JE MOŽNÁ PREVENCIA ARTÉRIOVEJ HYPERTENZIE ?

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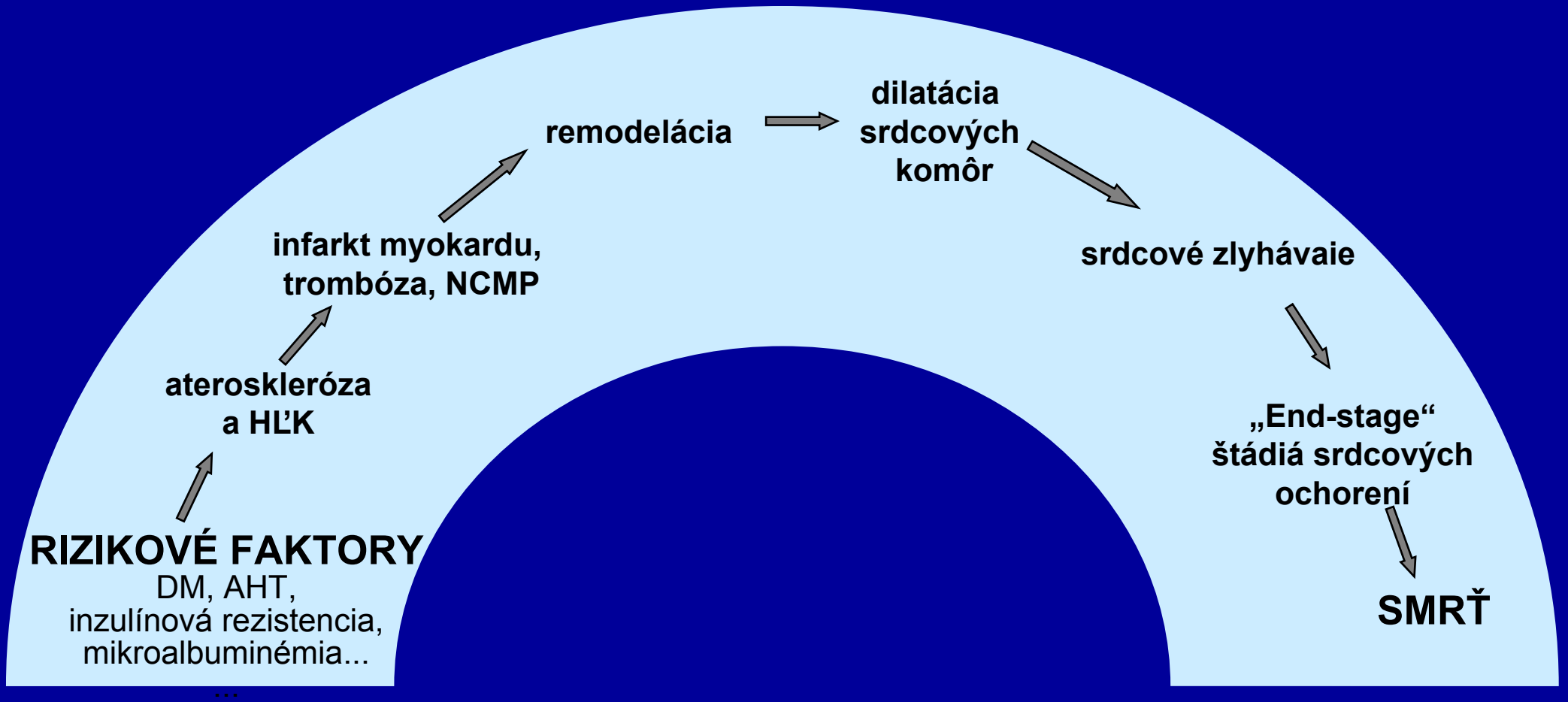
48. ODBORNÁ KONFERENCIA
SLOVENSKEJ SPOLOČNOSTI VŠEOBECNÉHO PRAKTICKÉHO LEKÁRSTVA (SSVPL SLS)
BOJNICE 27.- 28. OKTÓBRA 2006

Kardiovaskulárne kontinuum

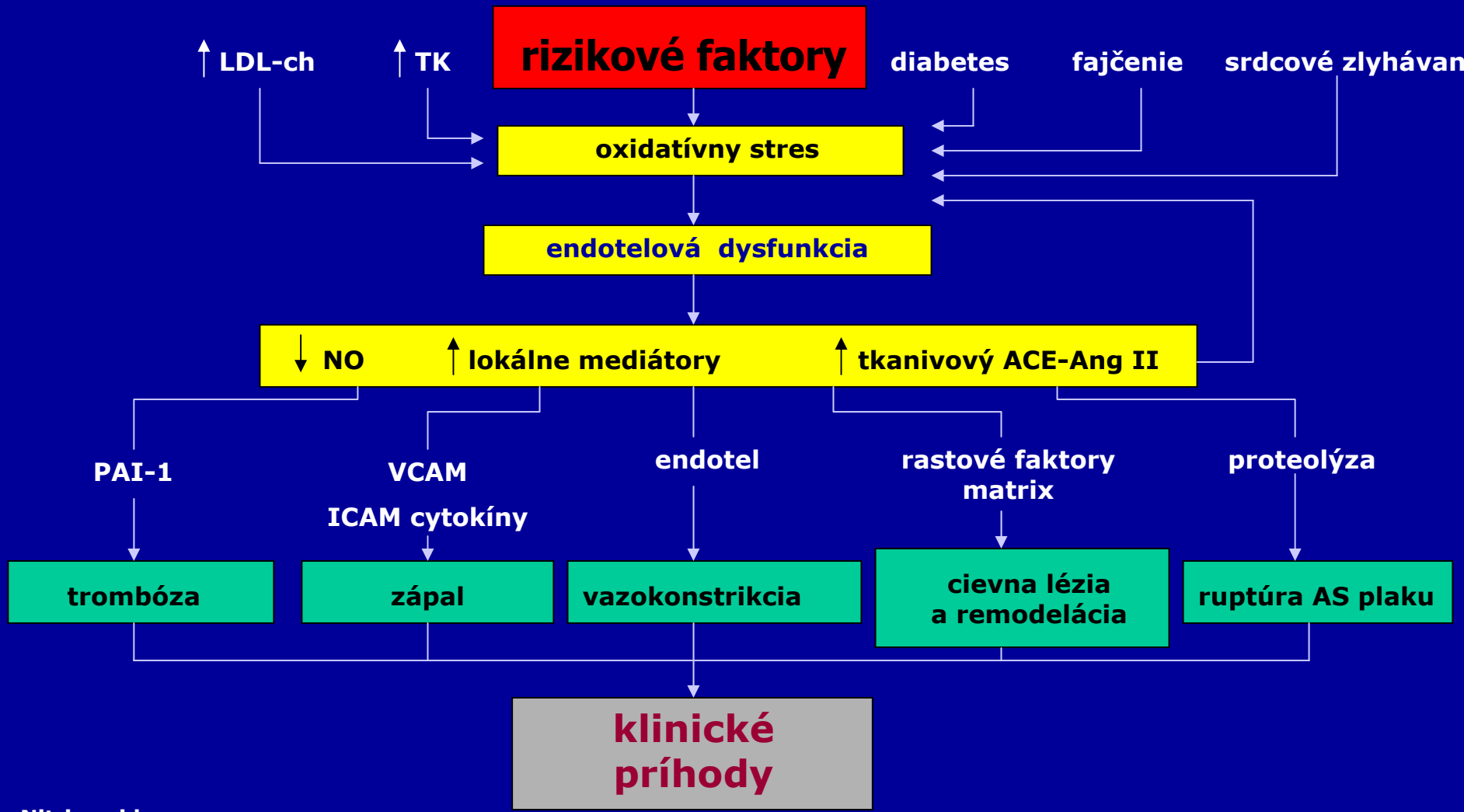
Upravené podľa : Dzau V, Braunwald E. *Am Heart J*. 1991;121:1244-1263.



VZŤAH HODNôT TK KU KARDIOVASKULÁRNEJ MORTALITE JE DOKÁZANÝ

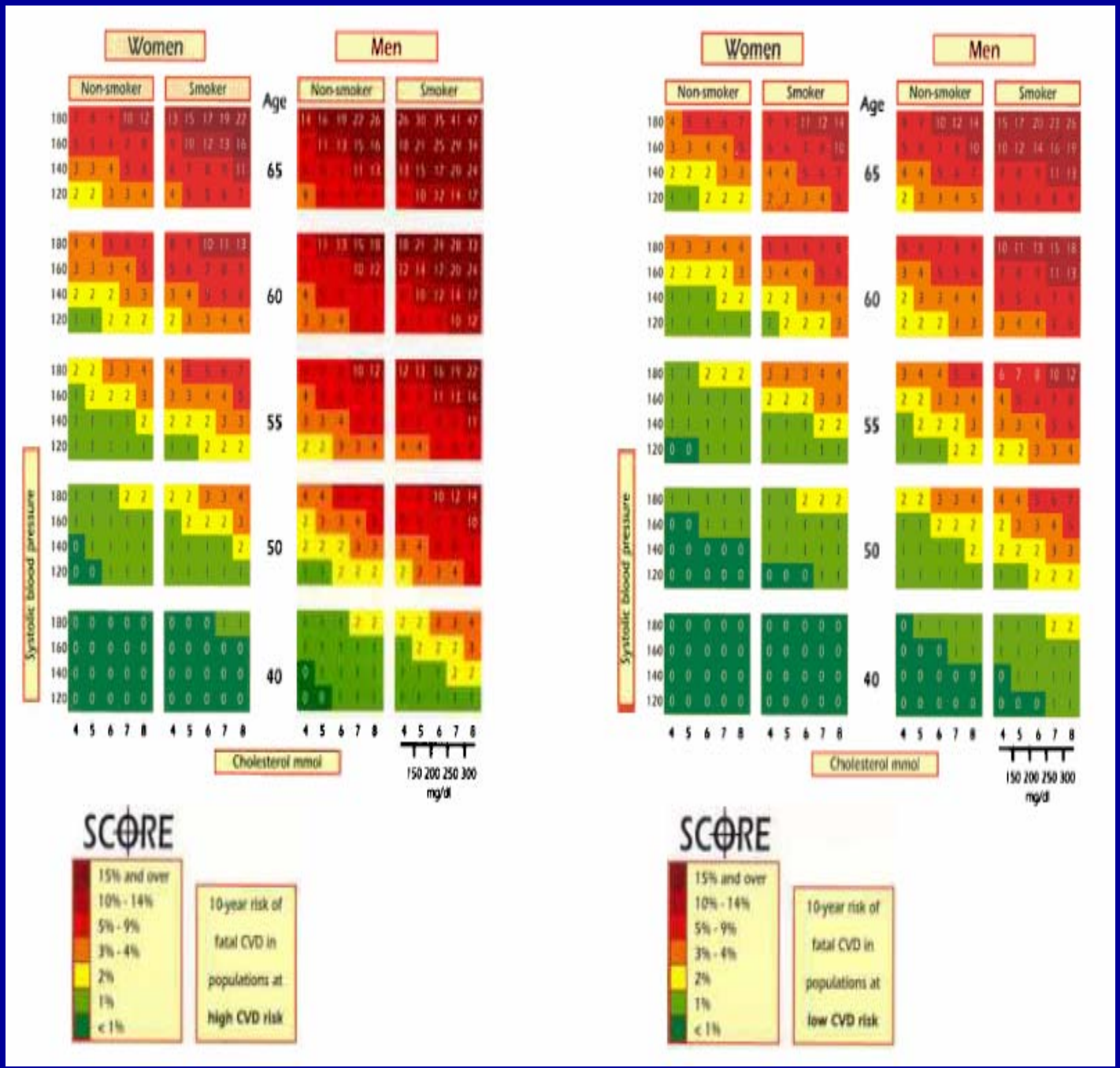
TK silne koreluje s rizikom KV mortality už v tzv. normálnom rozmedzí nadol až k hodnotám sTK 115 mmHg a dTK 75 mmHg

Progresia od KV rizikových faktorov k endotelovému poškodeniu a klinickým príhodám



NO = Nitric oxide

Gibbons GH, Dzau VJ. *N Engl J Med* 1994;**330**;1431-1438.



SCORE CARD

ESC SKS

American
Society of
Hypertension

PREHYPERTENZIA

PREHYPERTENZIA

Názov pre rozmedzie hodnôt TK medzi jasne normálnymi hodnotami a jasne hypertenznými hodnotami uvedený v Odporúčaniach JNC VII z roku 2003 ako *prehypertenzia* (predtým „hraničná hypertenzia“ alebo „vysoko normálne hodnoty TK“).

EBM: Existujú dôkazy o významne vyššej morbidite a mortalite z KV príčin oproti hodnotám nižším.

sTK: dTK:

130-139 mmHg / 85-89 mmHg

PREHYPERTENZIA

je preukázaná ako prekurzor 1. stupňa hypertenzie a prediktor KV morbidity a mortality

Ale máme racionálny dôvod v bežnej praxi

na včasnú diagnostiku ?

na včasnú farmakologickú liečbu ?

a tým predchádzať prvému stupňu hypertenzie ?

PREHYPERTENZIA

včasná diagnostika

1. merať TK pri každom lekárskom vyšetrení

málo využívané:

2. presorická reakcia na **psychickú záťaž**
   (mentálna aritmetika)
3. presorická reakcia na **fyzickú záťaž**
   a – klasické ergometrické protokoly
   b - odporúčané odlišné dávky záťaže
   (rozmedzie 50-100 W so stúpaním po 10 W alebo 25 W)
   (podľa Franza, 1998)

PREHYPERTENZIA
reakcia na fyzickú záťaž

normálne hodnoty:

Franz, 1998:
20-50 roční normotonici < 200 / < a = 100 mmHg
51-70 roční normotonici:
pri záťaži 70 W: do 200 / do 105 mmHg
pri záťaži 100 W: < 215 / < a = 105 mmHg

Weisser a spol. (2001)
limit n e z á v i s l ý na veku:

pri bicyklovej záťaži 100W horný limit pre **sTK** **180 mmHg**

PREHYPERTENZIA
reakcia na fyzickú záťaž

Presorická reakcia (podľa sTK) na telesnú záťaž u normotonikov
je prediktorom vyššieho rizika budúcej hypertenzie.

Abnormálna reakcia sTK na záťaž predvída pozdejší vznik orgánového postihnutia (u inak zdravých 40-59 ročných mužov s kazuálnym sTK viac ako 140 mmHg). (Kjedersen a spol., 1994)

Meranie ***dTK*** pri záťaži je málo presné
(nad- aj pod- hodnocovanie skutočnej hodnoty)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Feasibility of Treating Prehypertension with an Angiotensin-Receptor Blocker

Stevo Julius, M.D., Sc.D., Shawna D. Nesbitt, M.D., Brent M. Egan, M.D., Michael A. Weber, M.D., Eric L. Michelson, M.D., Niko Kaciroti, Ph.D., Henry R. Black, M.D., Richard H. Grimm, Jr., M.D., Ph.D., Franz H. Messerli, M.D., Suzanne Oparil, M.D., and M. Anthony Schork, Ph.D., for the Trial of Preventing Hypertension (TROPHY) Study Investigators*

N Engl J Med 2006;354.

N Engl J Med 2006;354.

TROPHY
Trial of Preventing Hypertension

Ciel':

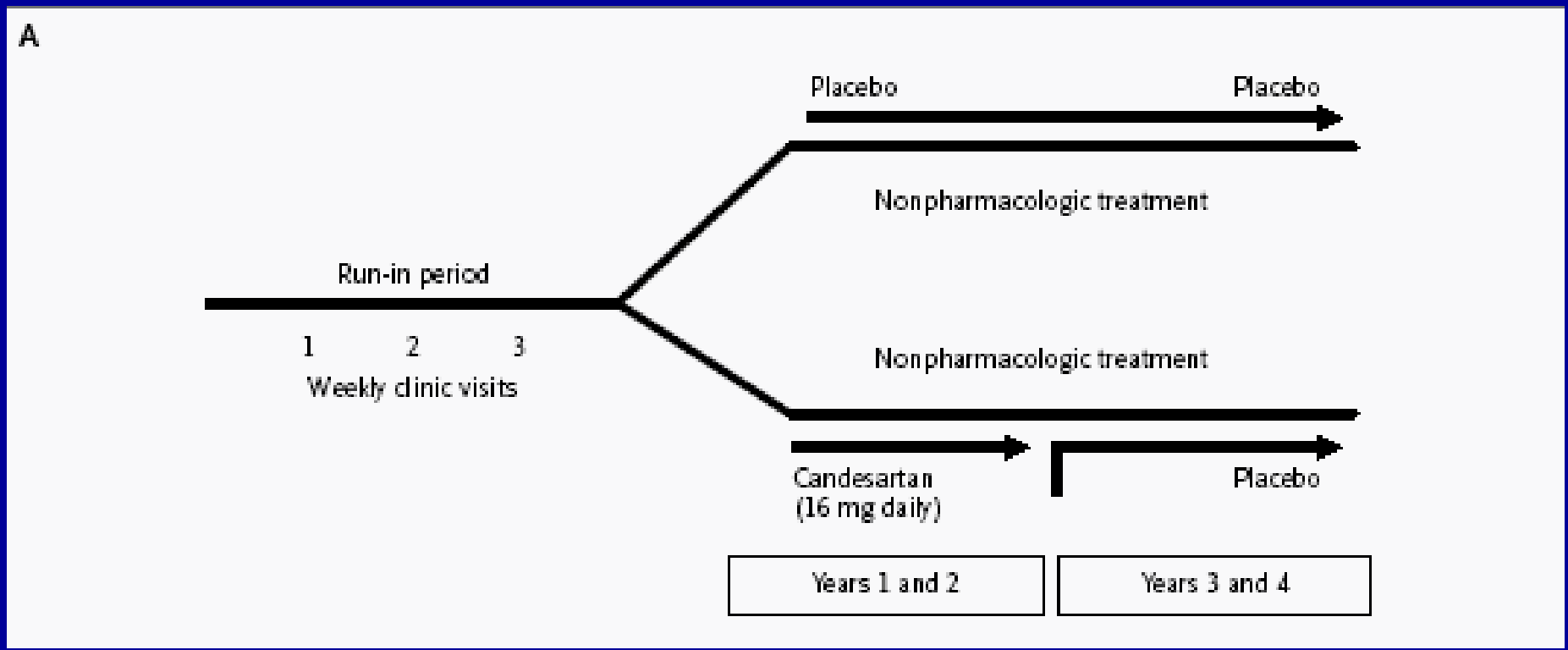
Či liečba prehypertenzie definovanej
akosTK 130 -139 mmHg a dTK 89 mmHg a menej
alebo
sTK 139 a menej a dTK 85-89 mmHg

zabráni alebo oddiali následnej incidencii artériovej hypertenzie

TROPHY

N Engl J Med 2006;354.

802 probandov priemerný vek 48,5 r., 59,65% M
randomizácia 409 candesartan 16 mg denne
400 placebo
trvanie: 4 roky



N Engl J Med 2006;354.

TROPHY

po 2 rokoch:

AHT sa vyvinula u 154 jedincov v sk. placebo
u 53 jedincov v sk. candesartan
redukcia RR 66,3%, p< 0,001

po 4 rokoch:

AHT sa vyvinula u 240 jedincov v sk. placebo
u 208 jedincov v sk. candesartan
redukcia RR 15,6%, p< 0,007

významné nežiaduce príhody:

u 5,9% v sk. placebo
u 3,5 % v sk. candesartan

N Engl J Med 2006;354.

Table 2. Incident Hypertension

	Candesartan Group (N=391)	Placebo Group (N=381)	P Value	Relative Risk (95% CI)
New-onset hypertension				
No. of participants in whom hypertension developed	208	240		
Hypertension at year 2 visit — %	13.6	40.4	<0.001†	0.34 (0.25–0.44)
Hypertension at year 4 visit — %	53.2	63.0	0.007†	0.84 (0.75–0.95)
Hypertension during study period			<0.001‡	0.58 (0.49–0.70)
Clinical criteria for end-point determination				
BP at three clinic visits, ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	142 (36)	168 (44)	0.03†	0.82 (0.69–0.98)
BP at any clinic visit ≥160 mm Hg systolic, ≥100 mm Hg diastolic, or both — no. (%)	15 (3.8)	19 (5.0)	0.49†	0.77 (0.40–1.49)
BP requiring pharmacologic treatment — no. (%)	45 (12)	48 (13)	0.66†	0.91 (0.62–1.34)
BP at month 48 clinic visit ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	6 (1.5)	5 (1.3)	>0.99†	1.17 (0.36–3.80)

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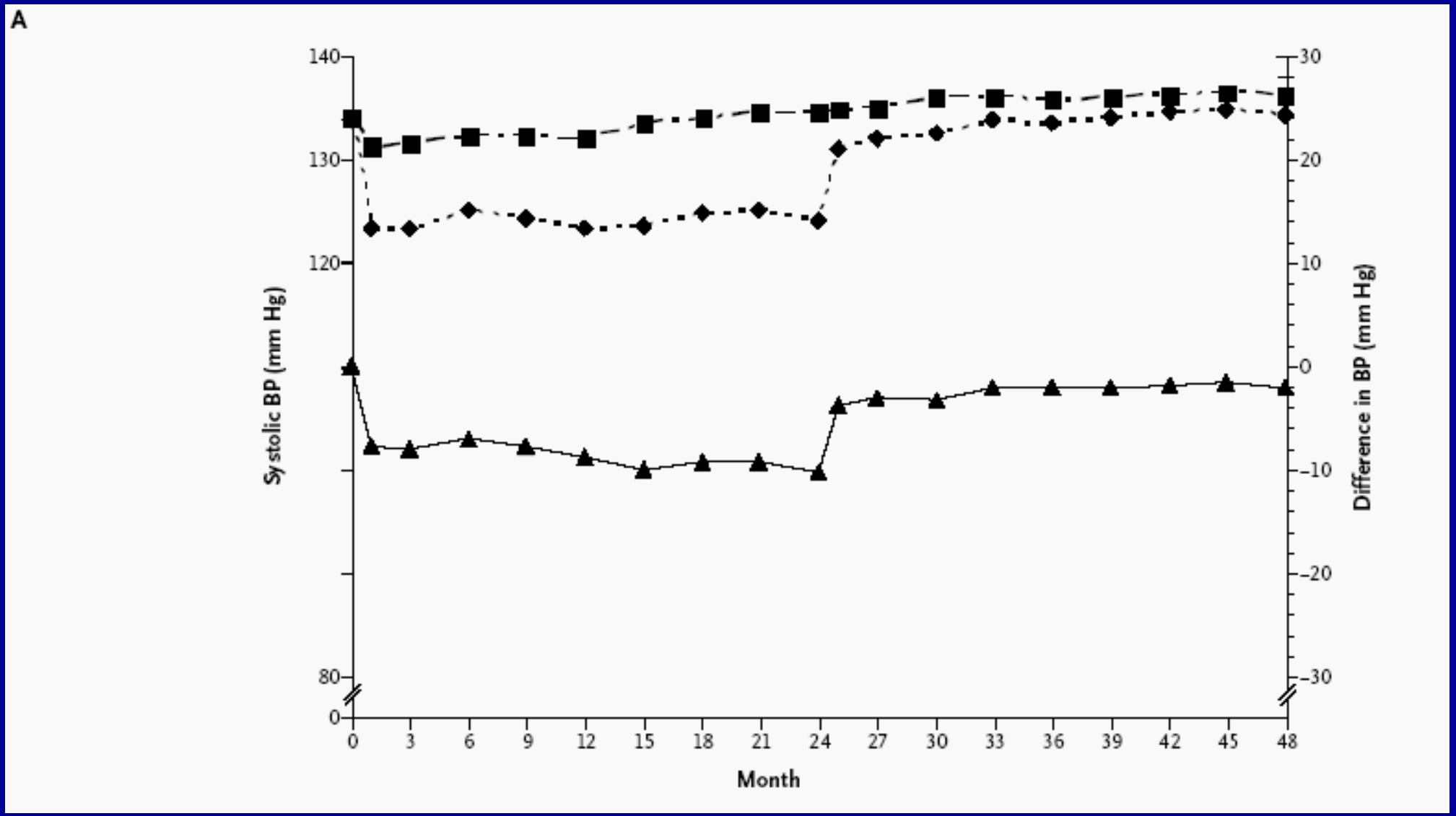

Figure 4. Blood Pressure in the Two Study Groups.

Squares represent the placebo group, and diamonds the candesartan group; triangles represent the difference between the two groups. Below the graphs are the cumulative percentages of participants in the two groups receiving antihypertension treatment at each clinic visit. Blood-pressure readings were obtained in the clinic with the use of an automated device. BP denotes blood pressure.

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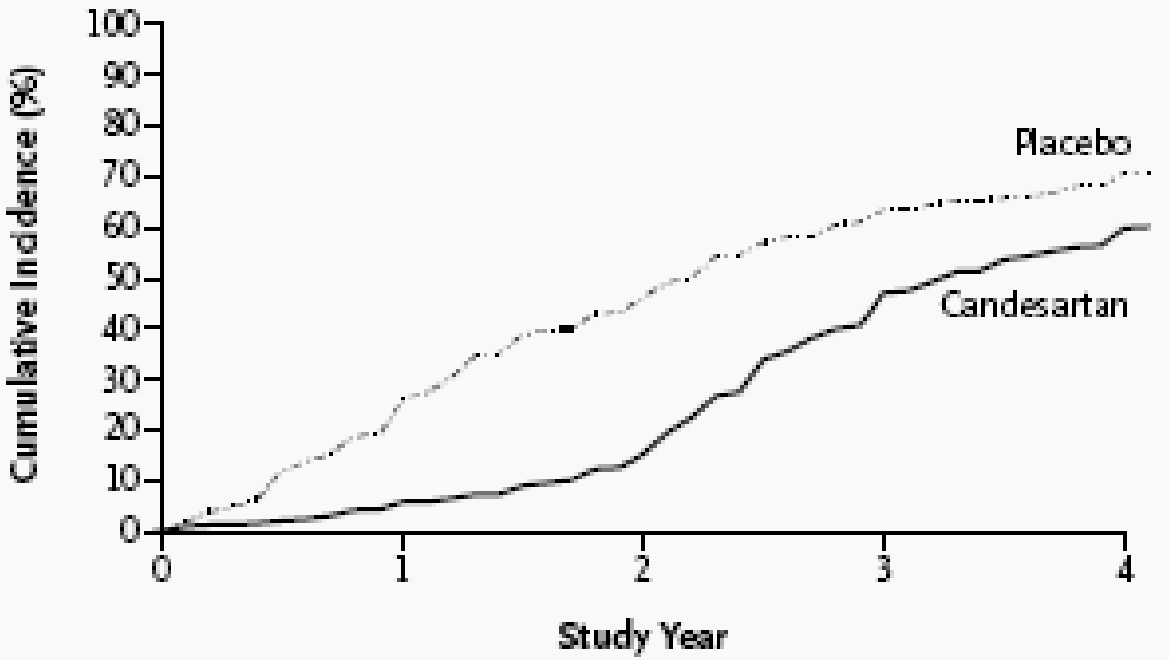

No. of Patients without Hypertension					
Candesartan group	391	356	309	191	127
Placebo group	381	269	184	118	85

Figure 2. Kaplan–Meier Analysis of New-Onset Clinical Hypertension.

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	Candesartan Group (N=396)	Placebo Group (N=391)
	no. (%)	
Incidence of adverse events		
Participants with any serious adverse event	14 (3.5)	23 (5.9)
Organ system		
Cardiovascular	1 (0.3)	6 (1.5)
Gastrointestinal	4 (1.0)	2 (0.5)
Cancer	4 (1.0)	3 (0.8)
Endocrine disorders	2 (0.5)	0
Infections	2 (0.5)	4 (1.0)
Peripheral-nerve disorders	2 (0.5)	0
Abnormal liver-function tests	1 (0.3)	1 (0.3)
Musculoskeletal and connective-tissue disorders	1 (0.3)	3 (0.8)
Psychiatric disorders	1 (0.3)	0
Vascular disorders	1 (0.3)	0

PREVENCIA AHT ?

áno – významný rizikový faktor AS a KV komplikácií

Hraničné hodnoty TK (prehypertenziu) vieme diagnostikovať.

Medikamentózna terapia pri prehypertenzných hodnotách: máme *prvé výsledky EBM* o tom, že liečba predchádza vzniku / spomaľuje incidenciu AHT 1.št.
– Nepremietlo sa ešte do odporúčaní !

ĎAKUJEM
ZA POZORNOSŤ

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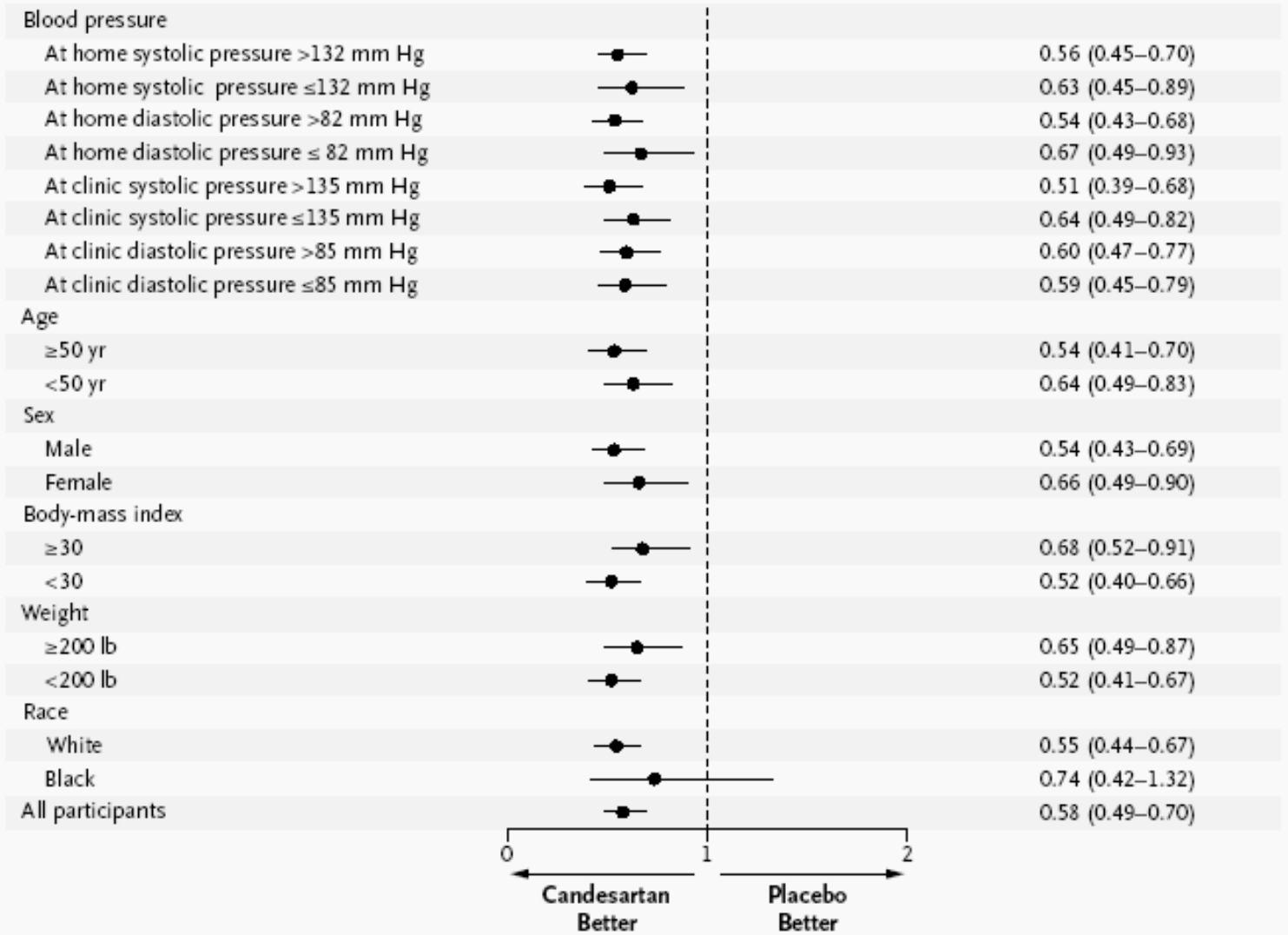

Figure 3. Hazard Ratios for New-Onset Hypertension in Various Subgroups.

Hazard ratios of time to event throughout the four years of the study were calculated by Cox proportional-hazards regression analysis. BMI denotes body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and CI confidence interval. To convert pounds to kilograms, multiply by 0.45. Race was self-reported.

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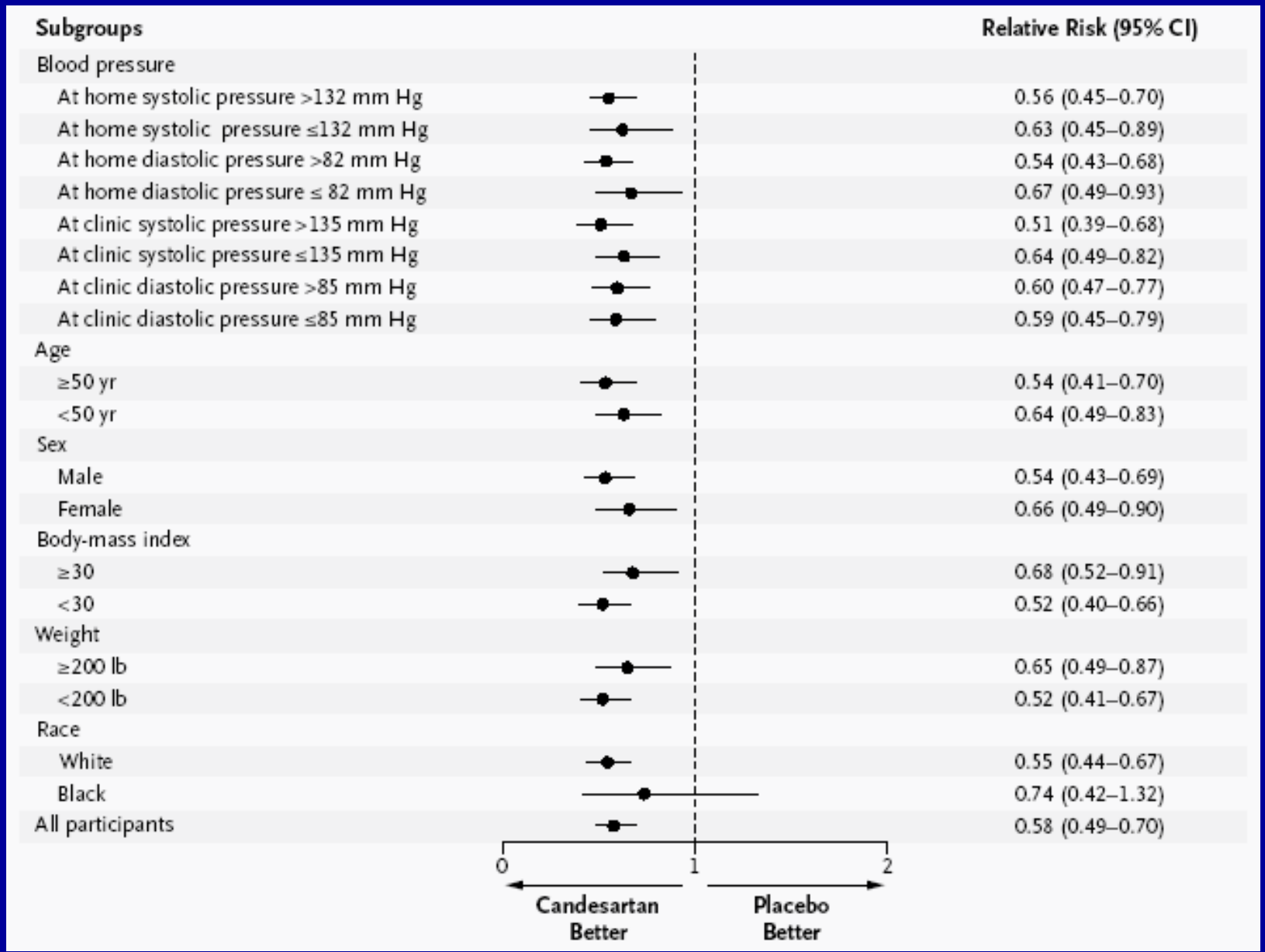

BACKGROUND

Prehypertension is considered a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk. We investigated whether pharmacologic treatment of prehypertension prevents or postpones stage 1 hypertension.

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METHODS

Participants with repeated measurements of systolic pressure of 130 to 139 mm Hg and diastolic pressure of 89 mm Hg or lower, or systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg, were randomly assigned to receive two years of candesartan (Atacand, AstraZeneca) or placebo, followed by two years of placebo for all. When a participant reached the study end point of stage 1 hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce blood pressure throughout the trial.

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RESULTS

A total of 809 participants were randomized (409 were assigned to candesartan, and 400 to placebo). Data on 772 participants (391 in the candesartan group and 381 in the placebo group; mean age, 48.5 years; 59.6 percent men) were available for analysis. During the first two years, hypertension developed in 154 participants in the placebo group and 53 of those in the candesartan group (relative risk reduction, 66.3 percent; $P<0.001$). After four years, hypertension had developed in 240 participants in the placebo group and 208 of those in the candesartan group (relative risk reduction, 15.6 percent; $P<0.007$). Serious adverse events occurred in 3.5 percent of the participants assigned to candesartan and 5.9 percent of those receiving placebo.

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CONCLUSIONS

Over a period of four years, stage 1 hypertension developed in nearly two thirds of patients with untreated prehypertension (the placebo group). Treatment of prehypertension with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period. Thus, treatment of prehypertension appears to be feasible. (ClinicalTrials.gov number, NCT00227318.)

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THE NAME OF THE RANGE OF BLOOD pressures between what is clearly normal and what is definitely hypertensive changed from "transient hypertension" in the 1940s[1] to "borderline hypertension" in the 1970s,[2] "high-normal blood pressure" in the 1990s,[3] and most recently, "prehypertension" in 2003.[4] Regardless of terminology, this condition is a precursor of hypertension[1,2,5,6] and is associated with excess morbidity and deaths from cardiovascular causes.[1,2,7-10] Furthermore, an association of prehypertension with other cardiovascular risk factors has been established.[11-14]

The Trial of Preventing Hypertension (TROPHY)[15] was an investigator-initiated study to examine whether early treatment of prehypertension, defined for this study as systolic pressure of 130 to 139 mm Hg and diastolic pressure of 89 mm Hg or lower and systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg, might prevent or delay the development of subsequent incident hypertension. We justified our study of pharmacologic intervention with the use of an angiotensin-receptor blocker in prehypertension on three grounds. First, in prehypertension, blood pressure remains a strong predictor of cardiovascular events after a statistical adjustment for other risk factors,[10,14,16] suggesting that lowering blood pressure might be beneficial. Hypertension is a self-accelerating condition. The transition from prehypertension to established hypertension reflects, in part, ongoing changes such as arteriolar hypertrophy[17] and endothelial dysfunction.[18] Increased vasoconstriction and diminished vasodilatation, consistent with these structural and functional findings, have been described in prehypertension.[19]

Second, growth factors mediated by stimulation of the sympathetic nervous system[20] and excess activity of the renin–angiotensin system[21] tend to promote vascular hypertrophy by direct as well as hemodynamic effects. Elevations in plasma norepinephrine and plasma renin concentrations[22,23] have been described in prehypertension. In humans, antihypertension treatment with angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers, but not with beta-blockers, has been reported to cause regression of arteriolar hypertrophy.[24,25] In studies in rats, brief treatment with ACE inhibitors during the early life of rats with spontaneous hypertension attenuates the development of hypertension.[26,27]

Third, present guidelines recommend that prehypertension be managed with changes in the participant's lifestyle.[3,4] Weight loss,[28] salt restriction,[29] exercise,[30,31] and dietary modifications[32] have been shown to reduce blood pressure in clinics specializing in lifestyle modification. Despite intensive community efforts to promote healthful lifestyles, however, the prevalence of prehypertension[33] in the United States is increasing. In the absence of evidence of the long-term efficacy of lifestyle approaches to preventing hypertension, our study assessed the safety, tolerability, and efficacy of two years of treatment in participants with prehypertension.

METHODS

OBJECTIVE

The primary objective of the study was to determine whether in patients with prehypertension two years of treatment with candesartan (at a dose of 16 mg daily) reduces the incidence of hypertension for up to two years after the discontinuation of active treatment. A secondary objective was to evaluate the incidence of hypertension during two years of treatment with candesartan or placebo. These objectives were analyzed first according to the cumulative incidence of events at two and four years (unadjusted). They were then analyzed according to the time-to-event distribution during two and four years (adjusted).

DESIGN

This four-year, multicenter, randomized study involved untreated participants 30 to 65 years of age with blood pressure on study entry in the high-normal range, according to the classification developed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).[3] The design of the study is shown in Figure 1. Blood pressure was measured with the use of an automated reading and recording device (HEM-705CP, Omron Healthcare) or with a standard measuring tool (usual device) while participants were seated after five minutes of rest. Only automated readings of blood pressure were taken into consideration for enrollment and follow-up. The run-in period consisted of three consecutive weekly clinic visits during each of which blood-pressure readings were obtained. Participants were eligible for the trial if they were not being treated for hypertension, if at the first clinic visit the blood pressure was lower than 160/100 mm Hg, and if the average of the three blood-pressure readings at the three visits was a systolic pressure of 130 to 139 mm Hg and a diastolic pressure of 85 mm Hg or lower or a systolic pressure of 130 mm Hg or lower and a diastolic pressure of 85 to 89 mm Hg.

Participants who met these criteria underwent randomization to double-blind treatment with candesartan (at a dose of 16 mg daily) or matching placebo. Return visits were scheduled at month 1 and month 3 and every three months thereafter until the visit at month 24. In year 3 of the study, clinic visits were at months 25 and 27 and every third month thereafter to month 48. Patients also measured their blood pressure at home twice a day for seven days using the automated device before undergoing randomization and before the clinic visits at months 12, 24, 36, and 48.

The study consisted of a two-year, double-blind, placebo-controlled phase that was followed by a two-year phase in which all study patients received placebo. Throughout the second two-year phase, study investigators remained blinded to each patient's initial treatment assignment. No goal for blood pressure was set, and the participant's treatment regimen could be changed only if hypertension developed. Randomization was performed according to study site in blocks of four. The sizes

according to study site in blocks of four. The sites called an automated randomization system, which assigned the number of the bottle containing either candesartan tablets or matching placebo. On entry and throughout the study, all participants received printed materials about lifestyle modification. Participants' adherence to this diet and exercise regimen was reviewed and reinforced at all subsequent visits. Evaluation was performed at study entry and at annual intervals or at the endpoint visit and included a physical examination and taking of blood and urine samples for routine studies.

The study was managed by a clinical research organization (Omnicare Clinical Research). Biochemical testing was performed by Covance Laboratories (Indianapolis). The protocol was approved by the institutional review boards of the participating institutions, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The investigators submitted a proposal to Astra Merck (subsequently AstraZeneca). The protocol was revised by a group of experts (subsequently called the TROPHY executive committee) and the sponsor. The sponsor provided funding and organized the study. After completion of the study, statisticians at AstraZeneca implemented the prespecified data-analysis plan. Thereafter, the raw data were transferred to the senior authors of the study for verification and further analyses. The manuscript was prepared and submitted for publication by Drs. Julius, Nesbitt, and Egan, who attest to its veracity and completeness.

END POINTS

The main study end point was the development of clinical hypertension, defined as the first appearance of one of the following outcomes: an averaged reading at a clinic visit of systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher, or both, at any three visits during the four years of the study (not necessarily consecutive); an average reading during a clinic visit of systolic pressure of 160 mm Hg or higher or diastolic pressure of 100 mm Hg or higher at any visit during the four study years; a finding by the clinical investigator of target-organ damage or other reasons to initiate pharmacologic treatment; or an average reading of systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher at the visit at month 48.

After an end point was reached, antihypertension treatment with metoprolol (Toprol XL, AstraZeneca), at a dose of 50 mg daily, or hydrochlorothiazide (Microzide, Watson), at a dose of 12.5 mg daily, was offered at no cost. However, study physicians could prescribe other antihypertension medications, with the exception of angiotensin-receptor blockers. Further follow-up of participants in the study clinic was also offered. The study was monitored by a data and safety monitoring board that reviewed the safety data annually.

RESULTS

The first patient underwent randomization in June 1999, and the last participant completed the study in June 2005. We screened 1904 candidates, the two study groups, which were well matched. In the two groups, participants were overweight and had a high incidence of dyslipidemia. The main results of the study are summarized in Table 2 and Figure 2. New onset of hypertension was suppressed in the candesartan group at two years ($P<0.001$) and four years ($P<0.001$), as calculated by Fisher's exact test. This result was further tested with the use of logistic-regression analysis, with adjustment for the following significant baseline predictors: diastolic pressure as measured by the participant using the automatic device at home, systolic pressure as measured at clinic visits with the use of the automated device, hematocrit, plasma insulin:glucose ratio, and age. Throughout the study period a P value of less than 0.05 was considered to indicate statistical significance. There was an absolute difference of 26.8 percent between the two groups and a relative risk reduction of 66.3 percent in the candesartan group at year 2. At year 4, two years after discontinuation of candesartan, there was an absolute difference of 9.8 percent between the two groups and a relative reduction in the risk of new-onset hypertension of 15.6 percent in participants in the candesartan group.

In these analyses, we assumed that hypertension did not develop in patients who discontinued participation in the study early. A sensitivity analysis assuming that hypertension developed in all

Table 2. Incident Hypertension and Incidence of Serious Adverse Events.*

	Candesartan Group (N=391)	Placebo Group (N=381)	P Value	Relative Risk (95% CI)
New-onset hypertension				
No. of participants in whom hypertension developed	208	240		
Hypertension at year 2 visit — %	13.6	40.4	<0.001†	0.34 (0.25–0.44)
Hypertension at year 4 visit — %	53.2	63.0	0.007†	0.84 (0.75–0.95)
Hypertension during study period			<0.001‡	0.58 (0.49–0.70)
Clinical criteria for end-point determination				
BP at three clinic visits, ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	142 (36)	168 (44)	0.03†	0.82 (0.69–0.98)
BP at any clinic visit ≥160 mm Hg systolic, ≥100 mm Hg diastolic, or both — no. (%)	15 (3.8)	19 (5.0)	0.49†	0.77 (0.40–1.49)
BP requiring pharmacologic treatment — no. (%)	45 (12)	48 (13)	0.66†	0.91 (0.62–1.34)
BP at month 48 clinic visit ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	6 (1.5)	5 (1.3)	>0.99†	1.17 (0.36–3.80)

	Candesartan Group (N=396)	Placebo Group (N=391)
	no. (%)	
Incidence of adverse events		
Participants with any serious adverse event	14 (3.5)	23 (5.9)
Organ system		
Cardiovascular	1 (0.3)	6 (1.5)
Gastrointestinal	4 (1.0)	2 (0.5)
Cancer	4 (1.0)	3 (0.8)
Endocrine disorders	2 (0.5)	0
Infections	2 (0.5)	4 (1.0)
Peripheral-nerve disorders	2 (0.5)	0
Abnormal liver-function tests	1 (0.3)	1 (0.3)
Musculoskeletal and connective-tissue disorders	1 (0.3)	3 (0.8)
Psychiatric disorders	1 (0.3)	0
Vascular disorders	1 (0.3)	0

participants who dropped out did not change the results. Exclusion of the 49 participants in violation of the entry criteria did not alter the results ($P<0.001$ at year 2 and $P<0.001$ at year 4 [data not shown], by Fisher's exact test). The median time to the development of hypertension was 2.2 years (95 percent confidence interval, 2.0 to 2.5) in the placebo group and 3.3 years (95 percent confidence interval, 3.0 to 3.8) in the candesartan group.

The Kaplan–Meier curves for the study end point (new-onset hypertension) (Fig. 2) were significantly different throughout the four years of the study ($P<0.001$ by log-rank test and $P<0.001$ by Cox proportional-hazards regression analysis, after adjustment for predictors). After discontinuation of the study medication in the candesartan group, when all participants in the two groups were receiving placebo, the incidence of hypertension in the candesartan group increased but the Kaplan–Meier curves remained separated until the end of the study. Hazard ratios for new-onset hypertension in various subgroups (Fig. 3) were lower in the candesartan group.

Trends in blood pressure during the study period are shown in Figure 4. Blood pressure decreased more rapidly in the candesartan group than in the placebo group in the first two years, but in the third year, after discontinuation of the study medication in the candesartan group and when all participants were receiving placebo, blood pressure increased more rapidly in the candesartan group. At the end of the study, systolic pressure was 2.0 mm Hg lower in the candesartan group ($P=0.037$) and diastolic pressure 1.1 mm Hg lower ($P=0.073$).

Rates of serious adverse events during the first two years were low and were similar in the two groups (Table 2). Serious adverse events occurred in 3.5 percent of the participants in the candesartan group and in 5.9 percent of those in the placebo group. The incidence of other adverse events was similar in the two groups (88.9 percent in the candesartan group, and 88.5 percent in the placebo group) (Table 2). Laboratory values in the two groups were similar during the first two years (Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

Untreated hypertension is a self-accelerating condition. Evolving arteriolar hypertrophy[17] and endothelial dysfunction[18] facilitate the later increase of blood pressure and contribute to the transition from prehypertension to established hypertension. Abnormalities in cardiovascular structure and function and in neuroendocrine control occur in young adults with a predisposition to hypertension.[11,23,35,36] In rats with spontaneous hypertension, brief treatment of young animals with a renin–angiotensin antagonist has lifelong effects in reducing blood pressure.[26,27] Therefore, we hypothesized that an intervention in humans with prehypertension might alter the natural history and prevent or delay the onset of established hypertension.

The results of the study support our primary hypothesis[15] that pharmacologic treatment of prehypertension may prevent or postpone the devel-

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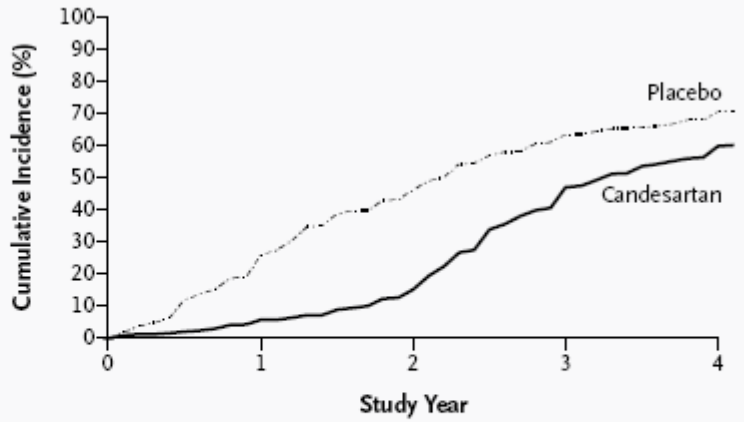
Hypertension during study period			<0.001‡	0.58 (0.49–0.70)
Clinical criteria for end-point determination				
BP at three clinic visits, ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	142 (36)	168 (44)	0.03†	0.82 (0.69–0.98)
BP at any clinic visit ≥160 mm Hg systolic, ≥100 mm Hg diastolic, or both — no. (%)	15 (3.8)	19 (5.0)	0.49†	0.77 (0.40–1.49)
BP requiring pharmacologic treatment — no. (%)	45 (12)	48 (13)	0.66†	0.91 (0.62–1.34)
BP at month 48 clinic visit ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	6 (1.5)	5 (1.3)	>0.99†	1.17 (0.36–3.80)

	Candesartan Group (N=396)	Placebo Group (N=391)
	no. (%)	

Incidence of adverse events		
Participants with any serious adverse event	14 (3.5)	23 (5.9)
Organ system		
Cardiovascular	1 (0.3)	6 (1.5)
Gastrointestinal	4 (1.0)	2 (0.5)
Cancer	4 (1.0)	3 (0.8)
Endocrine disorders	2 (0.5)	0
Infections	2 (0.5)	4 (1.0)
Peripheral-nerve disorders	2 (0.5)	0
Abnormal liver-function tests	1 (0.3)	1 (0.3)
Musculoskeletal and connective-tissue disorders	1 (0.3)	3 (0.8)
Psychiatric disorders	1 (0.3)	0
Vascular disorders	1 (0.3)	0

Table 2. (Continued.)		
Ear and labyrinth disorders	0	1 (0.3)
Hepatobiliary disorders	0	2 (0.5)
Reproductive system and breast disorders	0	1 (0.3)
General disorders	3 (0.8)	2 (0.5)
Other adverse events	352 (88.9)	346 (88.5)
Headache	85 (21.5)	74 (18.9)
Upper respiratory tract infection	57 (14.4)	52 (13.3)
Arthralgia	38 (9.6)	44 (11.3)
Nasopharyngitis	40 (10.1)	38 (9.7)
Back pain	37 (9.3)	40 (10.2)
Sinusitis	34 (8.6)	41 (10.5)
Dizziness	41 (10.4)	33 (8.4)
Bronchitis	21 (5.3)	34 (8.7)
Fatigue	32 (8.1)	21 (5.4)
Pain in an extremity	30 (7.6)	18 (4.6)
Depression	21 (5.3)	23 (5.9)
Gastroesophageal reflux	22 (5.6)	21 (5.4)
Insomnia	22 (5.6)	21 (5.4)
Nausea	16 (4.0)	27 (6.9)
Diarrhea	22 (5.6)	17 (4.3)
Anxiety	20 (5.1)	17 (4.3)
Hypotension	4 (1.0)	2 (0.5)
Syncope	2 (0.5)	1 (0.3)
Angioedema	0	1 (0.3)



No. of Patients without Hypertension					
Candesartan group	391	356	309	191	127
Placebo group	381	269	184	118	85

Figure 2. Kaplan–Meier Analysis of New-Onset Clinical Hypertension.

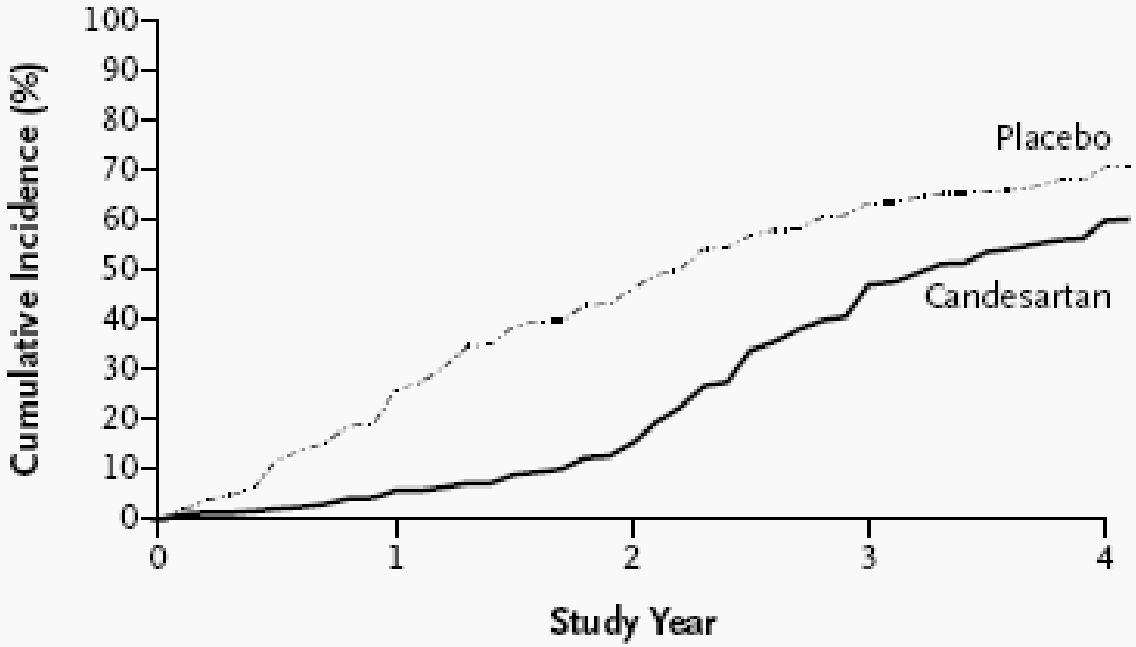


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Figure 2. Kaplan–Meier Analysis of New-Onset Clinical Hypertension.

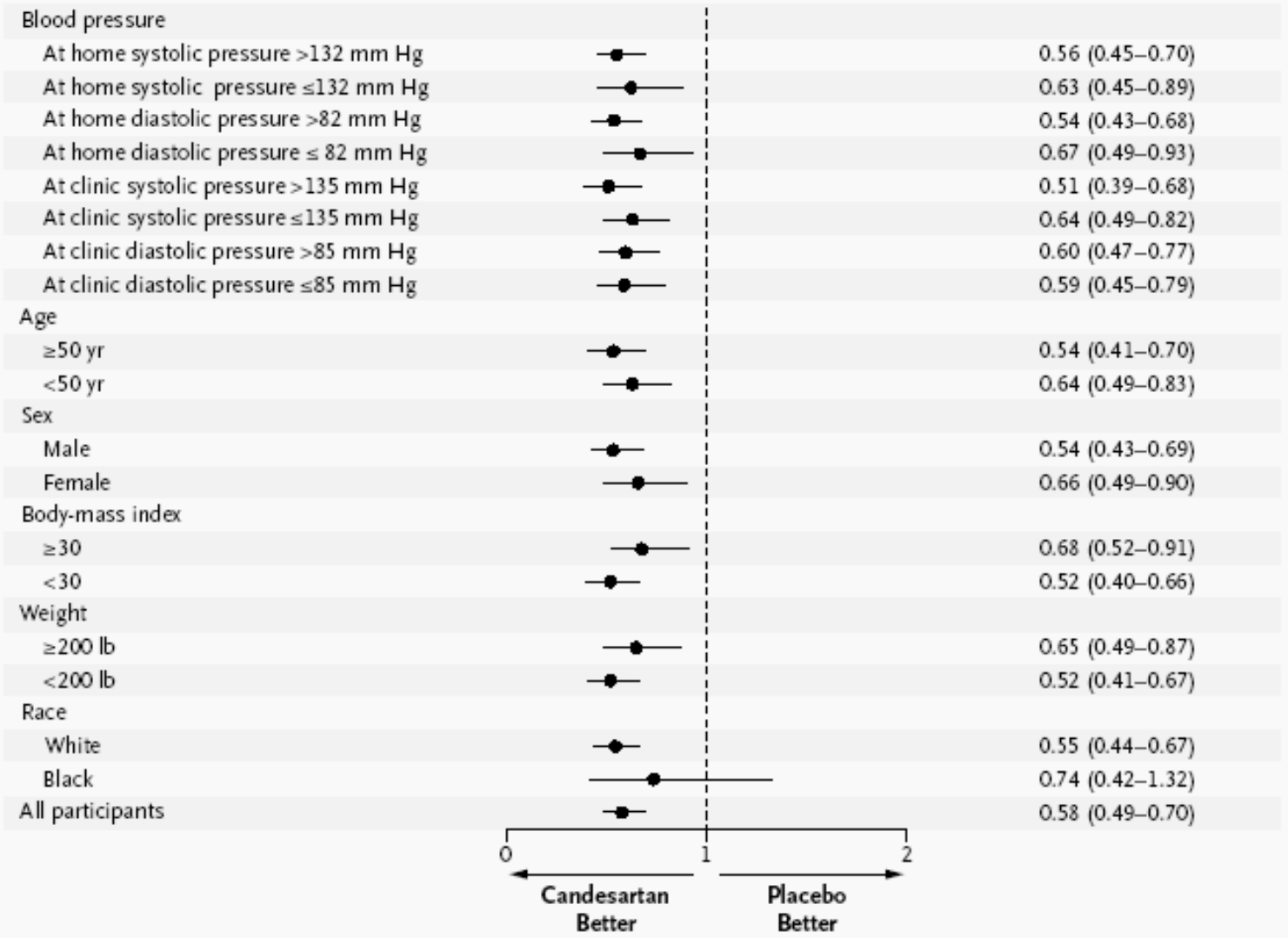
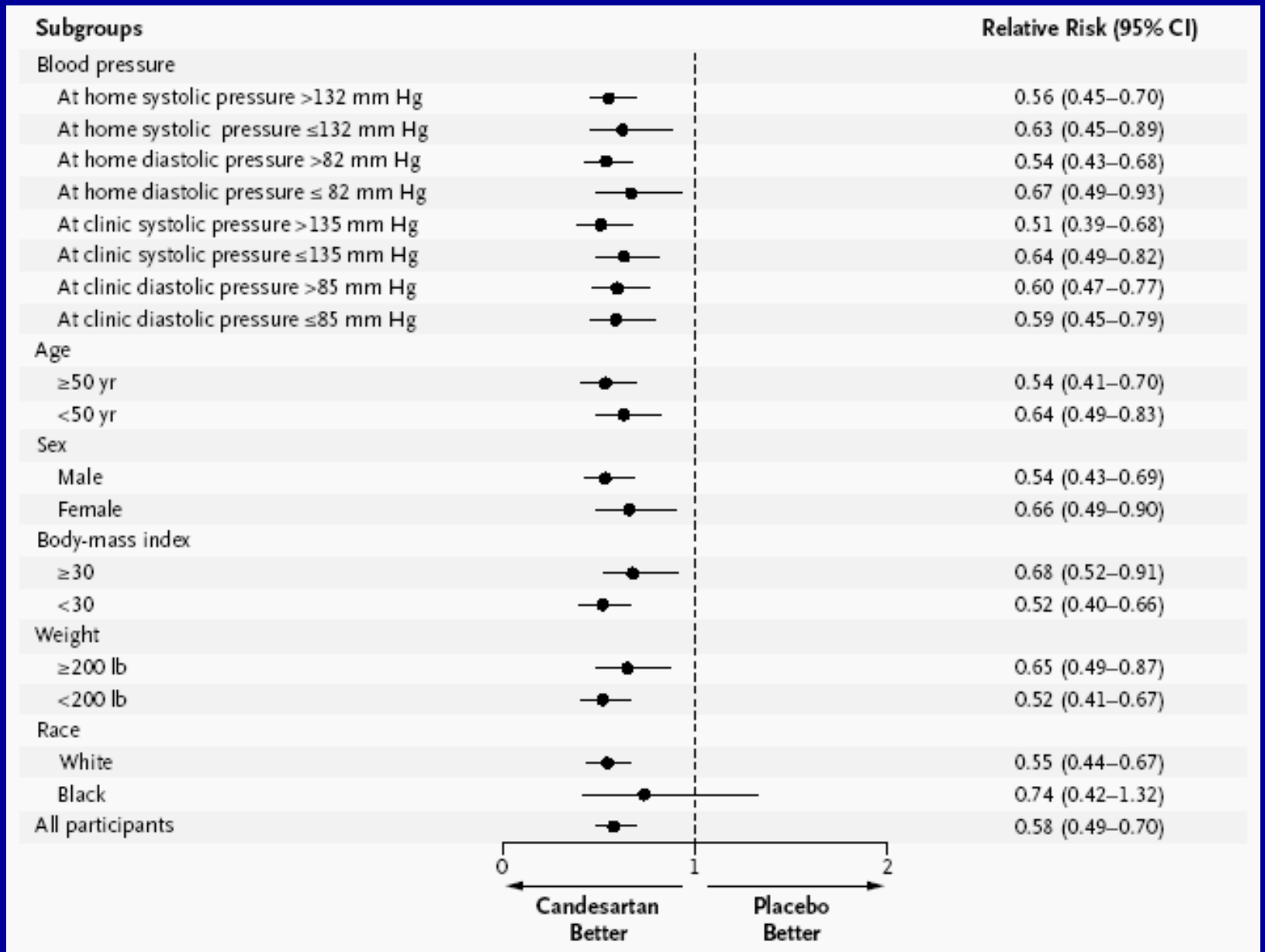


Figure 3. Hazard Ratios for New-Onset Hypertension in Various Subgroups.

Hazard ratios of time to event throughout the four years of the study were calculated by Cox proportional-hazards regression analysis. BMI denotes body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and CI confidence interval. To convert pounds to kilograms, multiply by 0.45. Race was self-reported.


Subgroups
Relative Risk (95% CI)
Blood pressure
At home systolic pressure >132 mm Hg
0.56 (0.45–0.70)
At home systolic pressure ≤132 mm Hg
0.63 (0.45–0.89)
At home diastolic pressure >82 mm Hg
0.54 (0.43–0.68)
At home diastolic pressure ≤ 82 mm Hg
0.67 (0.49–0.93)
At clinic systolic pressure >135 mm Hg
0.51 (0.39–0.68)
At clinic systolic pressure ≤135 mm Hg
0.64 (0.49–0.82)
At clinic diastolic pressure >85 mm Hg
0.60 (0.47–0.77)
At clinic diastolic pressure ≤85 mm Hg
0.59 (0.45–0.79)
Age
≥50 yr
0.54 (0.41–0.70)
<50 yr
0.64 (0.49–0.83)
Sex
Male
0.54 (0.43–0.69)
Female
0.66 (0.49–0.90)
Body-mass index
≥30
0.68 (0.52–0.91)
<30
0.52 (0.40–0.66)
Weight
≥200 lb
0.65 (0.49–0.87)
<200 lb
0.52 (0.41–0.67)
Race
White
0.55 (0.44–0.67)
Black
0.74 (0.42–1.32)
All participants
0.58 (0.49–0.70)
0
1
2
Candesartan Better
Placebo Better

opment of hypertension. At four years — two years after discontinuation of candesartan — there was a significant reduction in incident hypertension in participants with prehypertension who had received candesartan. The relative proportion of participants who were hypertension-free was 26.5 percent greater in the candesartan group.

The results of two years of candesartan treatment support our secondary hypothesis that pharmacologic treatment of prehypertension may suppress the development of hypertension. During the active treatment phase, we did not set a specific blood-pressure goal, and dose adjustment was not permitted. Nevertheless, there was a relative reduction of 66.3 percent in new-onset hypertension and an absolute reduction of 26.8 percent in new-onset hypertension in the candesartan group. Using the absolute difference between the two groups, we calculated that four participants with prehypertension needed to be treated for a set period (two years in the present study) to prevent one case of new-onset hypertension during that two-year period. Treatment with candesartan appeared to be safe; in a comparison between active treatment with candesartan and placebo for two years, serious adverse events and other side effects were infrequent, and the rates of each were similar in the two groups.

Current guidelines[4] recommend lifestyle modification for the management of prehypertension. The results of our study can be compared with findings of the Trials of Hypertension Prevention,[28] the only trial of lifestyle modification with a similar duration: the absolute reduction in the incidence of new-onset hypertension at two years with candesartan was 26.8 percent, as compared with 8 percent with the most successful lifestyle intervention in the Trials of Hypertension Prevention.

During the study, hypertension developed in 63 percent of those in the placebo group. Among an estimated 65 million persons in the United

States with prehypertension,[14,33,37] approximately 25 million have blood-pressure readings similar to those of the participants in our study. Hypertension will develop in almost 16 million of these persons in the next four years, given the results in the placebo group in our study. In the follow-up of the large-scale Multiple Risk Factor Intervention Trial (MRFIT) involving young and middle-age men,[9] 22.2 percent of the cohort had blood pressures of 130 to 139 mm Hg systolic and 85 to 89 mm Hg diastolic. As compared with members of that cohort with optimal blood pressure, the men in this group had age-adjusted relative risks of 1.61 and 2.14 for fatal coronary events and strokes, respectively. Death from cardiovascular causes among persons with prehypertension increased steeply over 16 years of observation.[9] A successful intervention in this large population might potentially have a substantial public health effect. The recommended lifestyle measures for blood-pressure control in prehypertension[3] have had no demonstrable effect on public health to date.[33] Consequently, we believe it was appropriate to evaluate whether pharmacologic treatment of prehypertension is feasible. In our study, candesartan suppressed the onset of hypertension. In the first phase of the study, new-onset stage 1 hypertension developed in 13.6 percent of the participants in the candesartan group, as compared with 40.4 percent of those in the placebo group. We did not test the long-term safety and efficacy of this form of pharmacotherapy for prehypertension.

Our study also indicates that the effect of active treatment on delaying the onset of hypertension can extend to up to two years after the discontinuation of treatment. However, the absolute reduction of 9.8 percent in incident hypertension in the study at four years was modest.

Although the observations in this study indicate that candesartan may ameliorate blood pressure in persons with prehypertension, we do not advocate treatment of the 25 million people with prehypertension. We are unaware of any ongoing prospective trials in prehypertension, and hope that the present results will stimulate further research. The public health implications of such research are potentially large. Further studies are needed to answer a number of questions.

The mean age of 48.5 years among participants in our study is younger than that in other recent studies of hypertension. Whether treatment in even younger persons could maximize the prevention of hypertension is unknown. It is also not known whether longer periods of treatment than in our study or a larger degree of blood-pressure lowering than was achieved in the study would yield different results. Whether the results of our study reflect only the blood-pressure–lowering actions of the study drug or other effects of angiotensin blockade has not been resolved. Potentially the largest effect would come from a study of clinical outcomes with pharmacologic intervention in prehypertension. Finally, the issue of cost-effectiveness has not been resolved. A head-to-head comparison of the cost-effectiveness of lifestyle modification and pharmacologic treatment of prehypertension would of great interest.

Treatment of prehypertension with candesartan monotherapy decreased incident hypertension in participants in this study. Additional studies will be needed to ascertain whether this or other strategies involving early pharmacologic treatment of prehypertension would positively affect clinical outcomes.

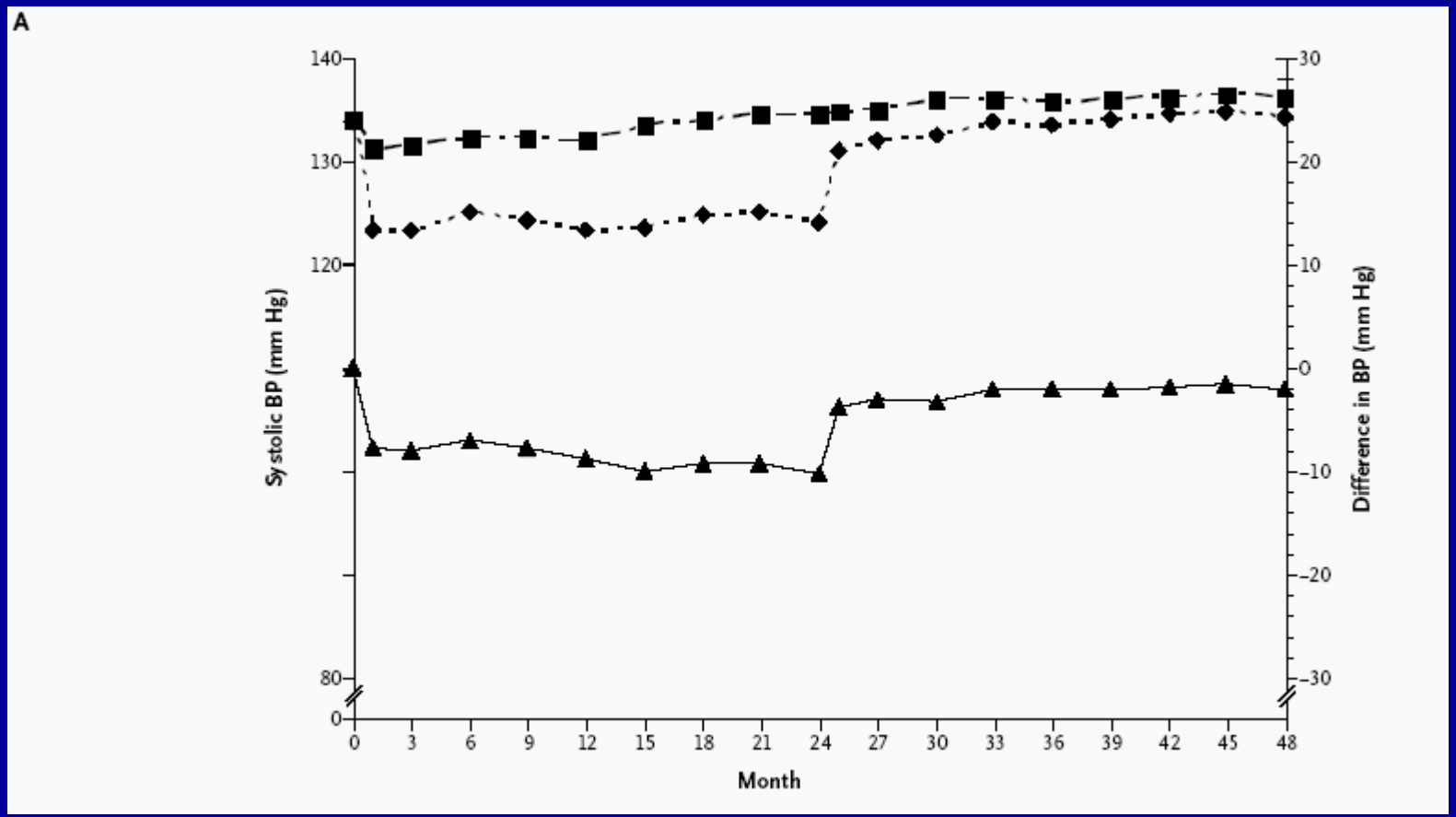
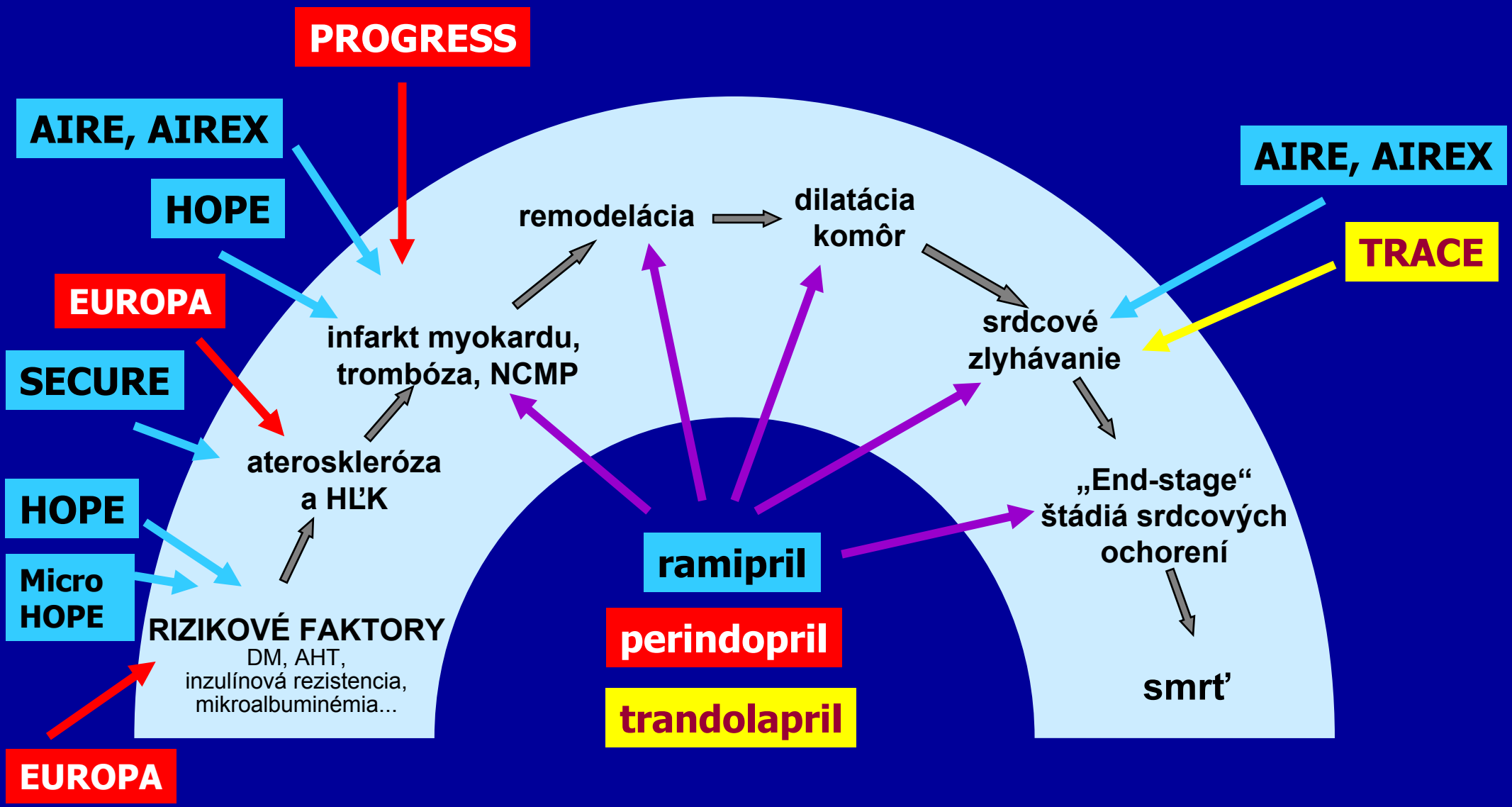


Figure 4. Blood Pressure in the Two Study Groups.

Squares represent the placebo group, and diamonds the candesartan group; triangles represent the difference between the two groups. Below the graphs are the cumulative percentages of participants in the two groups receiving antihypertension treatment at each clinic visit. Blood-pressure readings were obtained in the clinic with the use of an automated device. BP denotes blood pressure.

Kardiovaskulárne kontinuum a vybraté klinické štúdie s inhibítormi ACE v sekundárnej prevencii KVO



„CLASS EFFECT" ?

VIACERO ACE INHIBÍTOROV EXPERIMENTÁLNE
AJ KLINICKY PREUKÁZALI TAKÝ ROZSAH
PODOBNÝCH BENEFITOV,
ŽE SA ČASTO UVAŽUJE O TOM,
ČI SA NEJEDNÁ O TZV. „CLASS" EFEKT
- S VEDECKÝMI OBMEDZENIAMI - **ÁNO**.

SÚ VEDECKO-KLINICKÉ FAKTY
O JEDNOTLIVÝCH ACE INHIBÍTOROCH
PLNE APLIKOVATEĽNÉ A PRENOSNÉ PRE VŠETKY?
EBM HOVORÍ – **NIE**.

ĎAKUJEM
ZA POZORNOSŤ

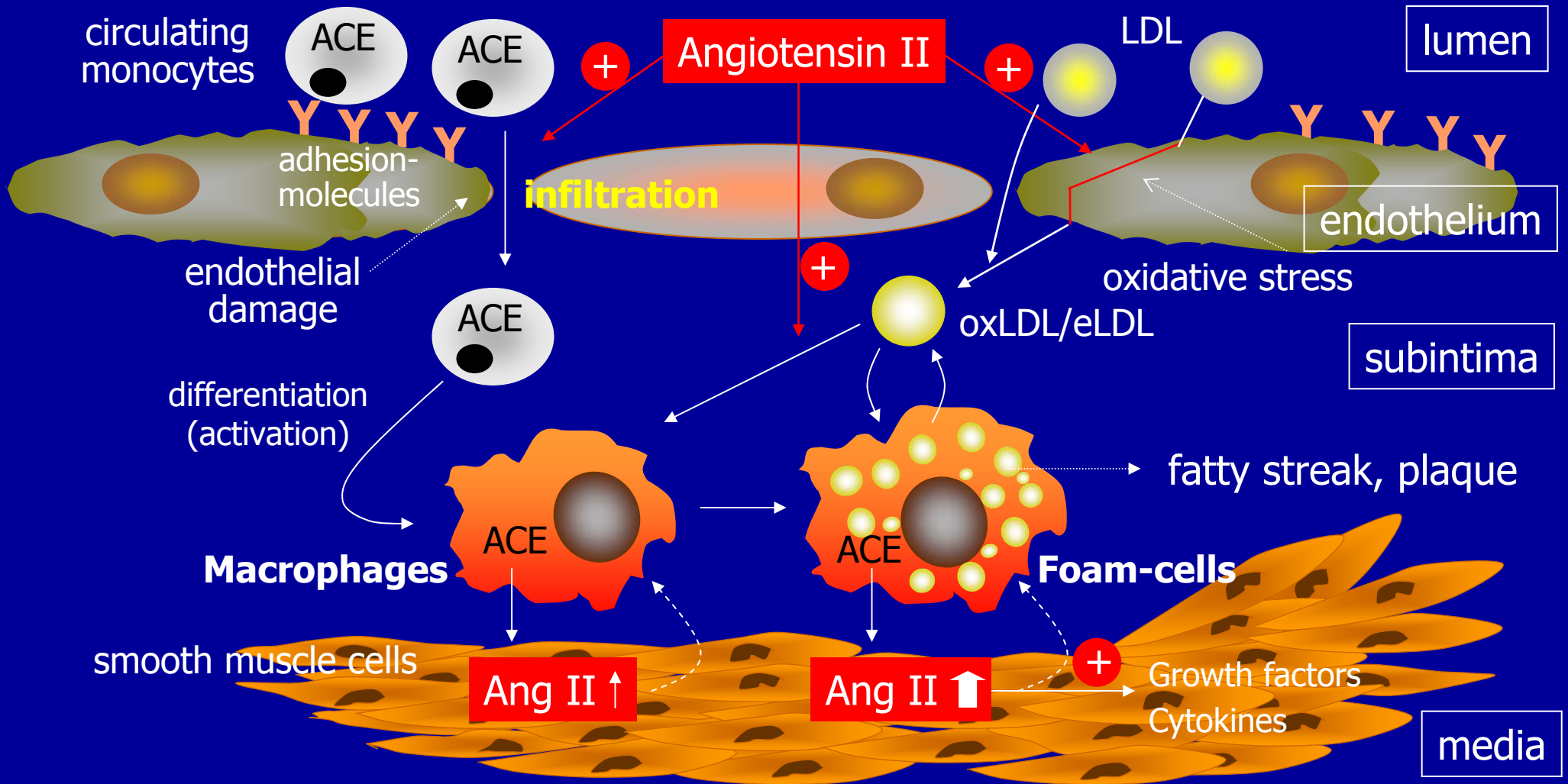
Lokálne RAAS

➡ Systémy generujúce angiotenzín II:

tkanivo/kompartment	bunkové systémy
srdce	myocyty
CNS	neuróny
obličky	tubul. mesangium
stena krvných ciev	endotel
AK plaky	makrofágy ?
testes	hladký sval ?
uterus	bunky zona glomerulosa
kôra nadobličiek	

mod.: Dzau V, Arch Intern Med 153 (1993)

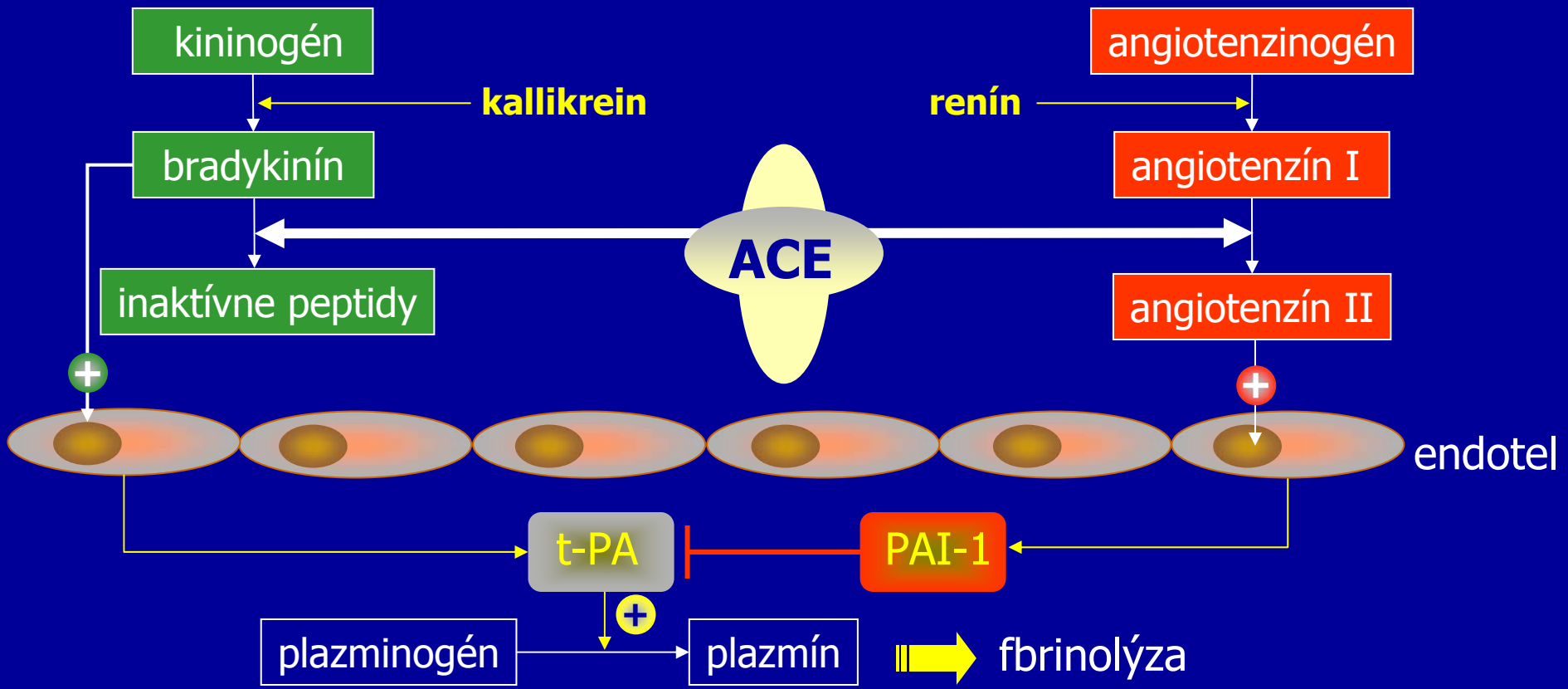
Lokálny angiotenzínový system v makrofágoch a jeho úloha v AS procese



podľa: Diaz et al., N Engl J Med 337 (1997)

ACE, ateroskleróza a endogénna fibrinolýza

➡ Úloha angiotenzínu II and bradykinínu:

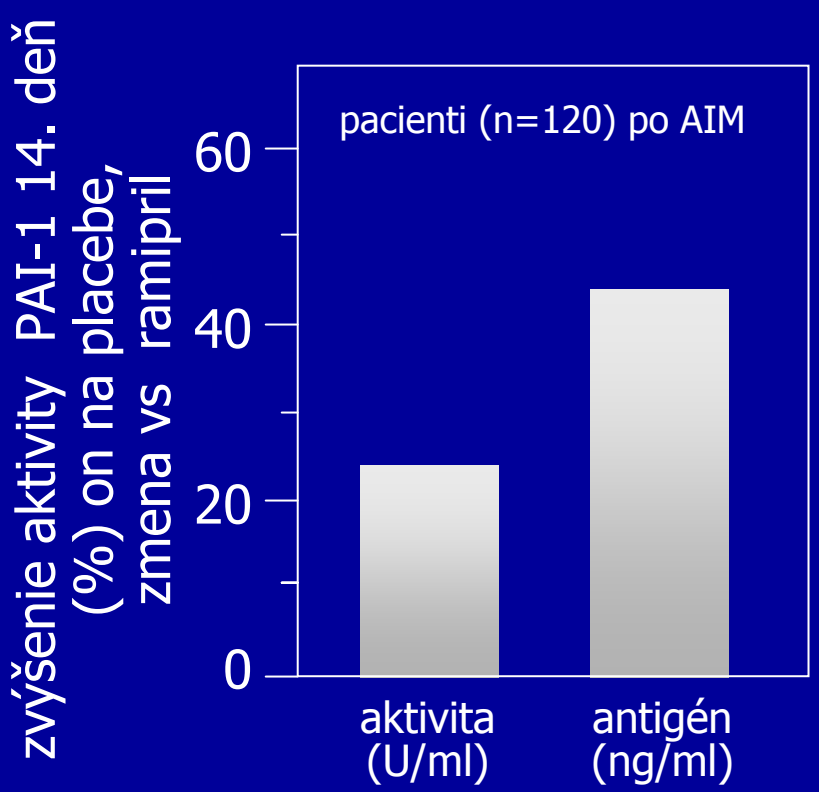


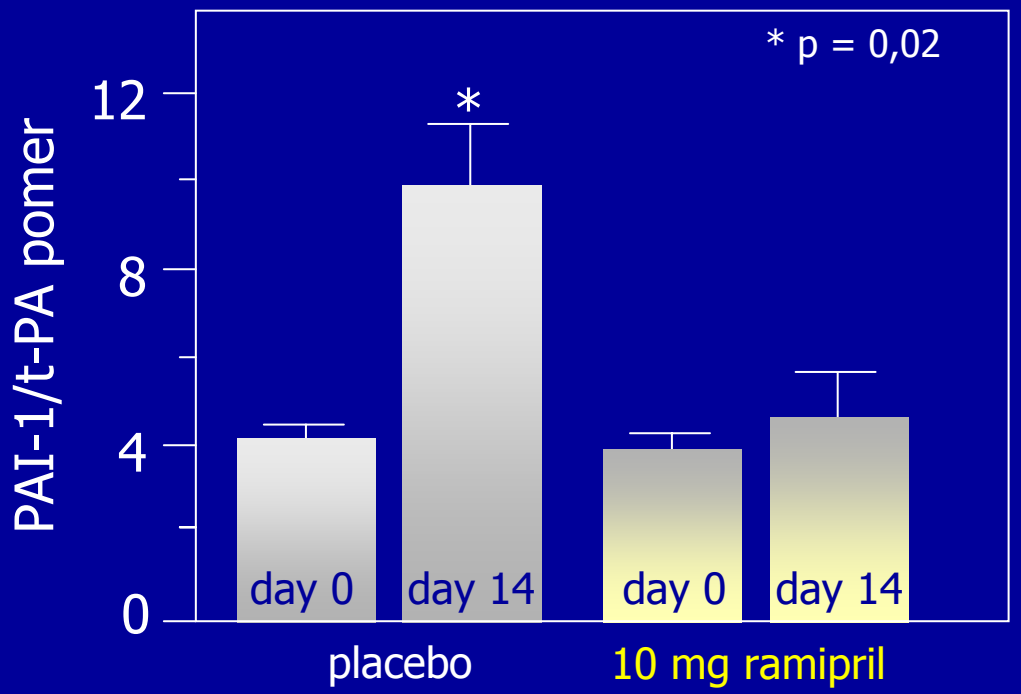
PAI = plasminogen activator inhibitor
t-PA = tissue-plasminogen activator

podľa: Brown et al., Circulation 97 (1998)

Akútny účinok inhibície ACE na endogénnu fibrinolýzu

➡ pro-fibrinolytický efekt ramiprilu:

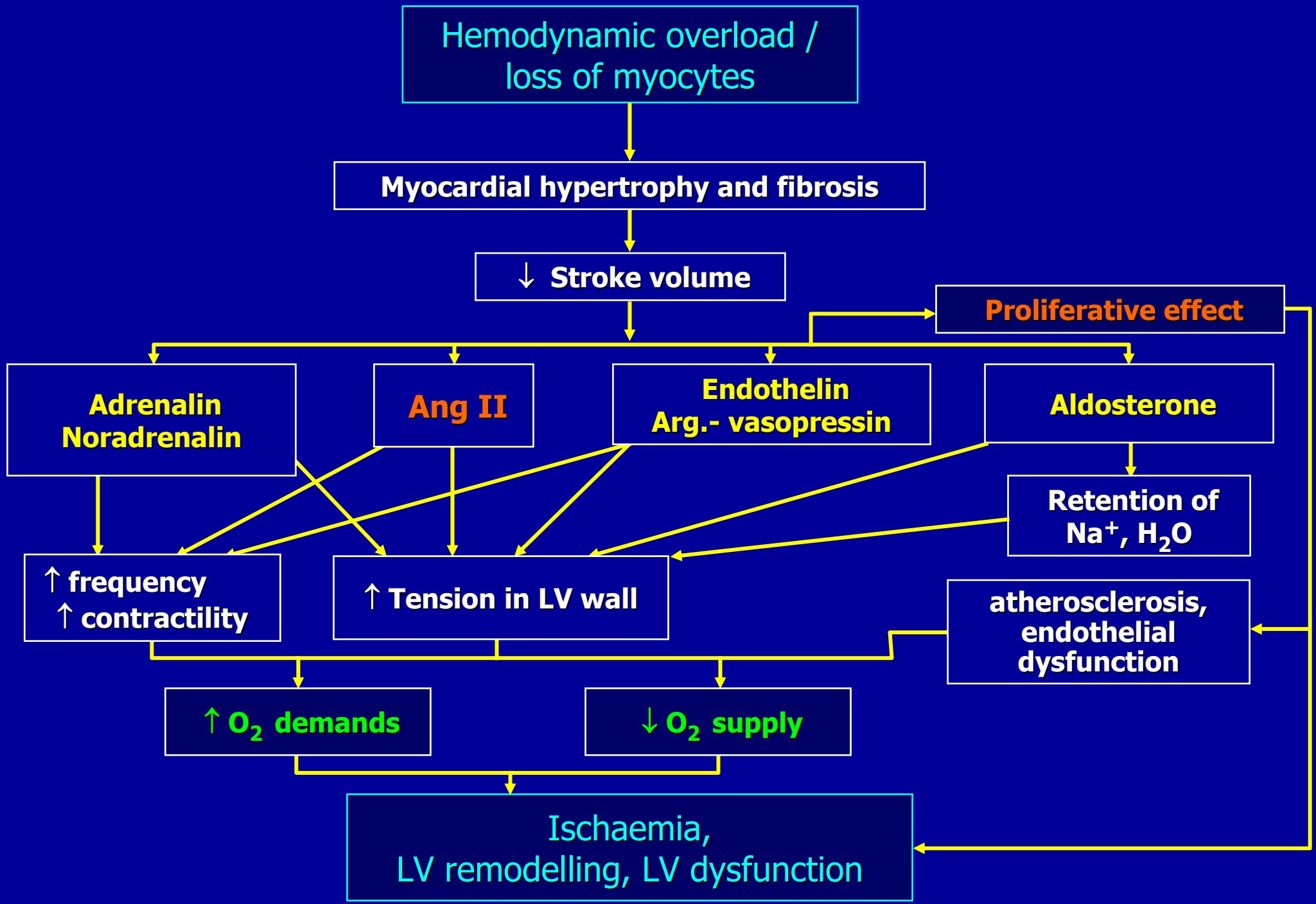




podľa: Vaughan et al., Circulation 96 (1997)

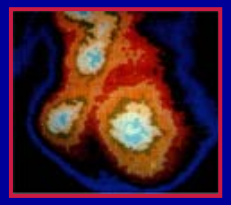
Sympatikový NS – celková adaptácia na stres

Pri strese dochádza k aktivácii a mobilizácii neurohumorálnych a energetických rezerv organizmu s cieľom režitia záťažovej situácie

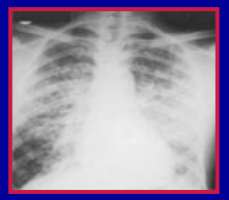

Hemodynamic overload / loss of myocytes
Myocardial hypertrophy and fibrosis
↓ Stroke volume
Proliferative effect
Adrenalin Noradrenalin
Ang II
Endothelin Arg.- vasopressin
Aldosterone
Retention of Na^+, H_2O
↑ frequency ↑ contractility
↑ Tension in LV wall
atherosclerosis, endothelial dysfunction
↑ O_2 demands
↓ O_2 supply
Ischaemia, LV remodelling, LV dysfunction

Dve tváre RAS

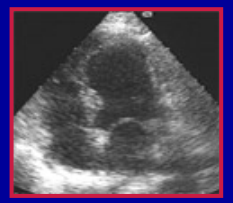
- **Akútna aktivácia** - mobilizuje cirku-lačné rezervy a umožňuje prežiť záťaž
- **Chronická aktivácia** - patologický rast tkanív, deplécia energie – zhoršenie prognózy



SAVE
Radionuclide
EF ≤ 40%
captopril

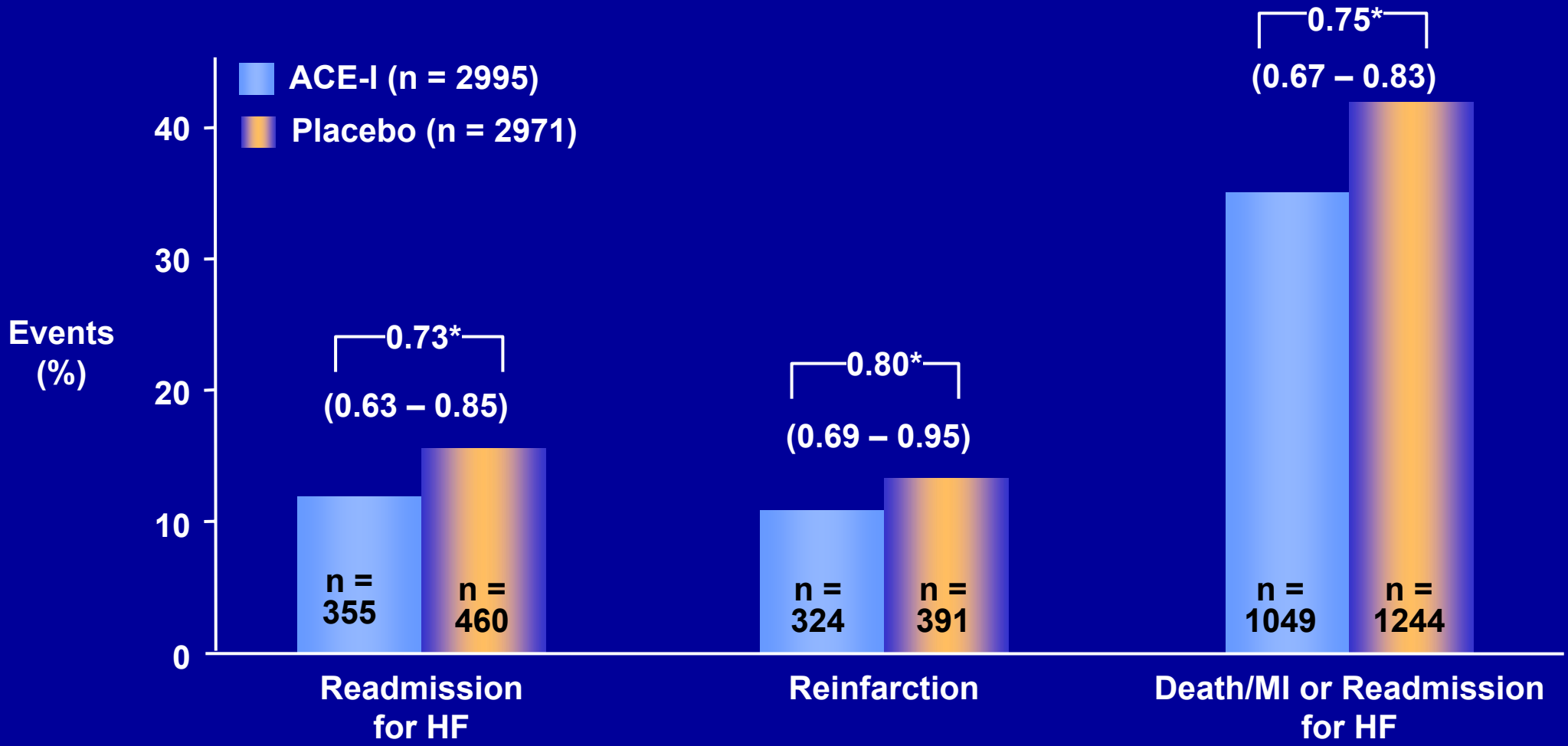


AIRE
Clinical and/or
radiographic signs of HF
ramipril



TRACE
Echocardiographic
EF ≤ 35%
trandolapril

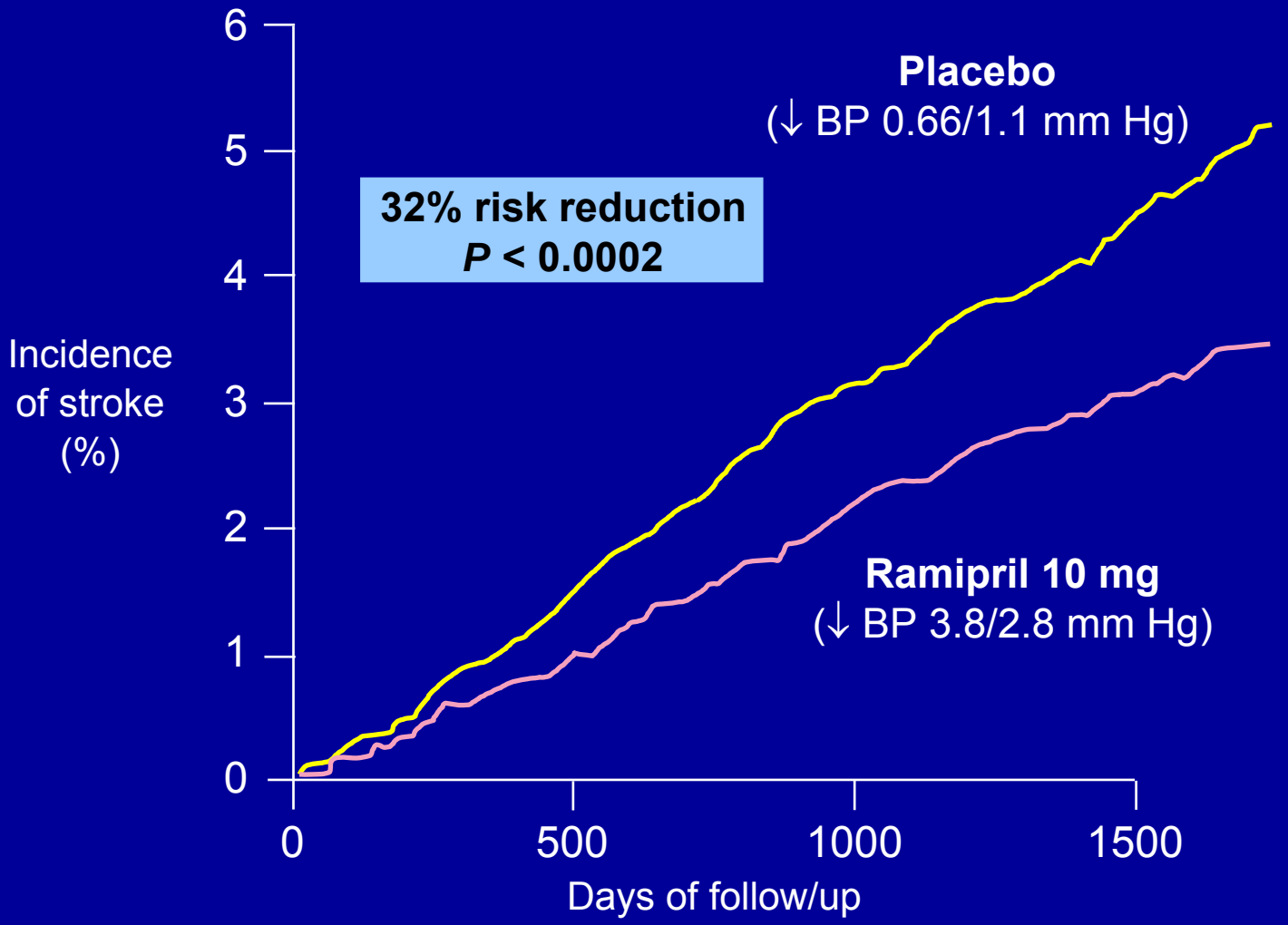
Smrť a veľké KV príhody



*Odds ratio (95% CI).

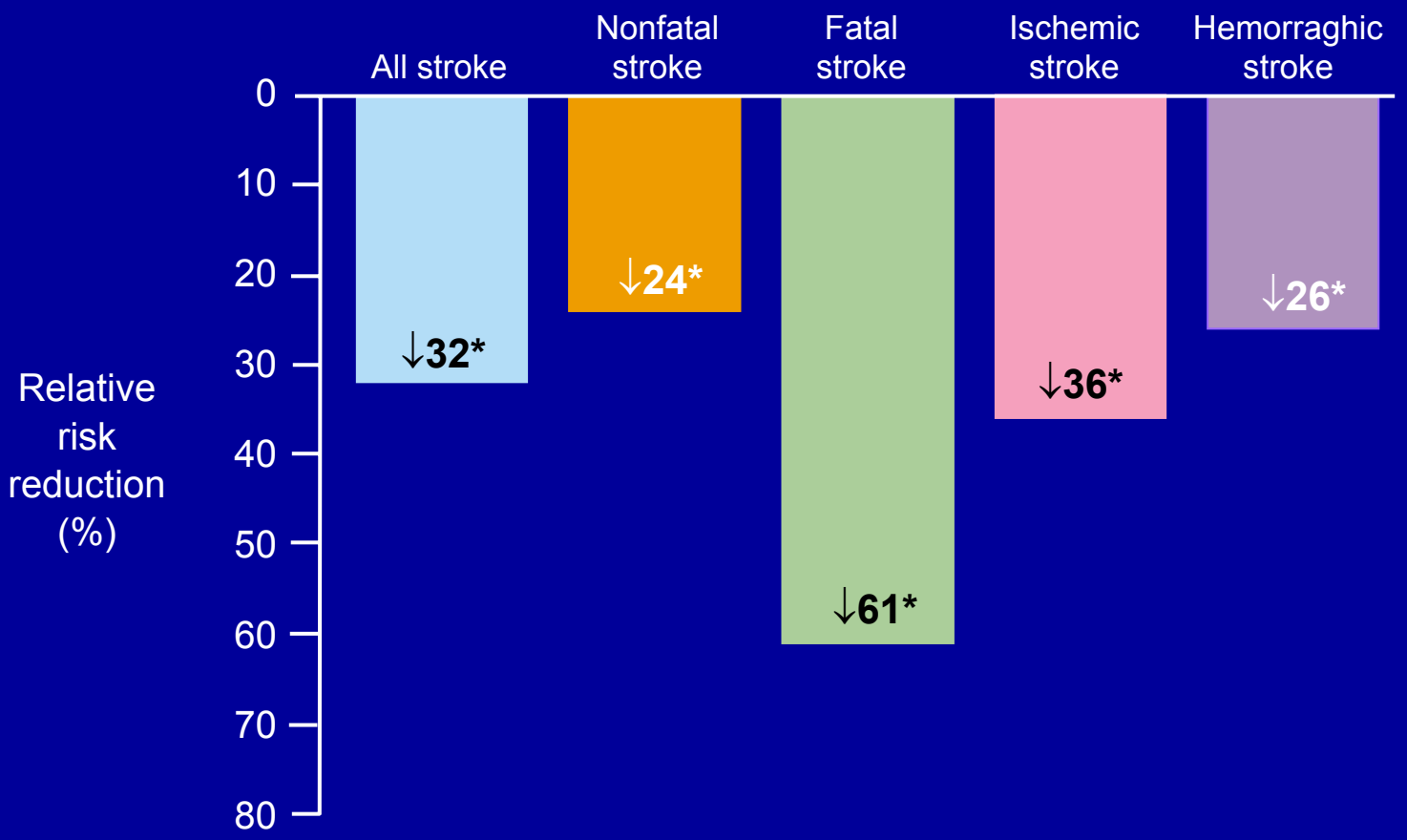
Flather MD et al. *Lancet*. 2000;355:1575-1581.

HOPE: Reduction in stroke with ramipril 10 mg



Bosch J, et al. *BMJ*. 2002;324:699-702.

HOPE: Risk reduction by stroke type



Beyond baseline therapy with:

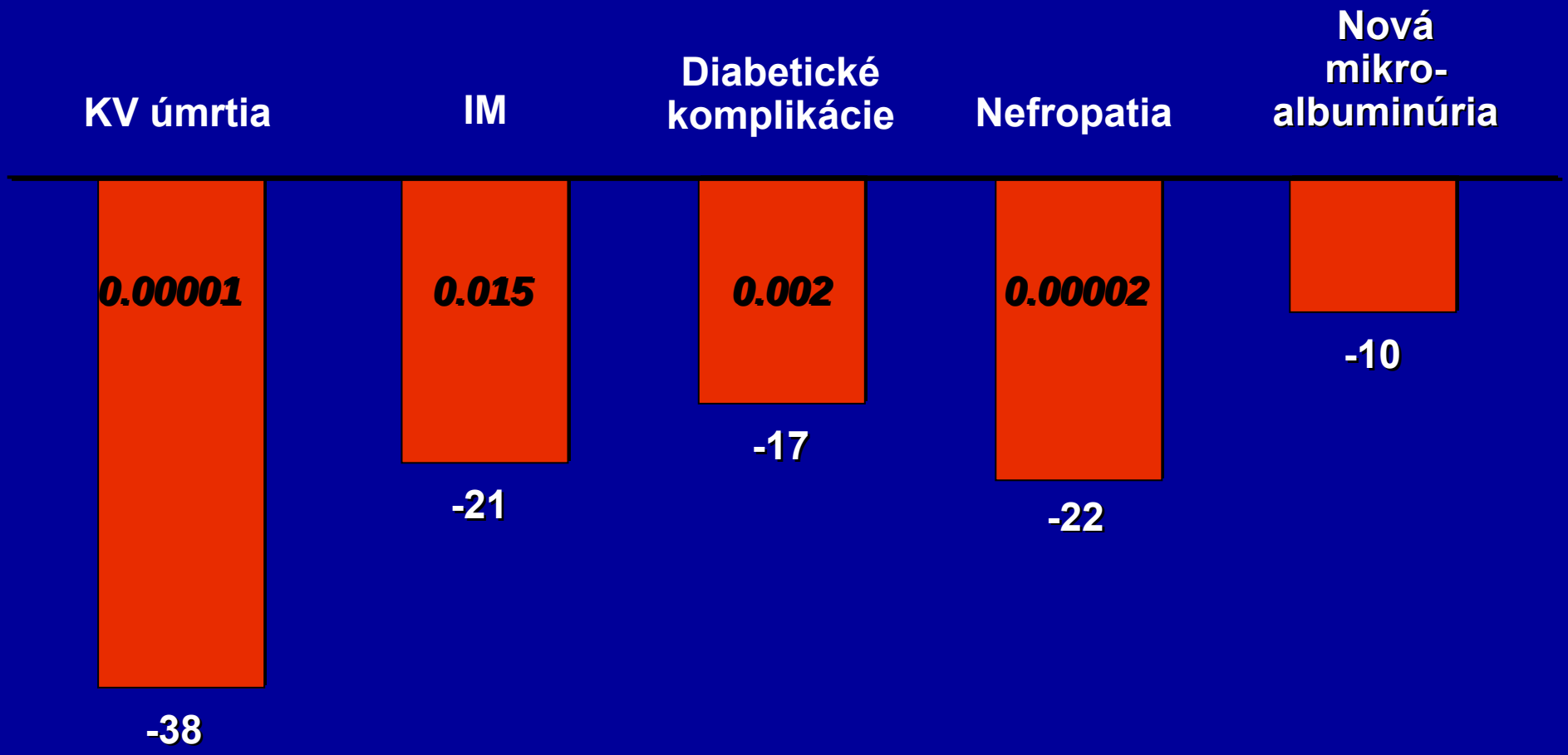
- **Aspirin**
- **Other antiplatelet agent**
- **Ca^{++} channel blockers**
- **Statins**
- **β-blockers**
- **Diuretics**

*Statistically significant difference compared with placebo

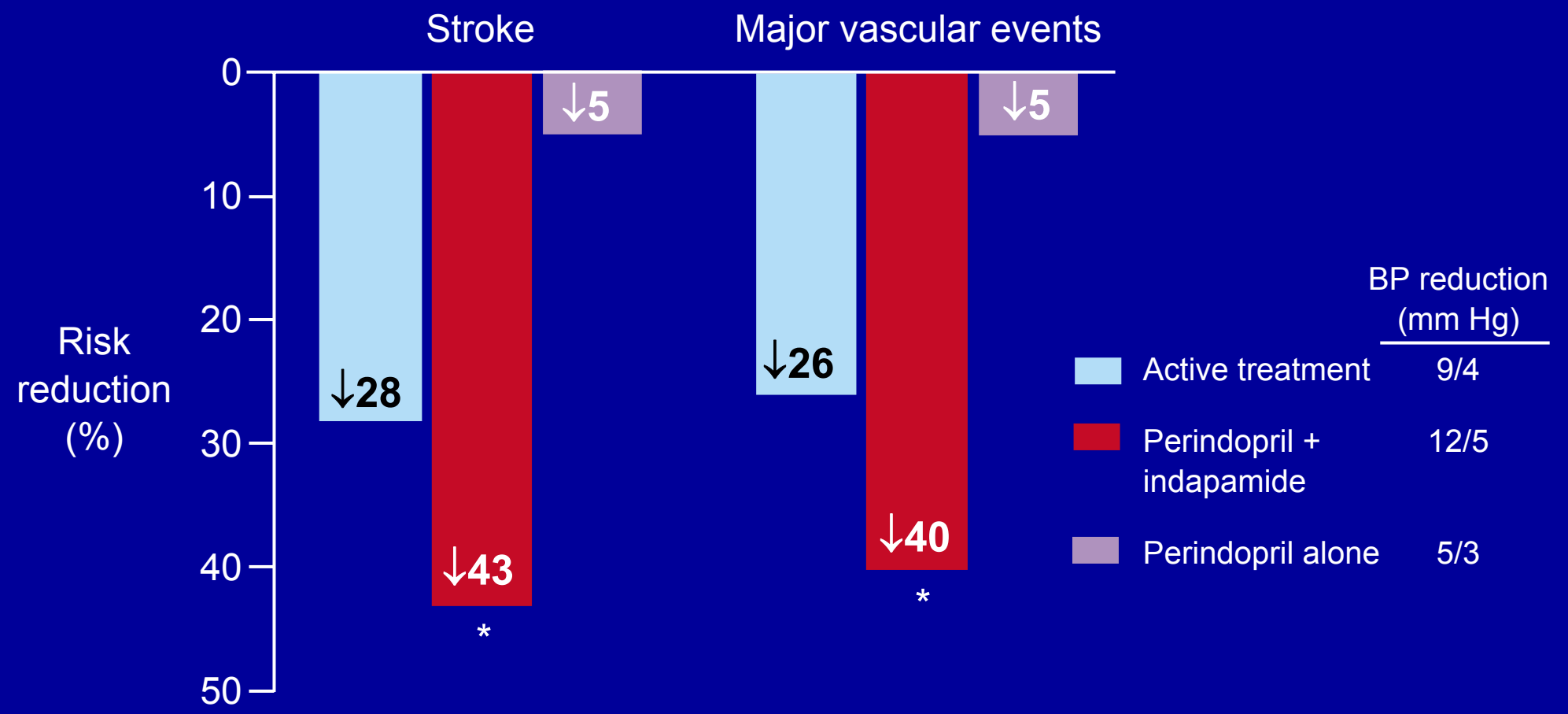
Bosch J, et al. *BMJ*. 2002;324:699-702.

MICRO HOPE

Zníženie rizika sledovaných ukazovateľov u diabetikov (%)



PROGRESS: Risk reduction by BP-lowering regimen



*$P < 0.0001$

PROGRESS Collaborative Group. *Lancet*. 2001;358:1033-1041.

HOPE vs PROGRESS: Key differences

HOPE

- **Including criteria:**
  History of MI, stroke, PAD, or diabetes + at least one other CV risk factor
- **Objective:**
  To evaluate effects of ramipril on CV death, MI, stroke
- **Dosing:** ramipril 10 mg
- **Baseline BP:** 139/79 mm Hg
- **BP reduction:** 3/2 mm Hg

PROGRESS

- **Including criteria:**
  History of stroke or TIA
- **Objective:**
  To evaluate effects of perindopil-based BP-lowering on recurrent stroke
- **Dosing:** perindopril 4 mg ± indapamide 2.0–2.5 mg
- **Baseline BP:** 147/86 mm Hg
- **BP reduction:**
  Perindopril + indapamide 12/5 mm Hg
  Perindopril alone 5/3 mm Hg

The HOPE Study Investigators. *N Engl J Med*. 2000;345:145-153.
PROGRESS Collaborative Group. *Lancet*. 2001;358:1033-1041.

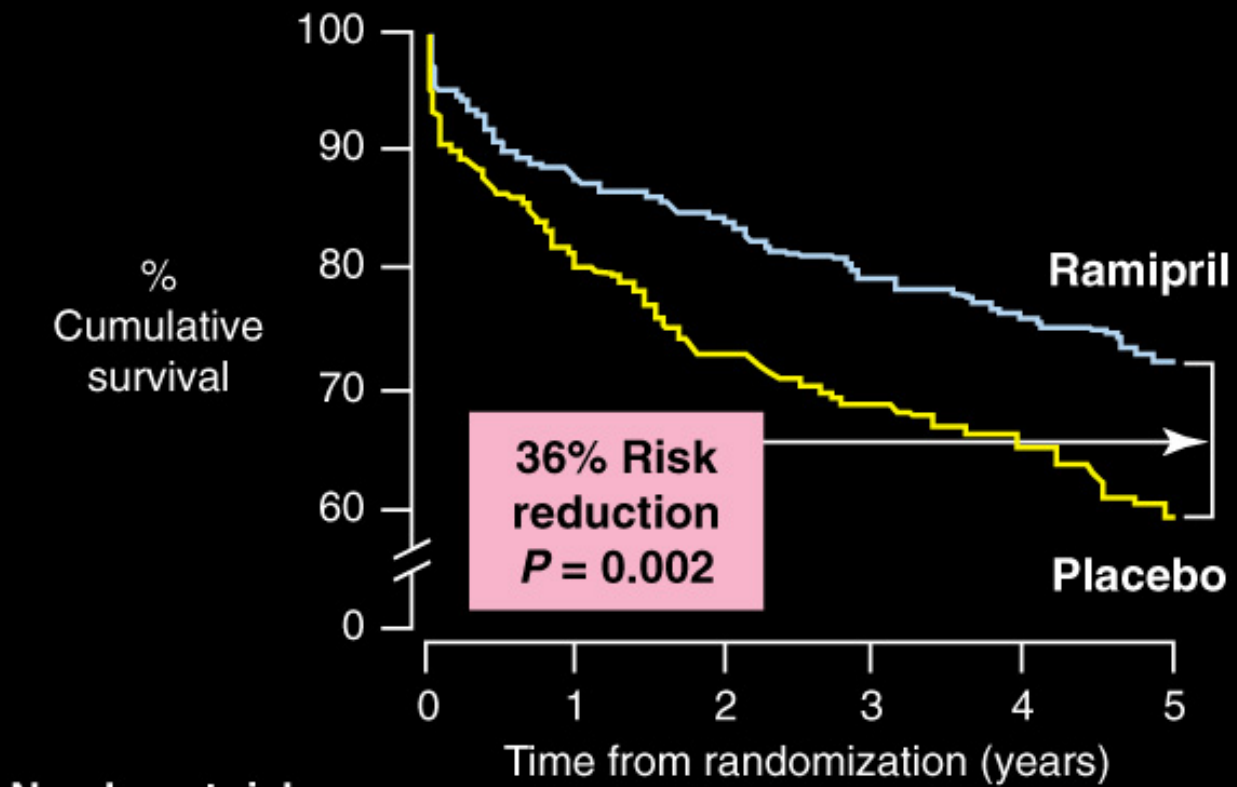
Ramipril in HOPE, MICRO-HOPE & SECURE

- HOPE:
  - First convincing evidence of a vasoprotective (antiischaemic) effect of ACE inhibition in patients with preserved left ventricular function
  - Ramipril 10 mg/day safely reduced major CV events, new cases of diabetes, and diabetic microvascular complications in a broad spectrum of high-risk patients

- MICRO-HOPE:
  - Confirmed therapeutic benefit of ramipril on renal and CV outcomes in high-risk diabetic patients

- SECURE:
  - Demonstrated that ramipril retards atherosclerosis progression (mechanism of reduced CVD risk)

AIREX: Long-term benefits of ramipril in post-MI heart failure



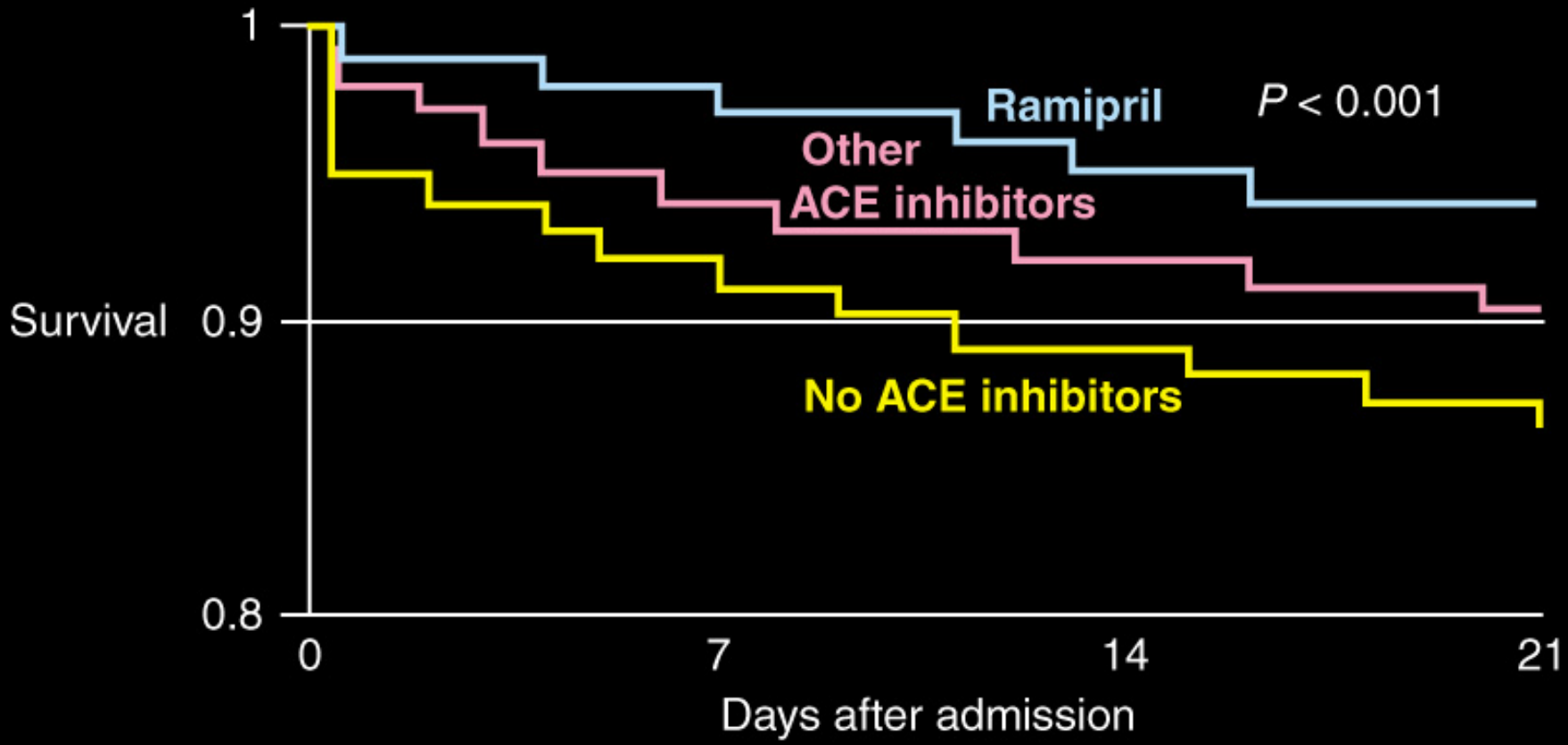
Number at risk

Ramipril	302	263	253	239	202	93
Placebo	301	242	220	206	168	71

Hall AS, et al. *Lancet.* 1997;349:1493-1497.

MITRA PLUS: Impact on post-MI survival—Benefits of ramipril

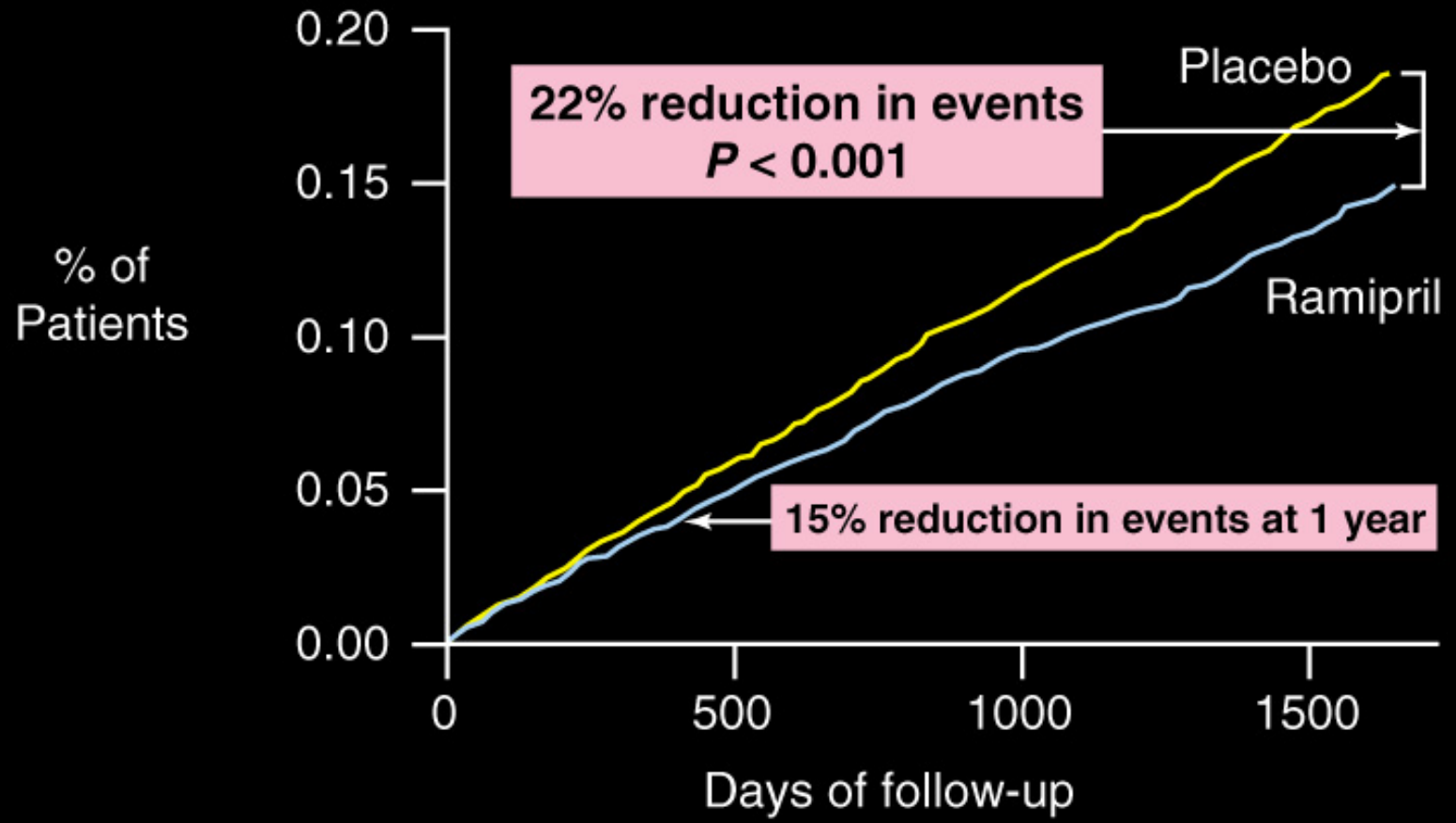
14 608 patients with ST-elevation acute MI



Wienbergen H, et al. *Am J Cardiol*. 2002;90:1045-1049.

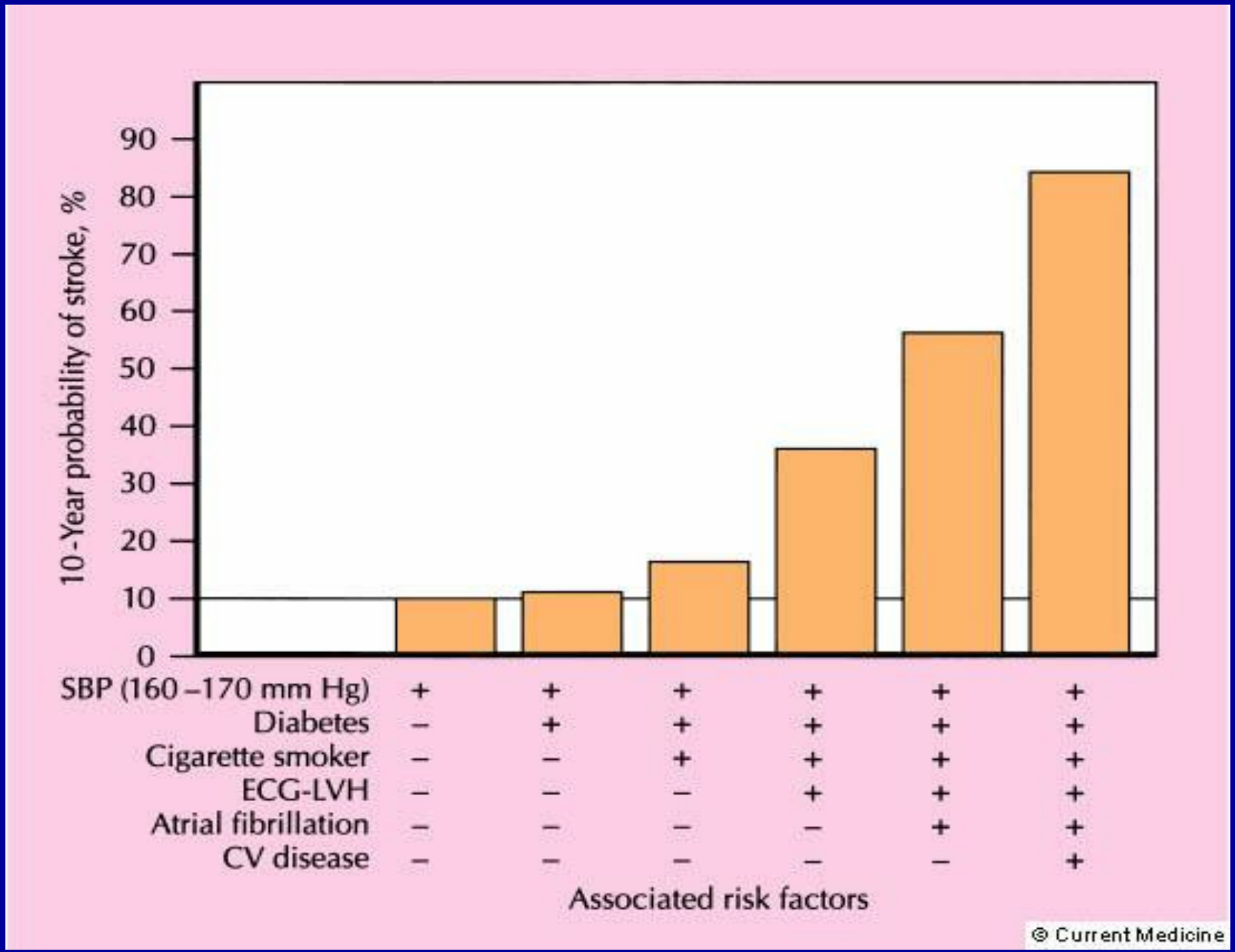
HOPE: Primary outcome

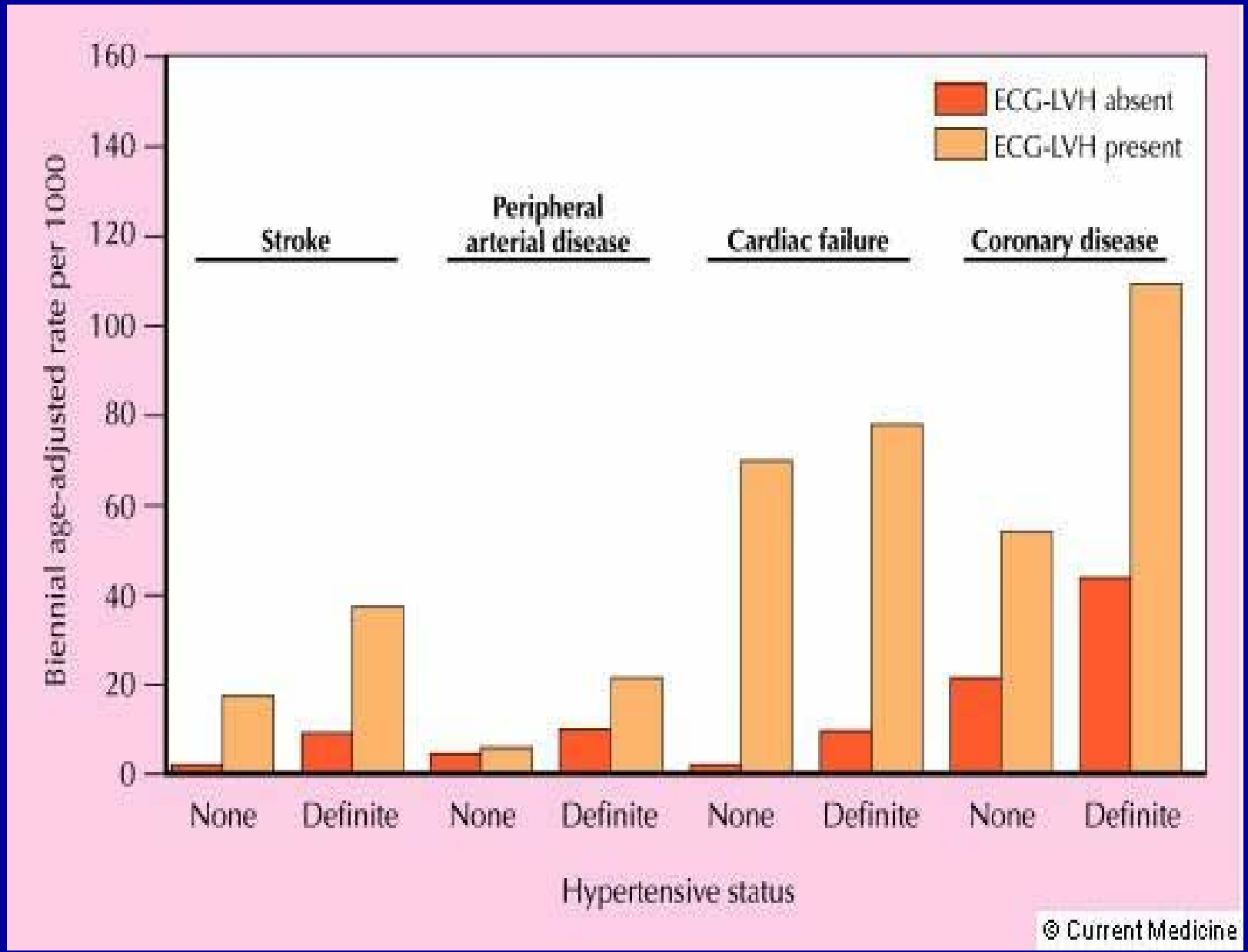
MI, stroke, CV death



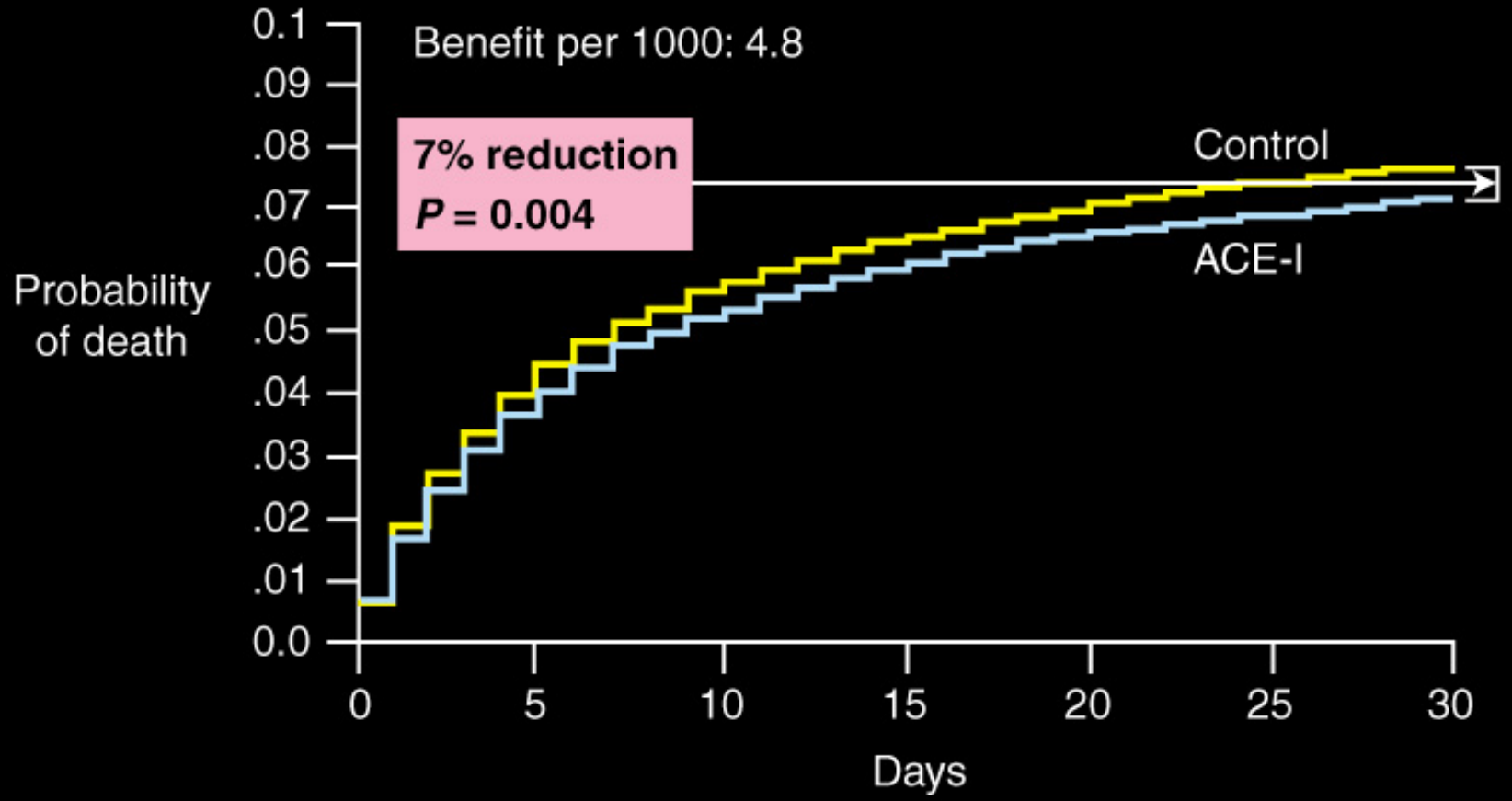
n = 9297

The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000;342:145-153.


10-Year probability of stroke, %
90
80
70
60
50
40
30
20
10
0
SBP (160–170 mm Hg) + + + + + +
Diabetes – + + + + +
Cigarette smoker – – + + + +
ECG-LVH – – – + + +
Atrial fibrillation – – – – + +
CV disease – – – – – +
Associated risk factors
© Current Medicine


160
140
120
100
80
60
40
20
0
Biennial age-adjusted rate per 1000
ECG-LVH absent
ECG-LVH present
Stroke
Peripheral arterial disease
Cardiac failure
Coronary disease
None
Definite
None
Definite
None
Definite
None
Definite
Hypertensive status
© Current Medicine

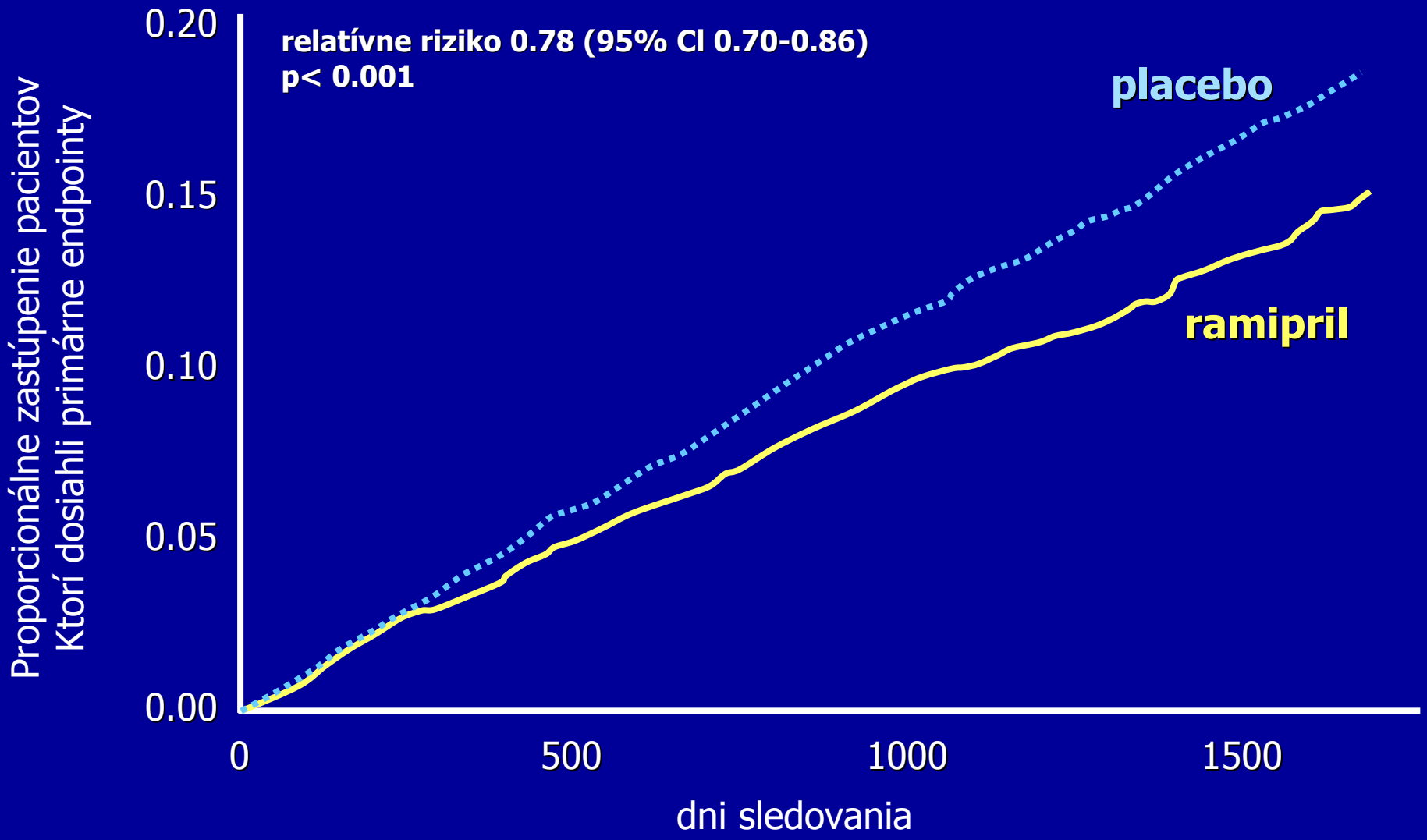
Mortality reduction with ACE inhibitors in acute MI



Enalapril, lisinopril, captopril

ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation*. 1998;97:2202-2212.

Kaplan-Meier kumulatívna krivka kombinovaných endpointov (IM, NCMP, KVS úmrtia) pacientov liečených ramiprilom vs. Placebo v štúdii HOPE

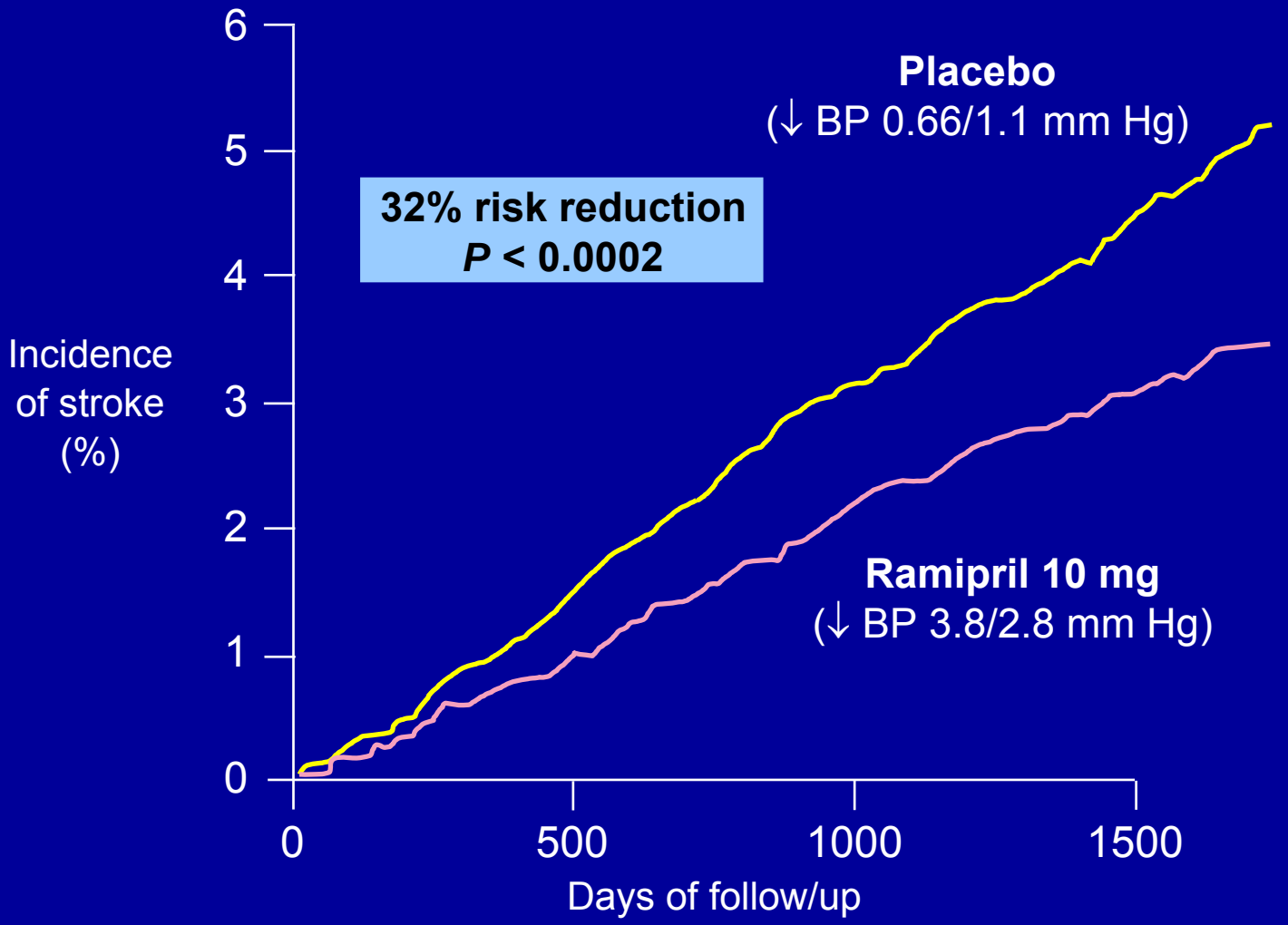


Int. J. Clin. Pract., vol. 55, No. 7, s. 453, 2001

Výsledky:
primárne sledované ukazovatele

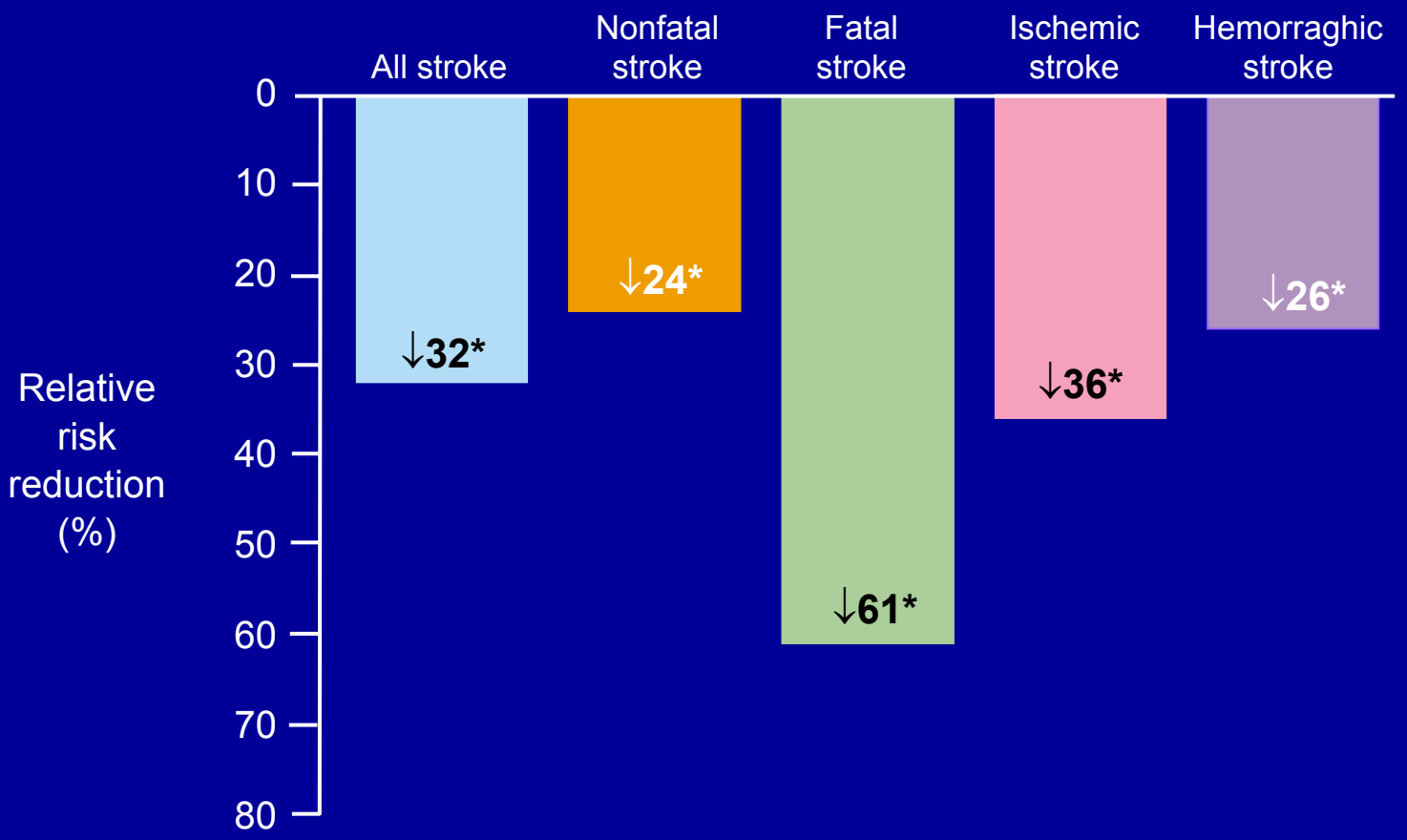
	ramipril (%)	placebo (%)	RR	95% CI	p
počet pacientov (n)	4645	4652			
IM + CV príhoda + KV úmrtie	14,1	17,7	0,78	0,70 - 0,86	0,000002
KV úmrtie	6,1	8,1	0,75	0,64 - 0,87	0,0002
IM	9,9	12,2	0,8	0,71 - 0,91	0,0005
CV príhoda	3,4	4,9	0,69	0,56 - 0,84	0,0003
Nie KV úmrtie	4,3	4,1	1,03	0,84 - 1,25	0,78
Mortalita	10,4	12,2	0,84	0,75 - 0,95	0,0058

HOPE: Reduction in stroke with ramipril 10 mg



Bosch J, et al. *BMJ*. 2002;324:699-702.

HOPE: Risk reduction by stroke type



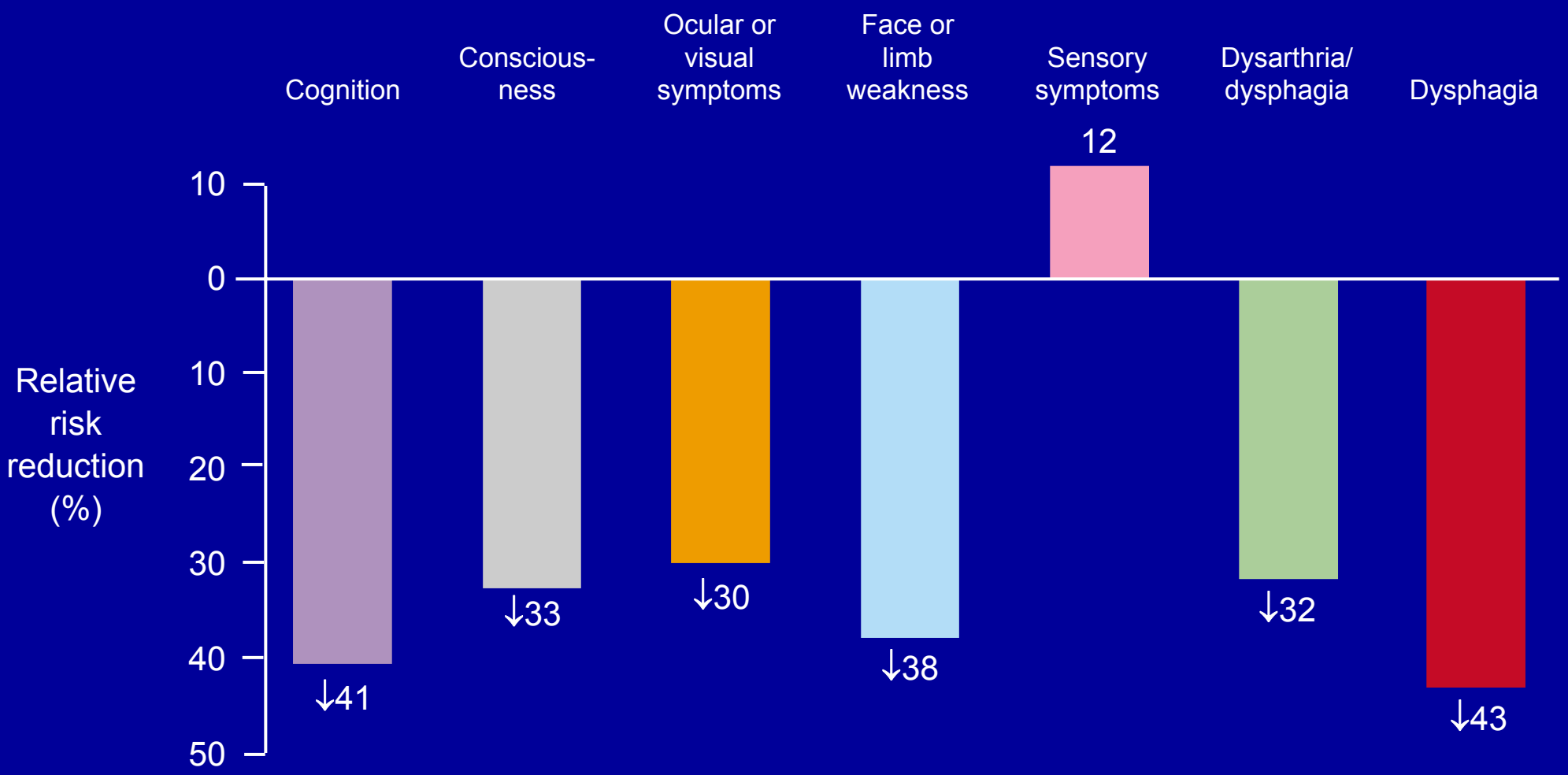
Beyond baseline therapy with:

- **Aspirin**
- **Other antiplatelet agent**
- **Ca^{++} channel blockers**
- **Statins**
- **β-blockers**
- **Diuretics**

*Statistically significant difference compared with placebo

Bosch J, et al. *BMJ*. 2002;324:699-702.

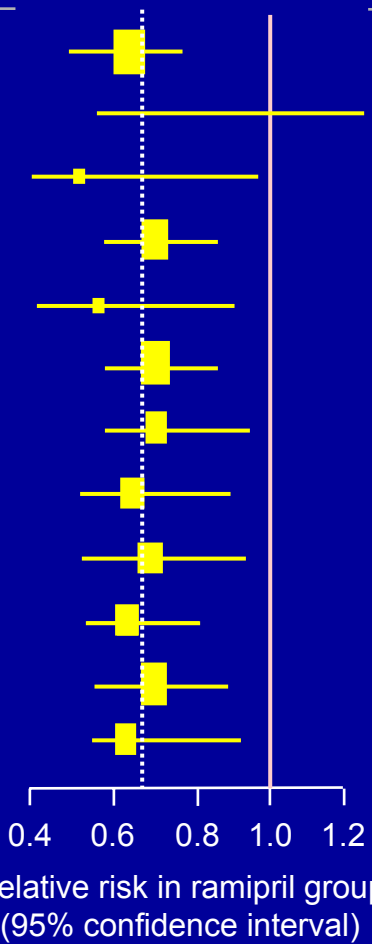
HOPE: Reduced risk of cognitive and motor changes



Bosch J, et al. *BMJ*. 2002;324:699-702.

HOPE: Stroke reduction in subgroups at highest risk

Subgroup	# of patients	Placebo stroke rate	*P**
Stroke/TIA–	8284	4.2%	0.21
Stroke/TIA+	1013	9.9%	
CVD–	1135	4.4%	0.38
CVD+	8162	4.9%	
CAD–	1820	6.1%	0.50
CAD+	7477	4.6%	
PAD–	5469	3.7%	0.79
PAD+	3828	6.4%	
HTN–	4942	4.0%	0.73
HTN+	4355	5.8%	
DM–	5720	4.1%	0.93
DM+	3577	6.1%	



*Interaction statistic derived from the χ^2 test

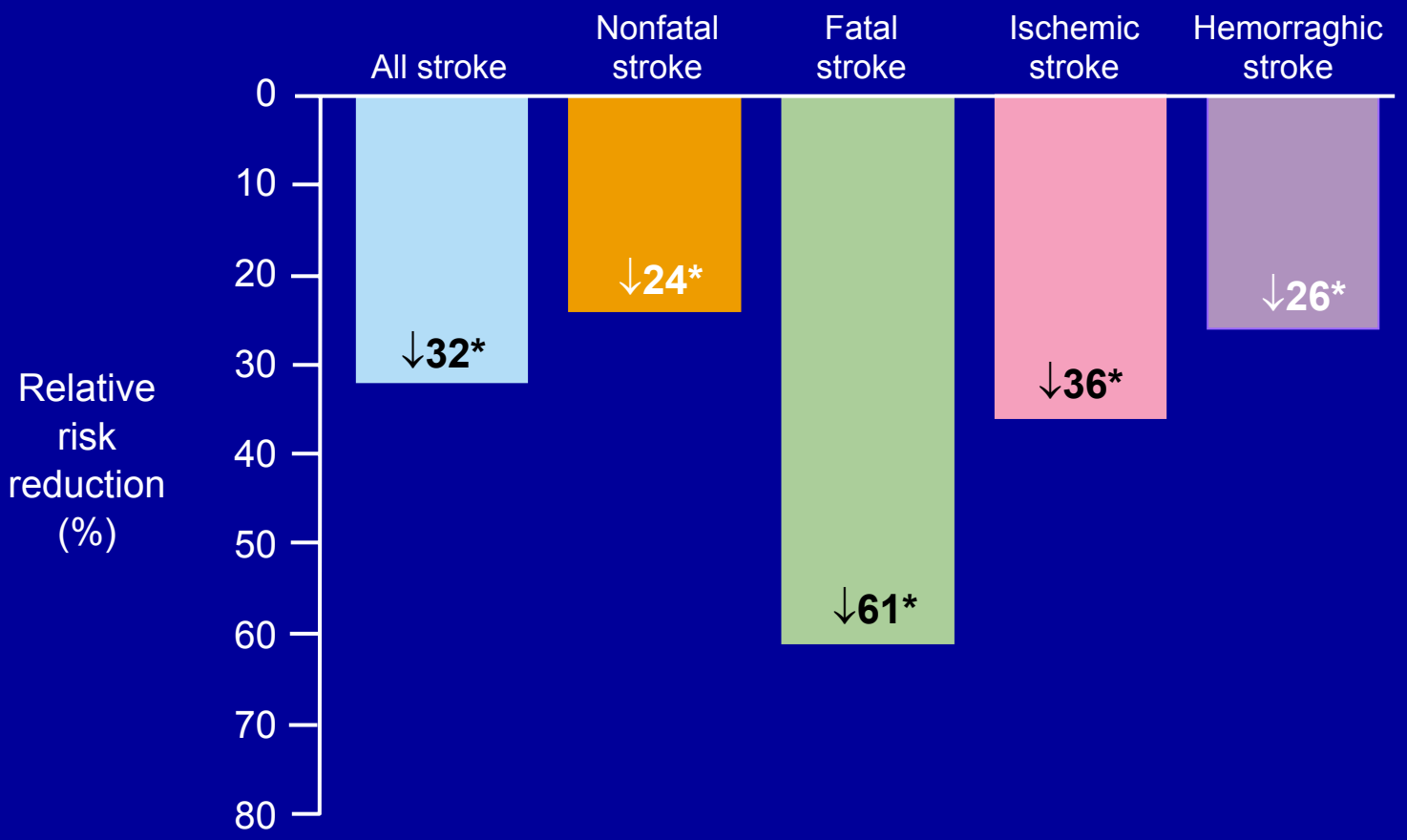
Bosch J, et al. *BMJ*. 2002;324:699-702.

HOPE: Stroke subanalysis - Main findings

- Ramipril significantly reduces risk of first/recurrent stroke
  - 32% for all strokes
  - 61% for fatal strokes
- Ramipril significantly reduces risk of cognitive and motor changes in patients with stroke
- Benefit is greater than that attributable to BP lowering (3.8/2.8 mm Hg)
  - Additional mechanisms likely involved

Bosch J, et al. *BMJ*. 2002;324:699-702.

HOPE: Risk reduction by stroke type



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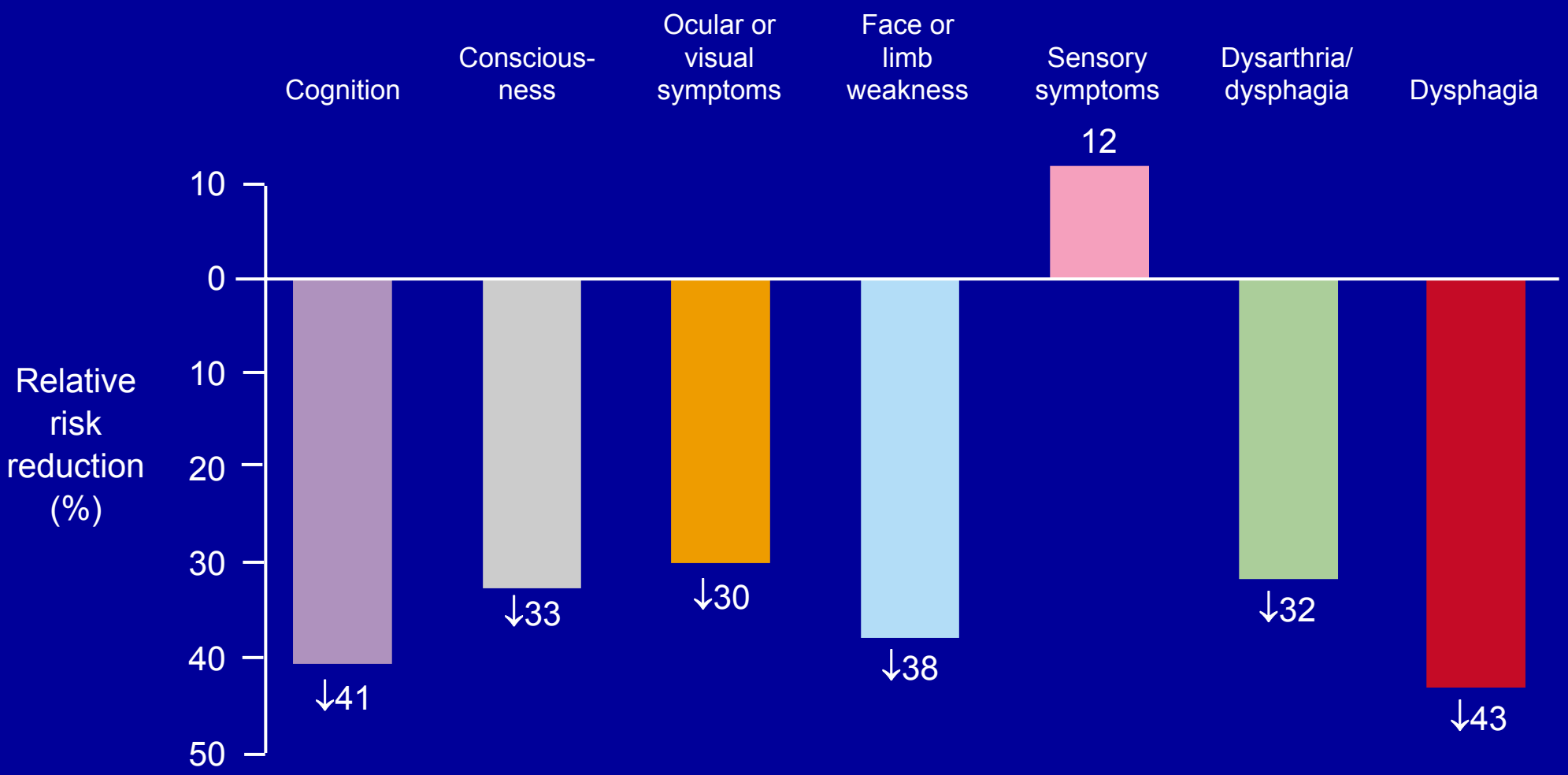
HOPE: Reduced risk of cognitive and motor changes

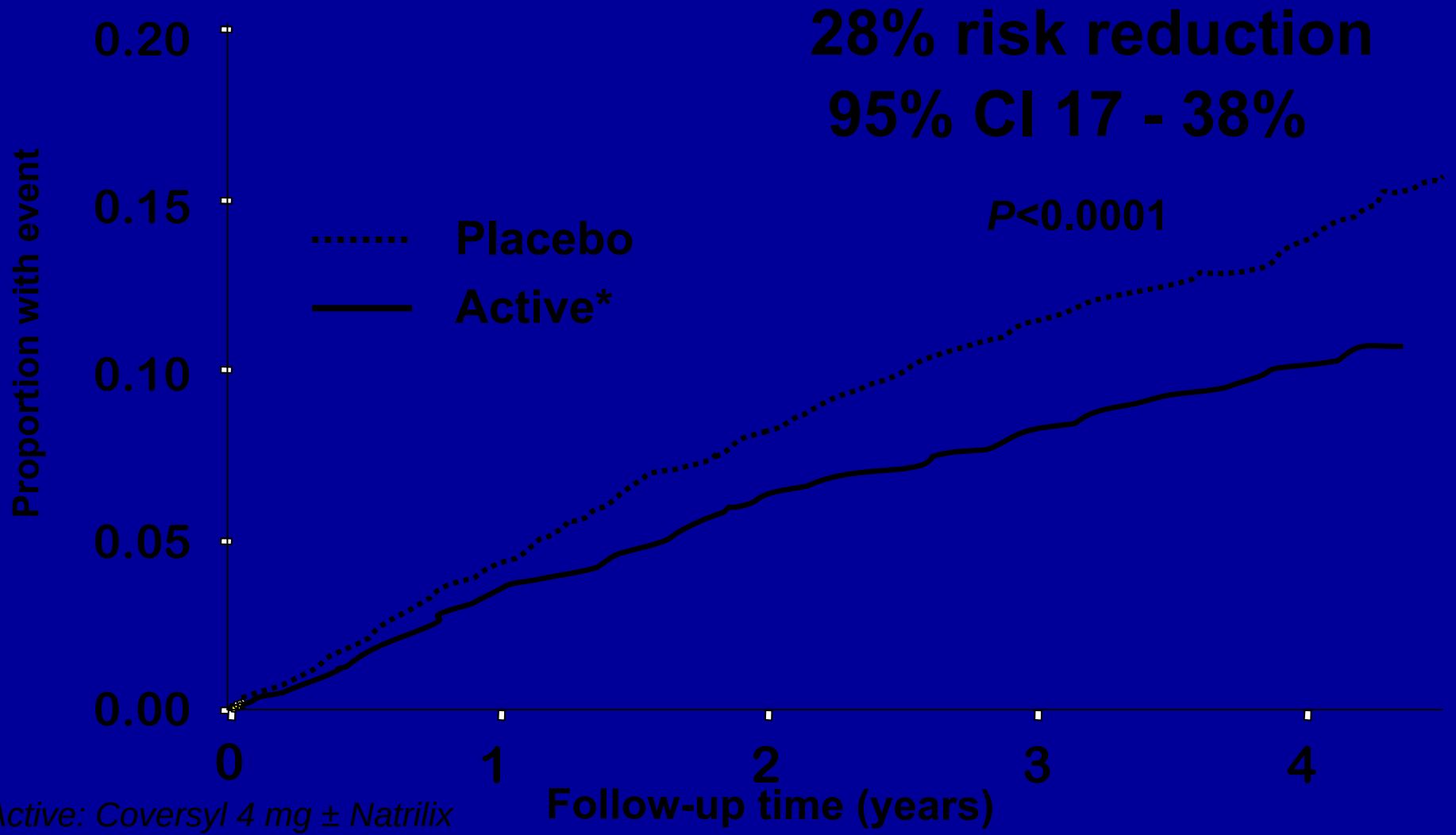


Bosch J, et al. *BMJ*. 2002;324:699-702.

Rationale Progress

- 50 million people suffer a stroke
- Strokes kill about 5 million people each year
- Cerebrovascular disease is the 2nd leading cause of death worldwide
- One in 5 survivors suffer another stroke within 5 years
- Need to identify safe and effective treatments for the prevention of recurrent stroke

Stroke risk reduction PROGRESS



Active: Coversyl 4 mg ± Natrilix

Reference: *Lancet* 2001; 358: 1033-41