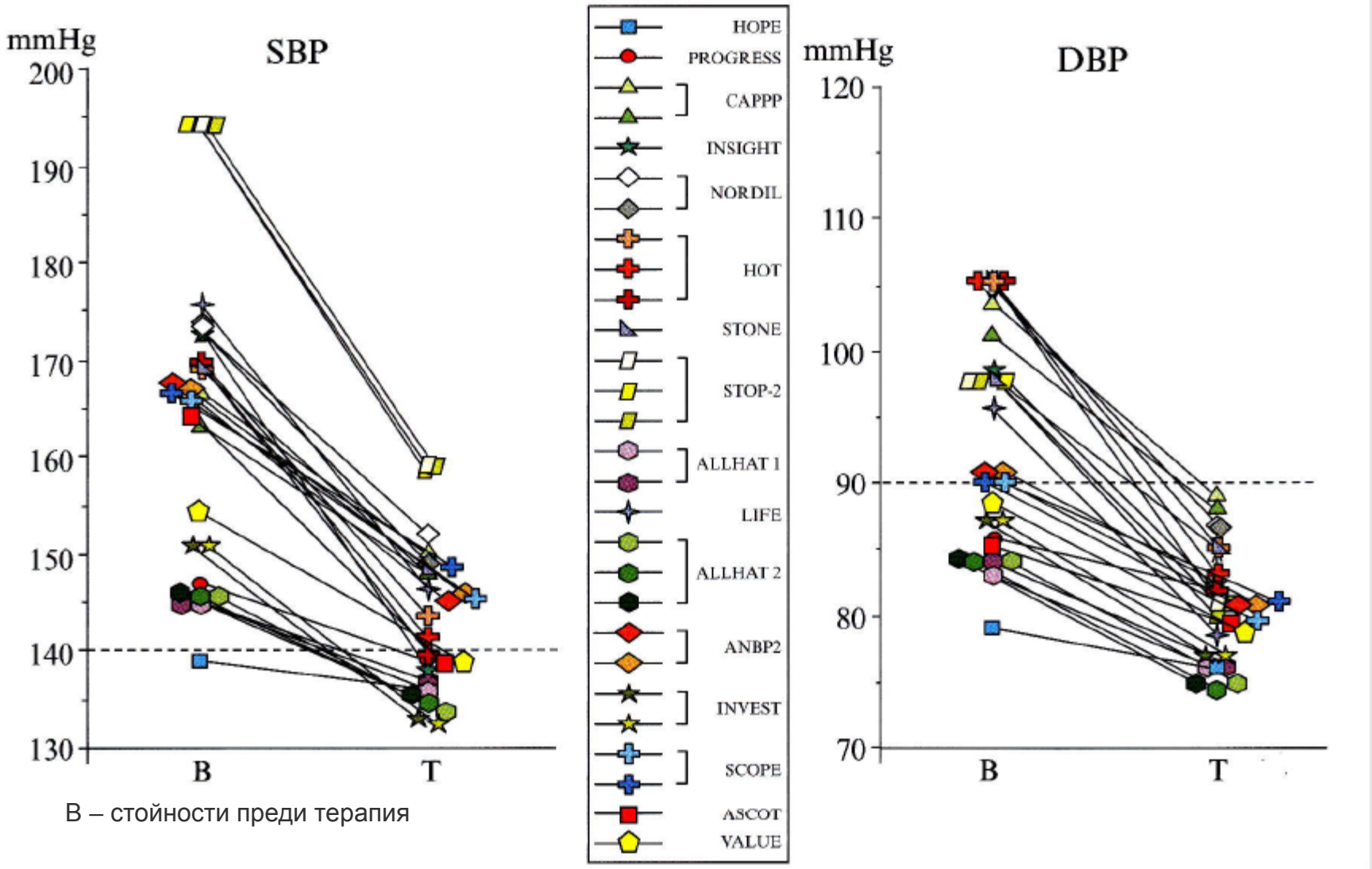
A Controlled Trial of Renal Denervation for Resistant Hypertension

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., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

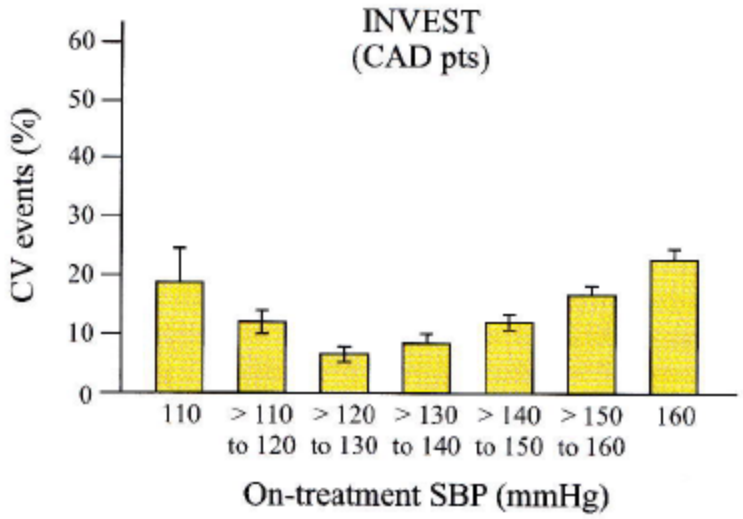
ПРОУЧВАНИЯ С ДАННИ ЗА J-КРИВА

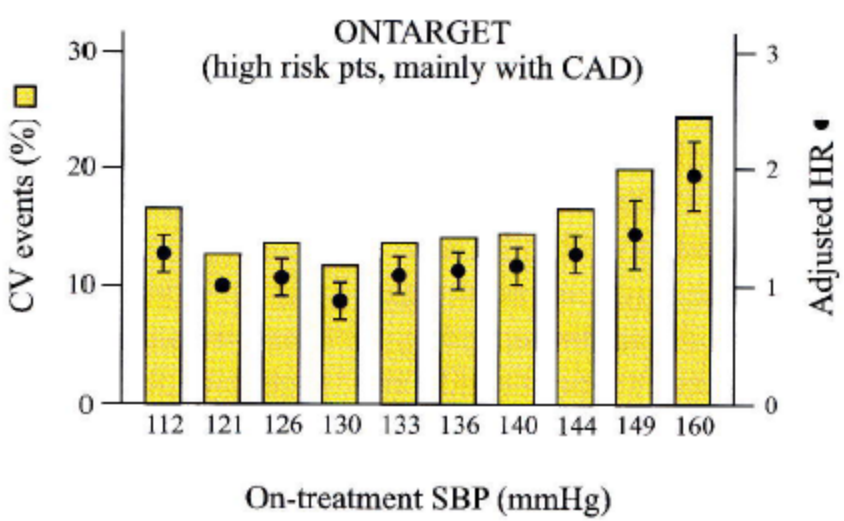
Намаление на САН и ДАН в резултат на терапия (Т)

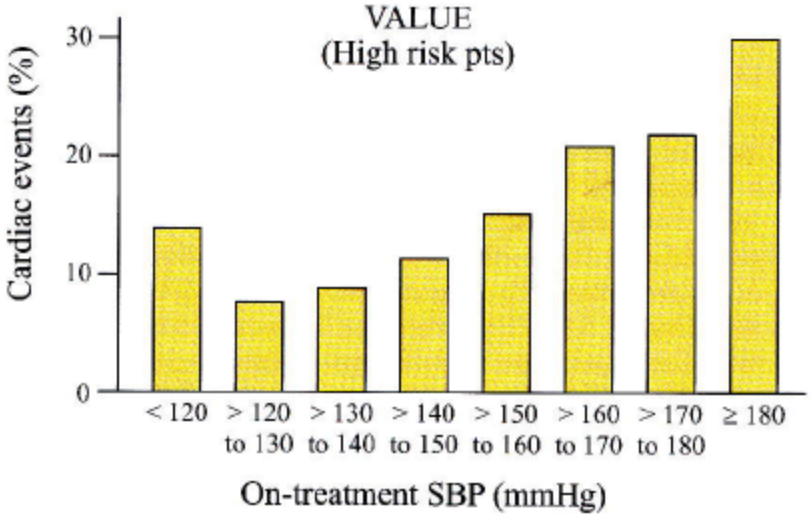


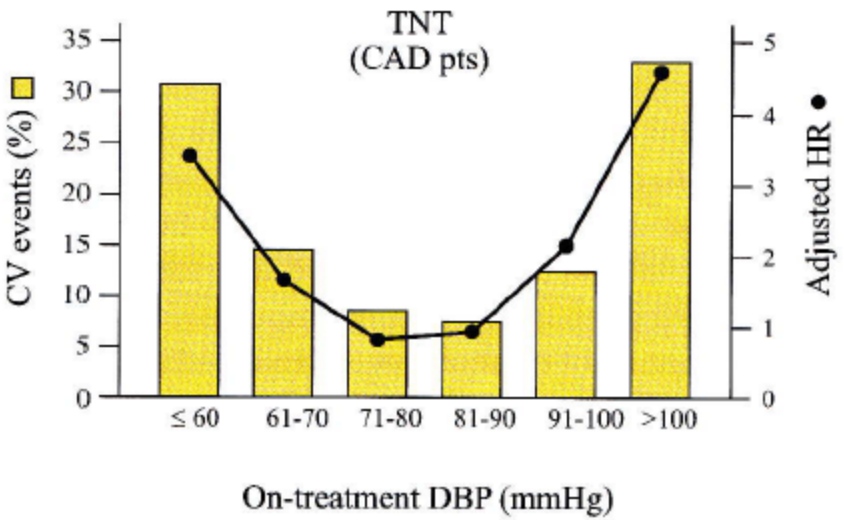
В – стойности преди терапия

Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. J Hypertens. 2002 Aug;20(8):1461-4

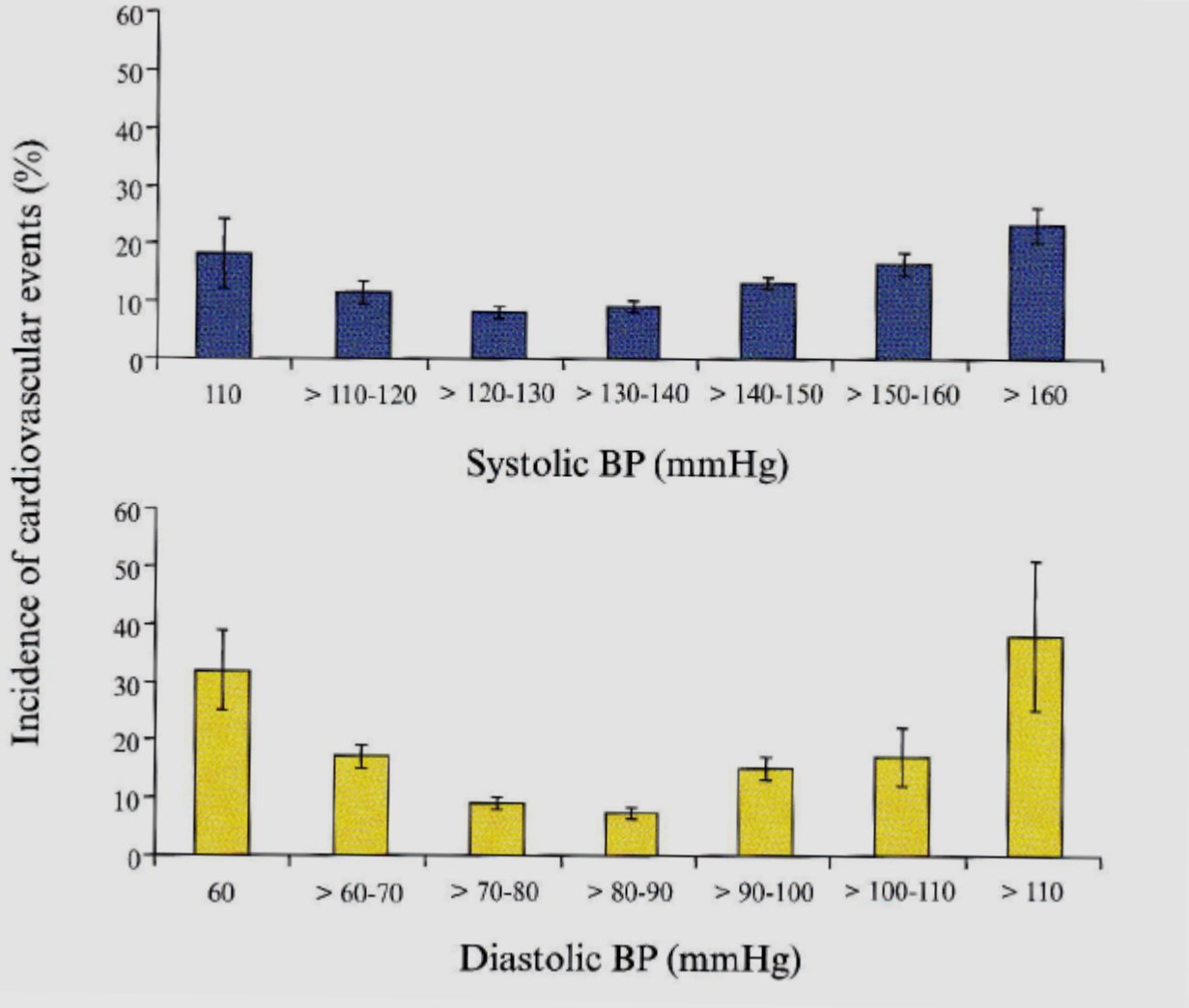

INVEST
(CAD pts)
CV events (%)
60
50
40
30
20
10
0
110
> 110 to 120
> 120 to 130
> 130 to 140
> 140 to 150
> 150 to 160
160
On-treatment SBP (mmHg)


ONTARGET
(high risk pts, mainly with CAD)
CV events (%)
Adjusted HR
30
20
10
0
3
2
1
0
112
121
126
130
133
136
140
144
149
160
On-treatment SBP (mmHg)


VALUE
(High risk pts)
Cardiac events (%)
30
20
10
0
< 120
> 120 to 130
> 130 to 140
> 140 to 150
> 150 to 160
> 160 to 170
> 170 to 180
≥ 180
On-treatment SBP (mmHg)


TNT
(CAD pts)
CV events (%)
Adjusted HR
35
30
25
20
15
10
5
0
5
4
3
2
1
0
≤ 60
61-70
71-80
81-90
91-100
>100
On-treatment DBP (mmHg)

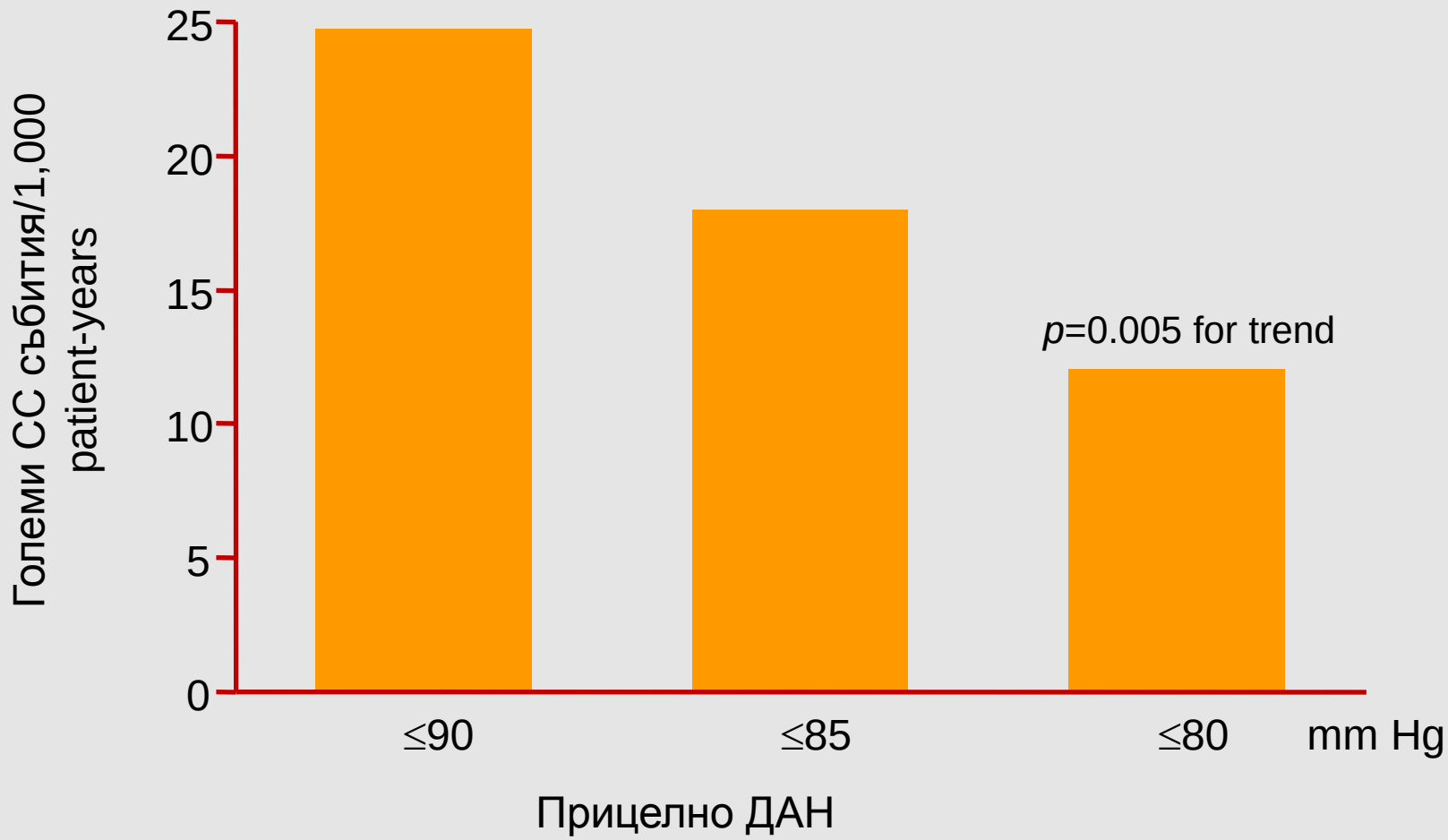
СС събития според САН и ДАН в проучване INVEST



Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous. Ann Intern Med. 2006;144:884–893

ПРОУЧВАНИЯ, НАЛОЖИЛИ КОРЕКЦИИ НА ПРИЦЕЛНИ СТОЙНОСТИ

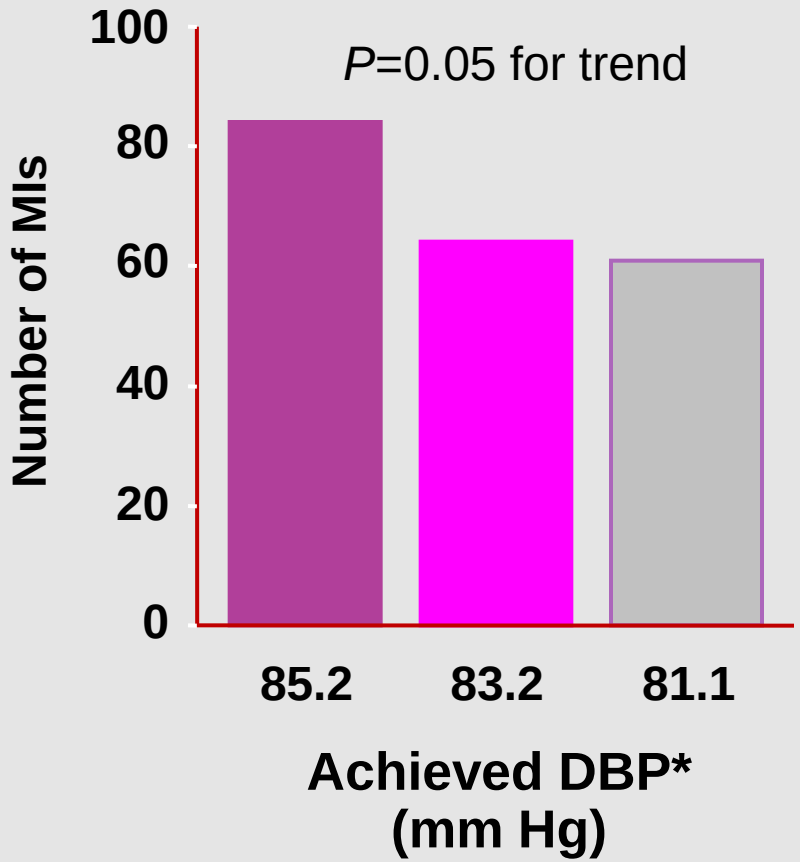
HOT Study: ползи при групата с диабет



Hansson L et al. *Lancet.* 1998;351:1755-1762.

HOT Study

Target DBP (mm Hg)	Achieved SBP (mm Hg)	Achieved DBP* (mm Hg)
≤90	143.7	85.2
≤85	141.4	83.2
≤80	138.7	81.1



*Mean BP from 6 months of follow-up to end of study.

Hansson L et al. *Lancet.* 1998;351:1755-1762.

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Diao D, Wright JM, Cundiff DK, Gueyffier F

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