Kam sa posunula liečba hypertenzie spojením amlodipínu s atorvastatínom

Ako sa zmenil pohľad na liečbu vysokého krvného tlaku a cholesterolu podľa ESC Odporúčaní KV prevencie z r. 2012?

MUDr. Peter Letavay

Prednáška podporená z edukačného grantu spoločnosti Pfizer

ESC odporúčania kardiovaskulárnej prevencie 2012

European Heart Journal
doi:10.1093/eurheartj/ehs092

JOINT ESC GUIDELINES

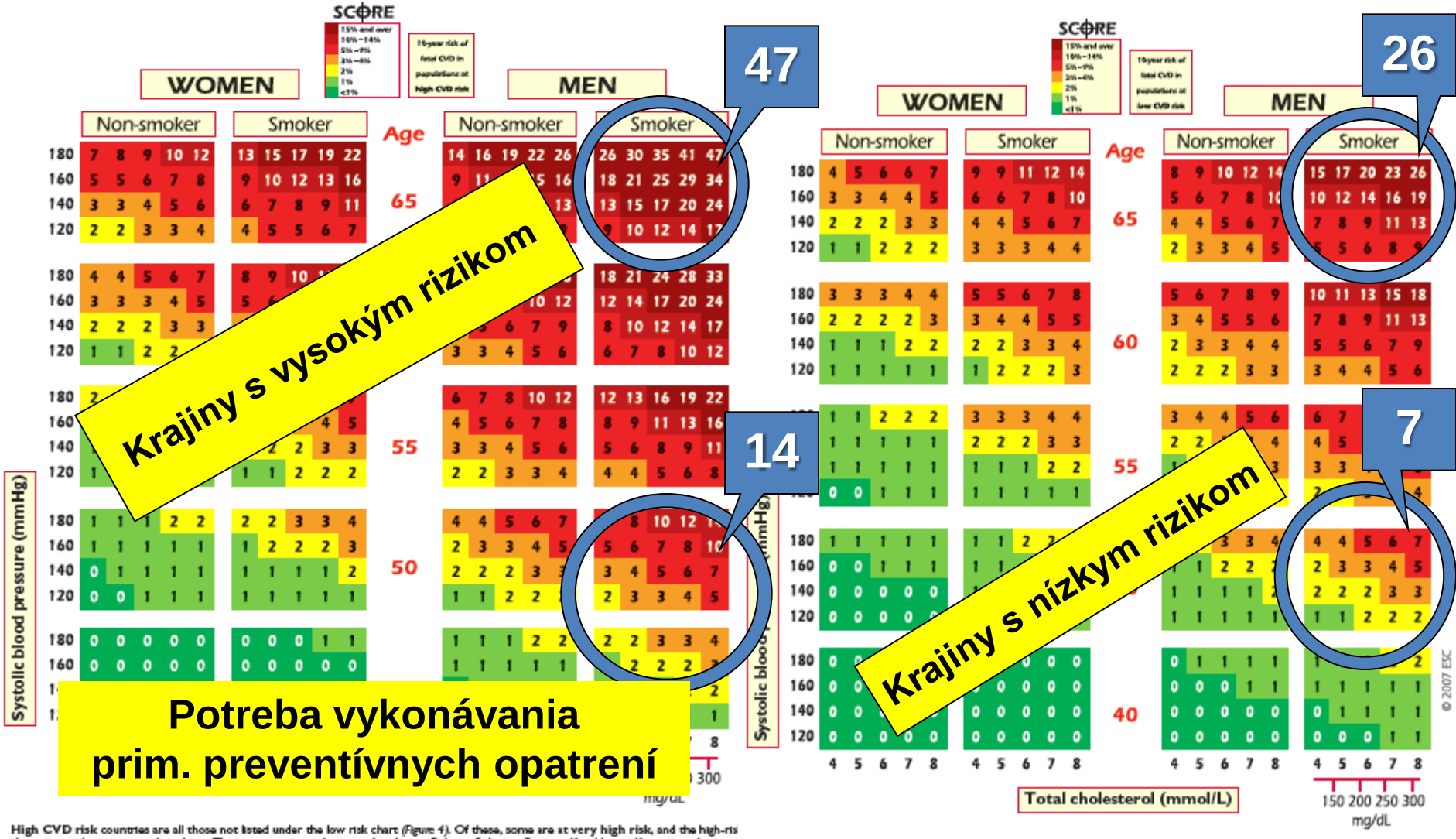
European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)†

Prečo nastáva potreba dôslednej prevencie KV ochorení na Slovensku?

ESC rozdelila krajiny EU na 2 skupiny: s vysokým a nízkym KV rizikom



Potreba vykonávania prim. preventívnych opatrení

High CVD risk countries are all those not listed under the low risk chart (Figure 4). Of these, some are at very high risk, and the high-risk chart may underestimate risk in these. These countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan.

Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Lukembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

Nástroje primárnej prevencie: nefarmakologické a farmakologické

Table 4 Guideline recommendations vs. achievements in patients with established coronary heart disease in EUROASPIRE III

Guideline recommendations	Proportions at goal
Smoking cessation among smokers	48
Regular physical activity	34
BMI <25 kg/m²	18
Waist circumference	
<94 cm (men)	25
<80 cm (women)	12
Blood pressure <140/90 mmHg	50
Total cholesterol <4.5 mmol/L (175 mg/dL)	49
LDL cholesterol <2.5 mmol/L (100 mg/dL)	55
Among patients with type 2 diabetes:	
Fasting glycaemia <7.0 mmol/L (125 mg/dL)	27
HbA_{1c} <6.5%	35

BMI = body mass index; HbA_{1c} = glycated haemoglobin; LDL = low-density lipoprotein.

- **Motivovať pacienta**
  - **cvičiť sa darí len v 34%**
  - **schudnúť len v 18%**

ESC odhaduje, že podiel modernej farmakolog. liečby na znižovaní KV mortality je 40%

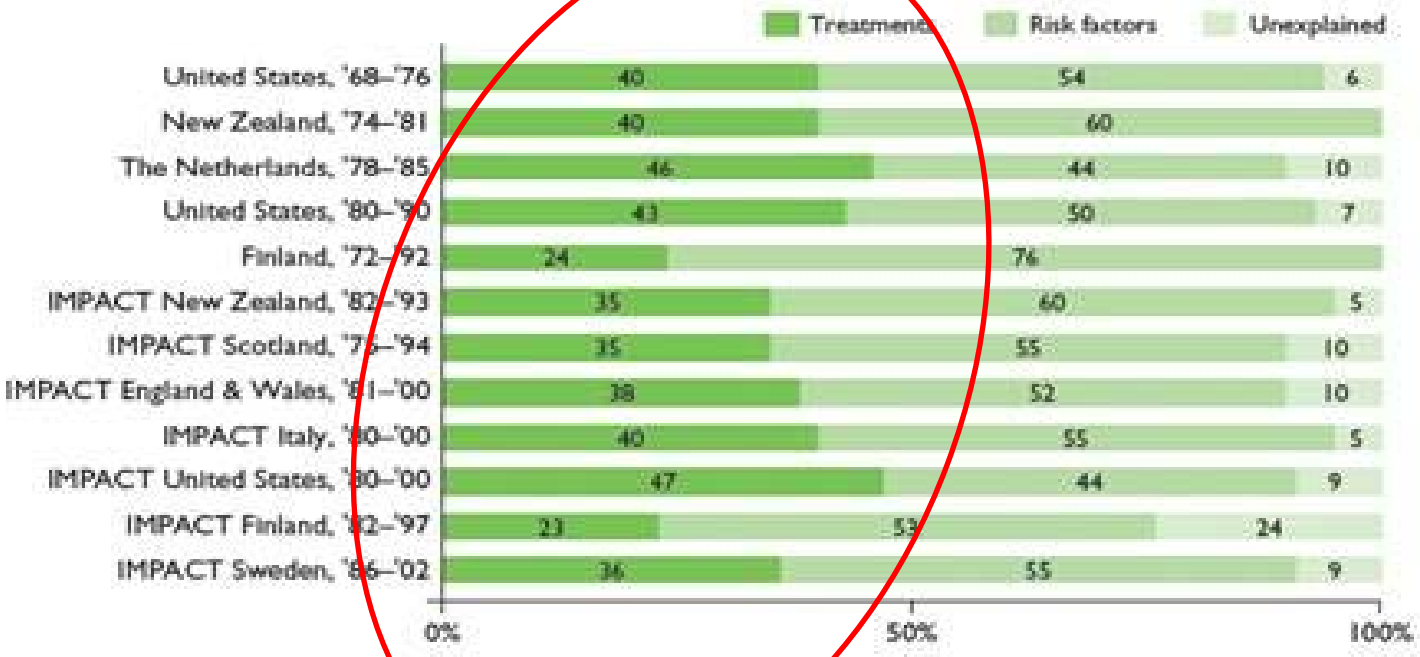


Figure 1 Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different populations (adapted from Di Chiara et al.[31])

Trend výraznejšej potreby farmakologických preventívnych opatrení

Ciele úspešnej prevencie KV ochorení podľa ESC

1. Zaistenie farmakoterapie, ktorá zníži mortalitu
2. Ovplyvnenie nielen TK, ale aj iných RF (lipidového spektra)
3. Zvýšenie adherencie k liečbe zjednodušením liečebného režimu

Existuje liečba, ktorá zahŕňa všetky tieto parametre ?

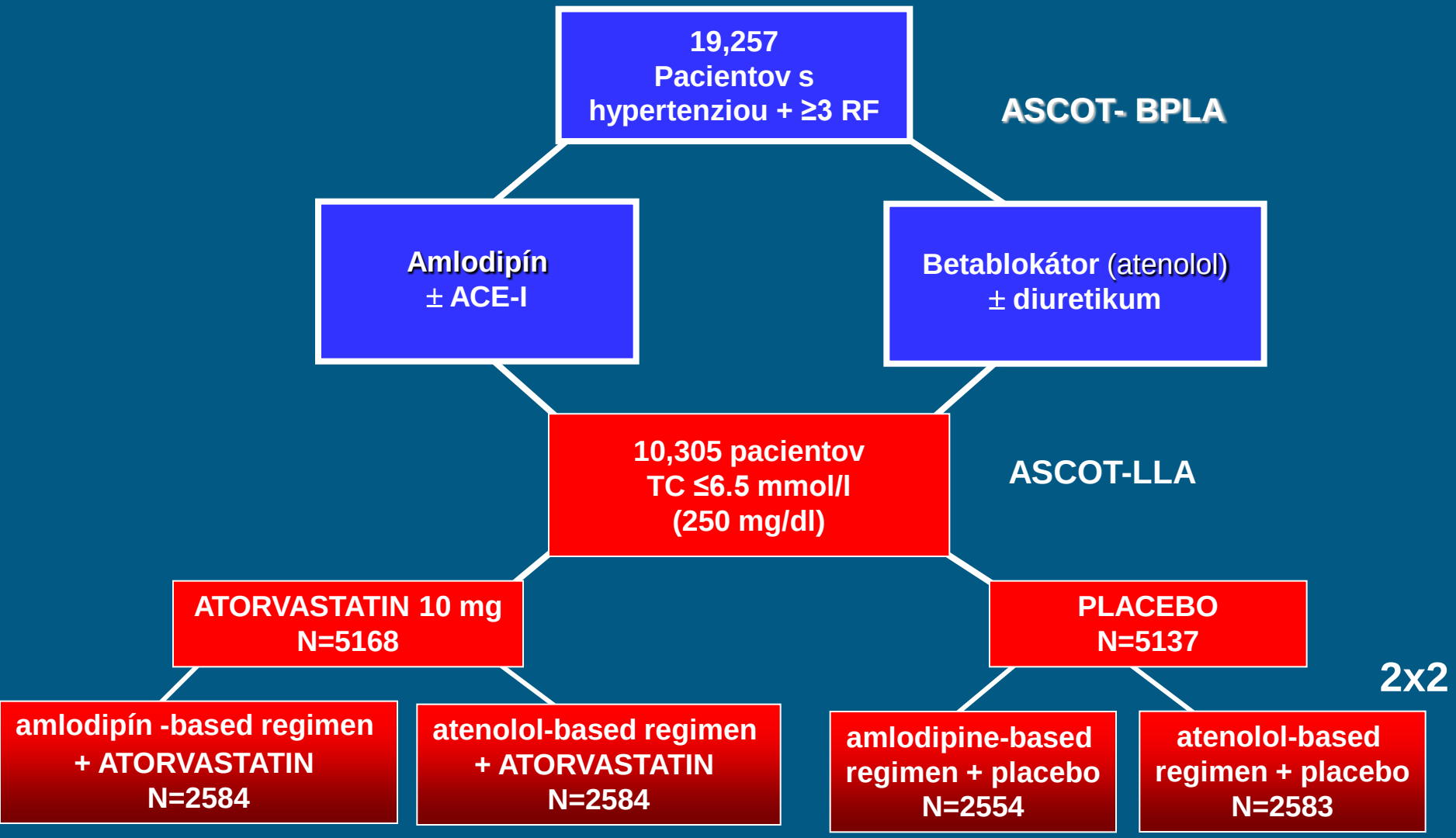
ASCOT : hypertonici s nízkym a stredným KV rizikom

- ASCOT - nezávislá, randomizovaná, multicentrická štúdia
- 19,342 pacientov s hypertenziou bez ICHS s minimálne 3 ďalšími RF
- Plánované : 5 ročné sledovanie

- **BPLA posudzovala** : efekt AH liečby a jej vplyv na kardiálnu morbiditu a mortalitu
- **Podštúdia ASCOT LLA** : porovnanie účinku atorvastatinu vs. placebo, ktoré boli pridané k AH liečbe u pac. s TC ≤6,5 mmol/l.

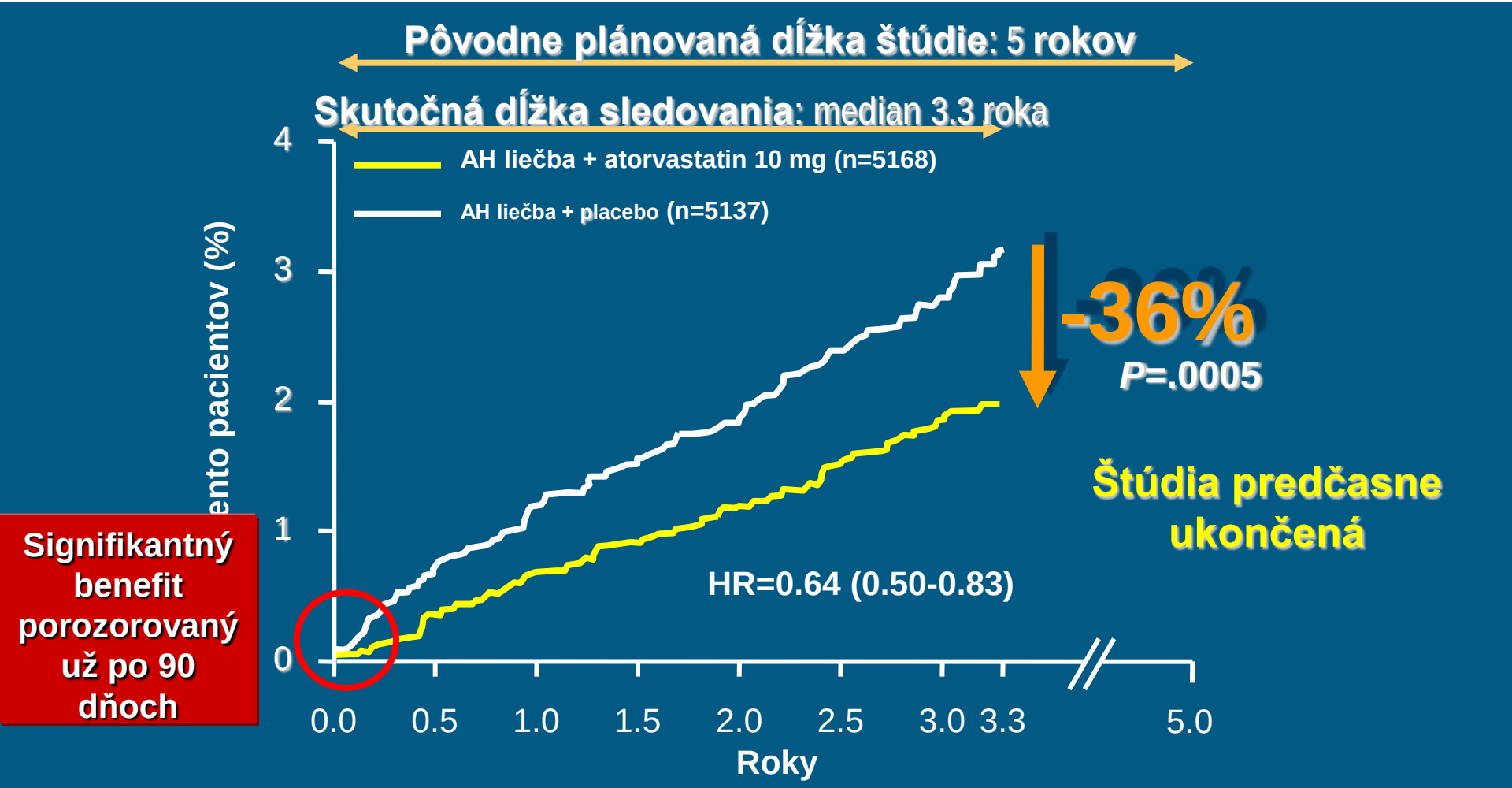
- **Primárny end point: nefatálny IM a fatálna ICHS**

Štúdia ASCOT: dizajn



Sever PS et al. *Lancet*. 2003;361:1149-1158.

ASCOT –LLA Atorvastatín + AH liečba : 36% redukcia nef. IM a fatálnej ICHS



Signifikantný benefit porozorovaný už po 90 dňoch

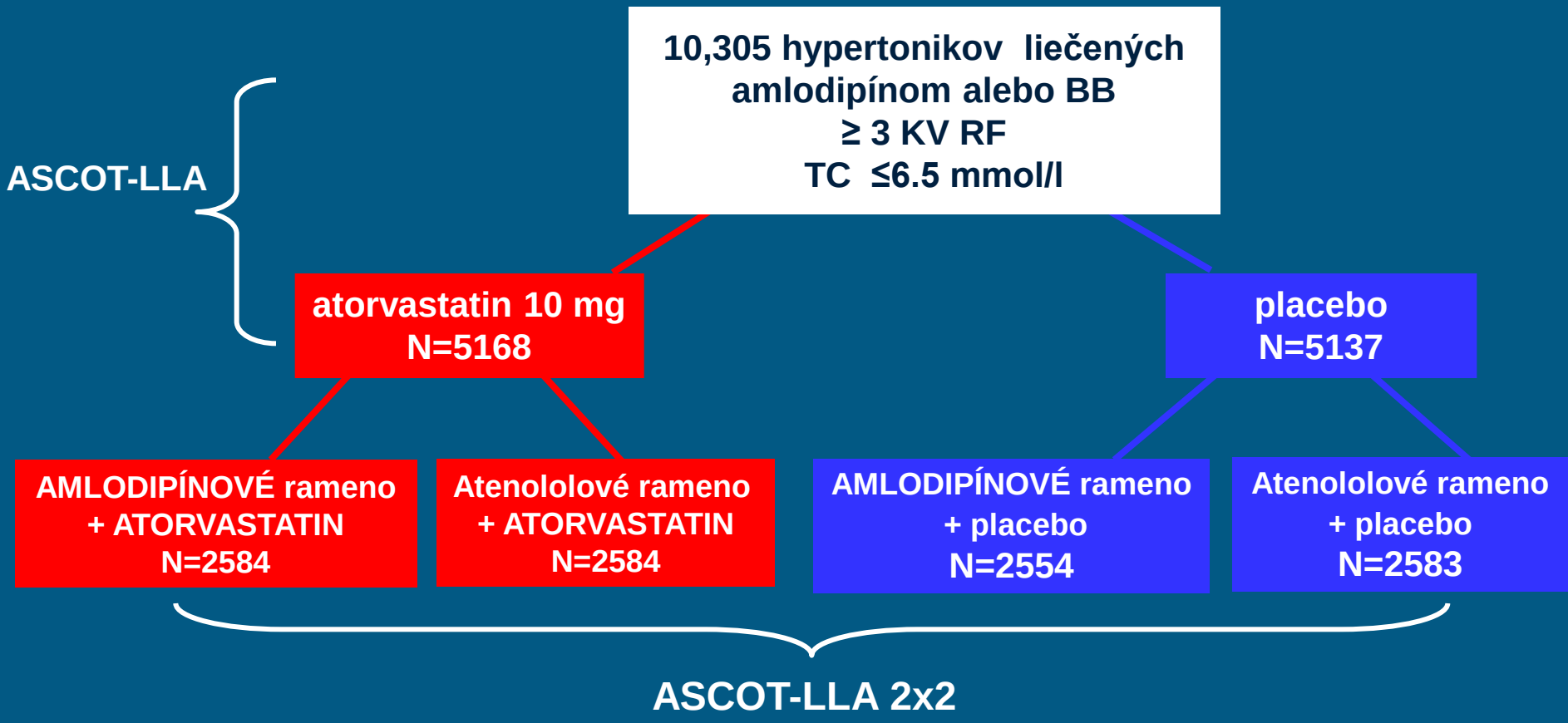
RRR=relative risk reduction.

Sever PS et al for the ASCOT Investigators. *Lancet.* 2003;361:1149-1158. Sever PS et al, for the ASCOT Investigators. *Am J Cardiol.* 2005;96:39F-44F.

ASCOT 2x2

Pridanie atorvastatínu k AH liečbe je prospešné!

... je výhodnejšie pridanie atorvastatínu k Amlo alebo BB ??

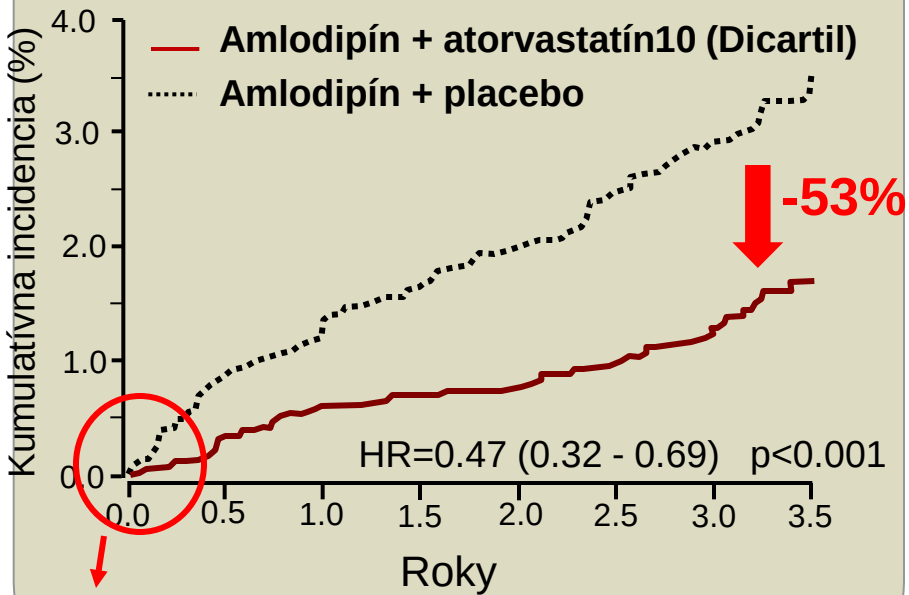


Sever PS et al. *Lancet*. 2003;361:1149-1158.

ASCOT 2x2: účinnosť závisí od antihypertenzíva, ku ktorému sa atorvastatín pridá

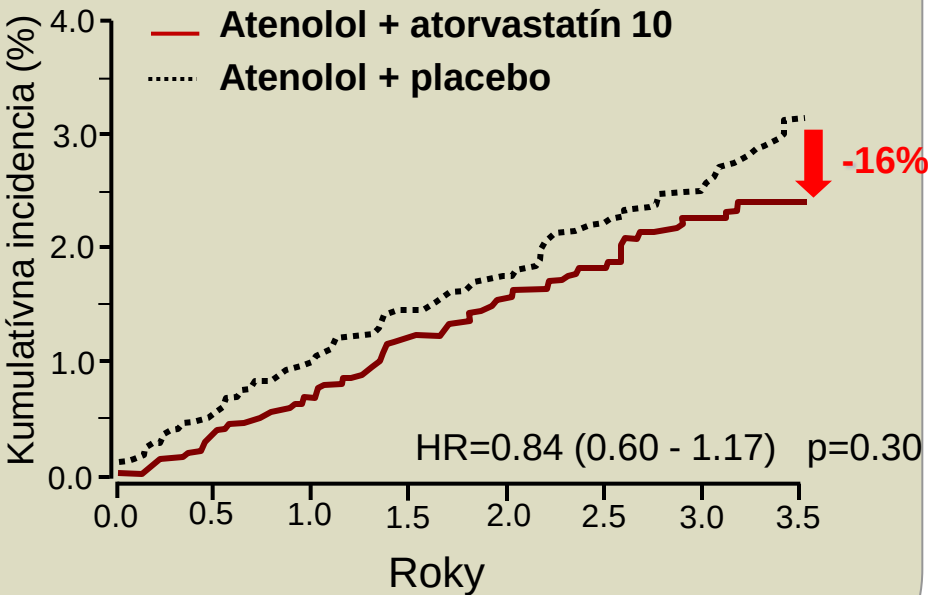
Primárny cieľ : nefatálny IM + fatálna ICHS

Liečba založená na amlodipíne



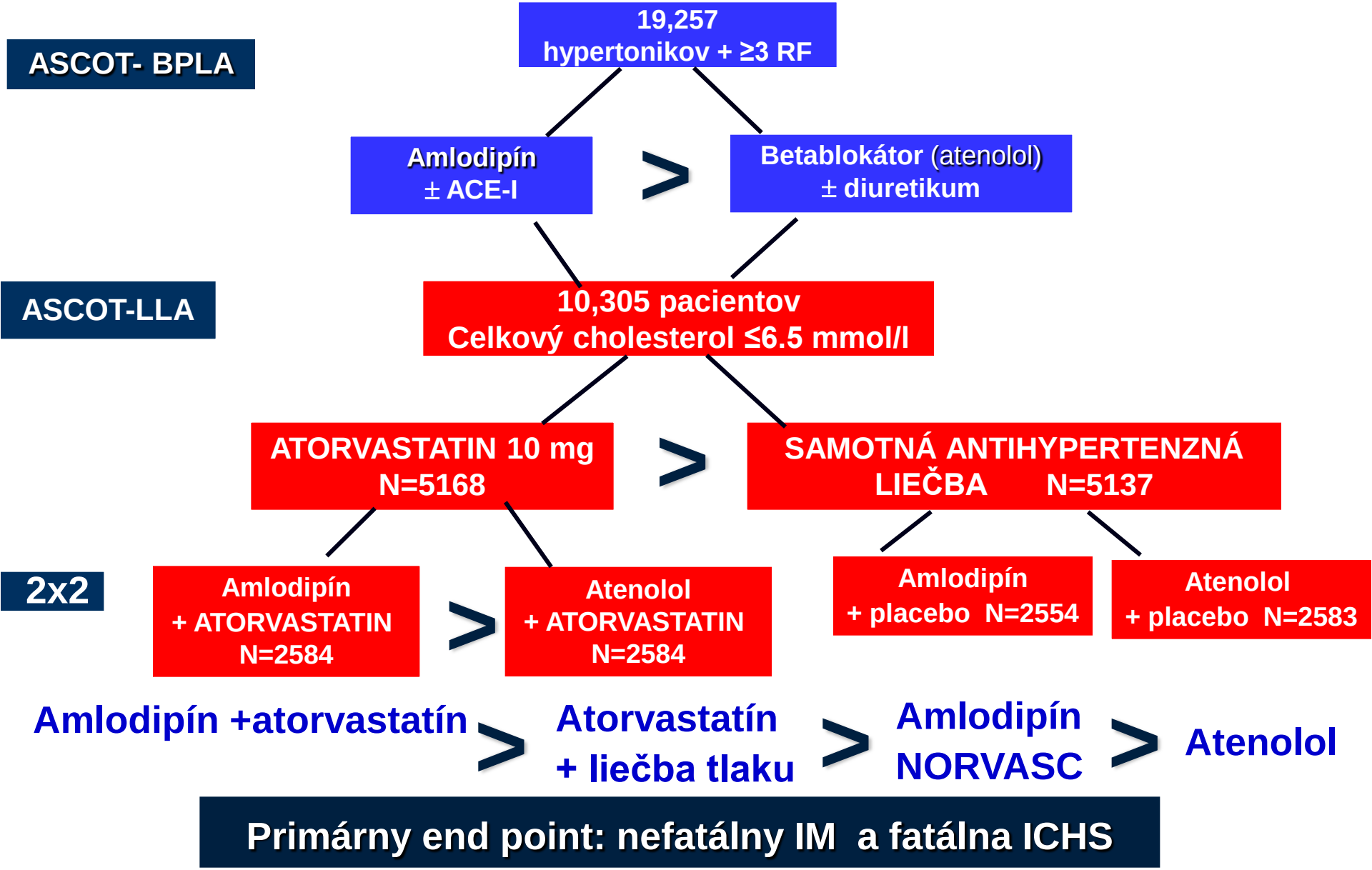
Včasný benefit pozorovaný už po 90 dňoch

Liečba založená na atenolole



Sever et al. Eur Heart J. 2006;27:2982-8.

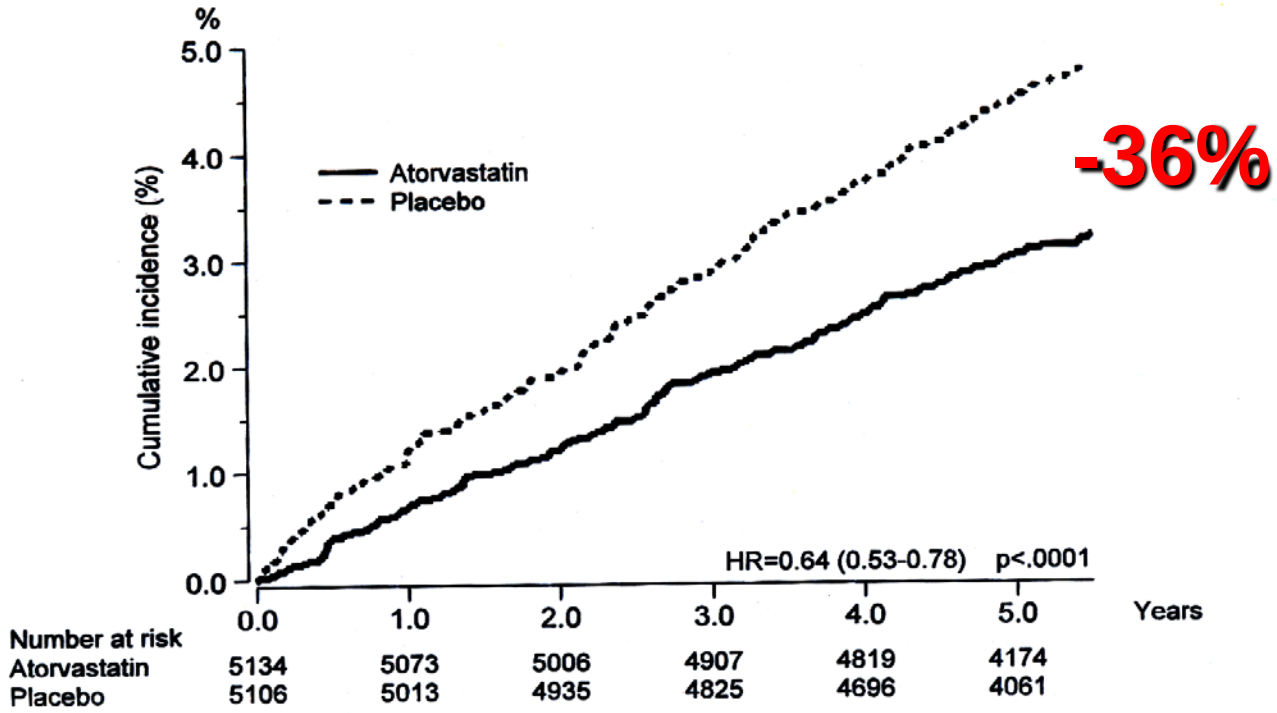
ASCOT - výsledky



ASCOT LLA po 5,5 rokoch

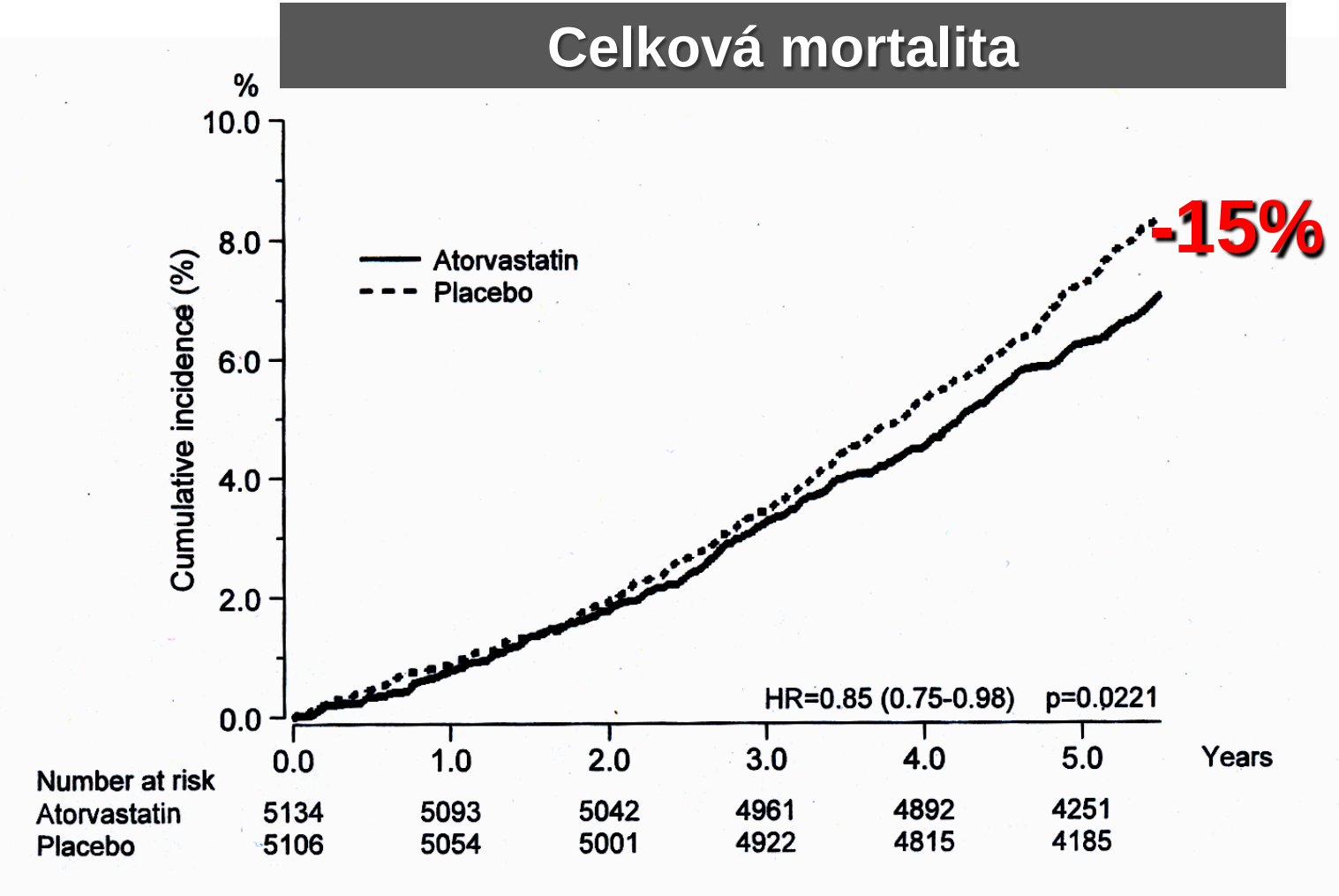
Všetkým pacientom bola po zastavení LLA po 3,3 roku ponúknutá statínová liečba, benefit včasnej statínovej liečby pretrvával aj po 5,5 rokoch

Nefatálny IM + fatálna ICHS

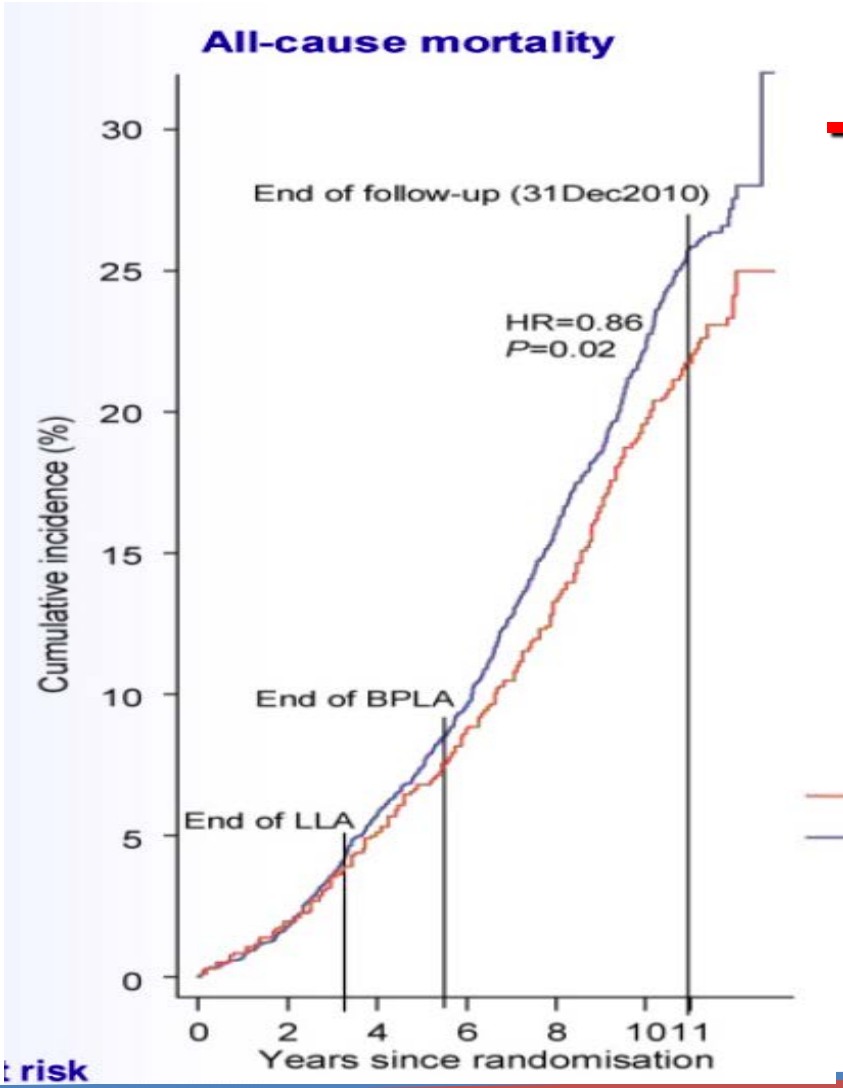


Eur H J 2008:29:499-508

ASCOT LLA po 5,5 rokoch



Po 11 rokoch: celková mortalita bola redukovaná o 14% u pacientov, ktorí boli včasne liečení statínom



-14%

Trend k benefitu na celkové prežívanie sa s narastajúcim časom liečby stal signifikantný

Anglo-Scandinavian ascot-11 Cardiac Outcomes Trial

European Heart Journal (2011 August)

ASCOT po 11 rokoch - záver

- **Atorvastatín pridaný k antihypertenzívnej liečbe preukázal signifikantný dlhodobý benefit na zníženie celkovej mortality**

- **Toto signifikantné zníženie mortality sa prejavilo napriek tomu, že po 3 rokoch mali takmer všetci pacienti v oboch ramenách statínovú liečbu**

Potvrdenie benefitu z včasného podania statínovej liečby

European Heart Journal (2011 August)

Štúdia CRUCIAL- dizajn:

Prospektívna, otvorená, kohortová štúdia s klastrovou randomizáciou

1.500 pacientov

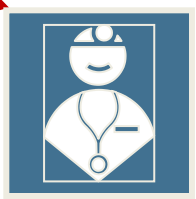
Vhodný pacient:

- **hypertonik**
- **bez známok ICHS**
- **TC ≤6.5 mmol/L**

klastrovaná randomizácia INVESTIGÁTOROV

(z dôvodu zachovania integrity bežnej praxe)

DICARTIL - fixná kombinácia amlodipín / atorvastatín (5/10 mg al.10/10 mg) + bežná liečba



BEŽNÁ LIEČBA samotná

(akékoľvek antihypertenzívum, hypolipidemikum, vrátane amlodipínu, atorvastatínu)

Každý pacient sledovaný 12 mesiacov

Primárny end-point:

- **Výpočet 10-ročného rizika vzniku koronárnej choroby po 12 mesiacoch liečby** pomocou Framinghamského skóre

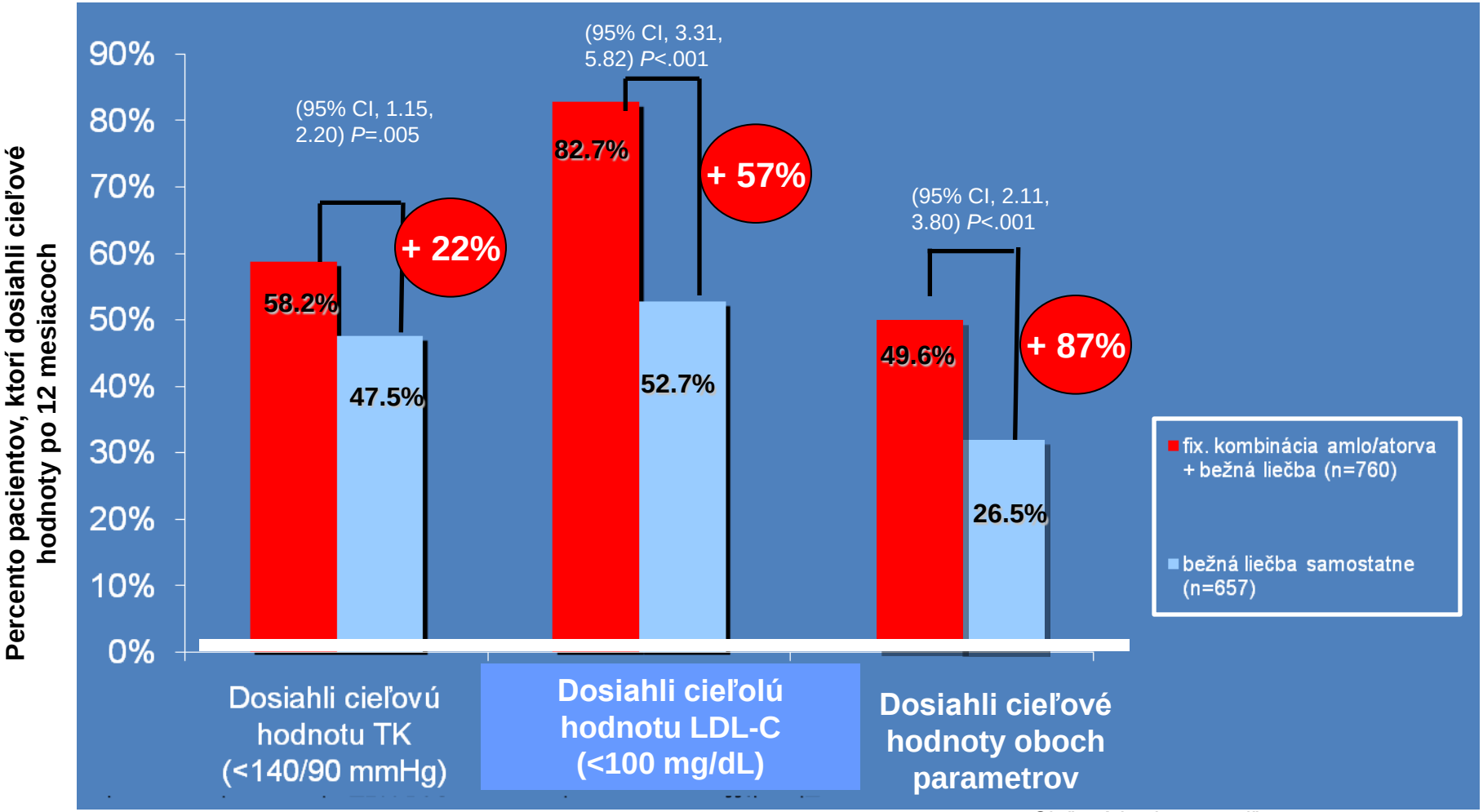
Sekundárny end-point:

- Dosahovanie cieľových hodnôt TK a cholesterolu

CRUCIAL trial. Curr Med Res Opin. 2011;27(4):821-833

Cieľové hodnoty TK a LDL-C

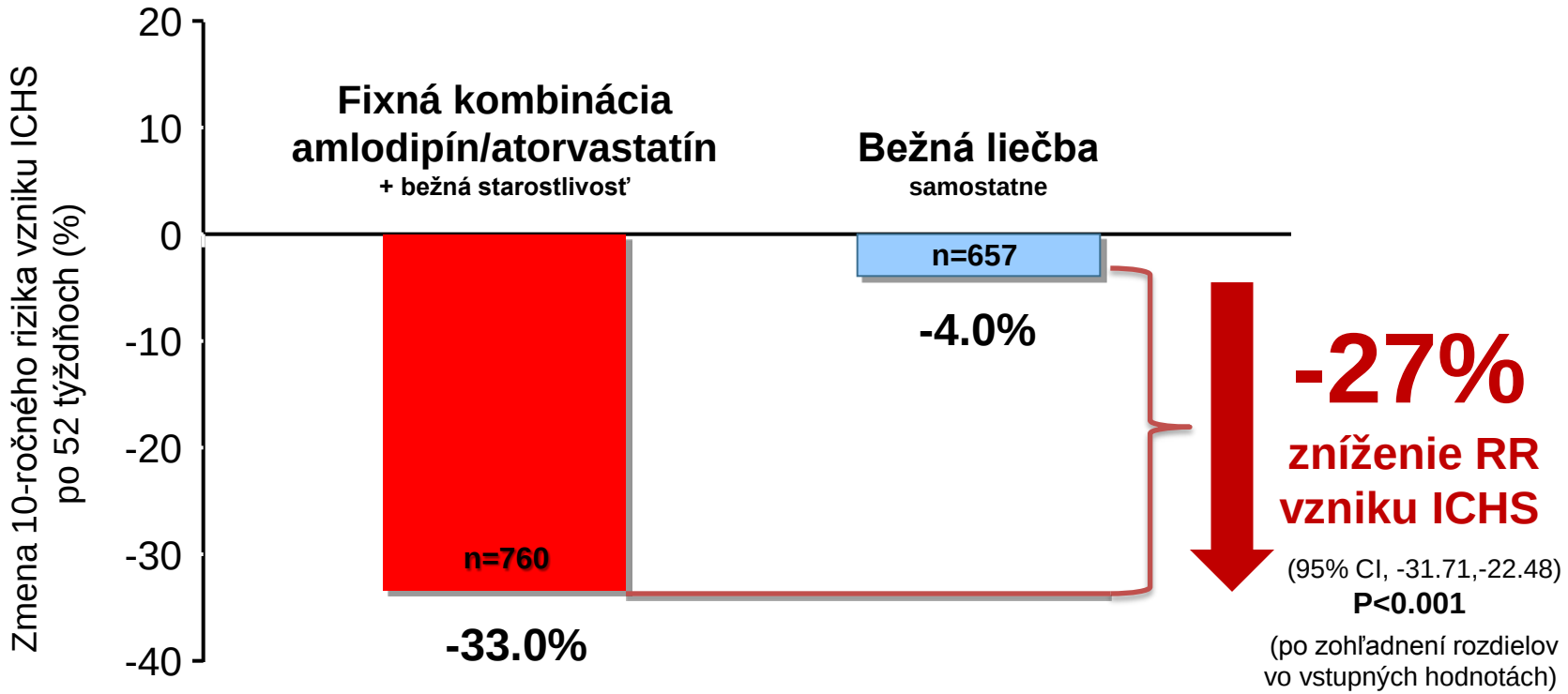
dosiahlo signifikantne viac pacientov na fixnej kombinácii amlodipín/atorvastatín ako na samostatnej bežnej liečbe



Cieľové hodnoty podľa JNC-7 a NCEP

CRUCIAL trial. Curr Med Res Opin. 2011;27(4):821-833

Štúdia CRUCIAL:
Fixná kombinácia amlodipín/atorvastatín znížila riziko vzniku ICHS o 27% v porovnaní s bežnou liečbou po 1 roku liečby



(merané Framinghamským skóre)

CRUCIAL trial. Curr Med Res Opin. 2011;27(4):821-833

Štúdia CRUCIAL - ZÁVER

- **Fixnou kombináciou amlodipín/atorvastatín**
  - **je možné dosiahnuť cieľové hodnoty tlaku a cholesterolu u takmer 2-násobného* počtu pacientov**

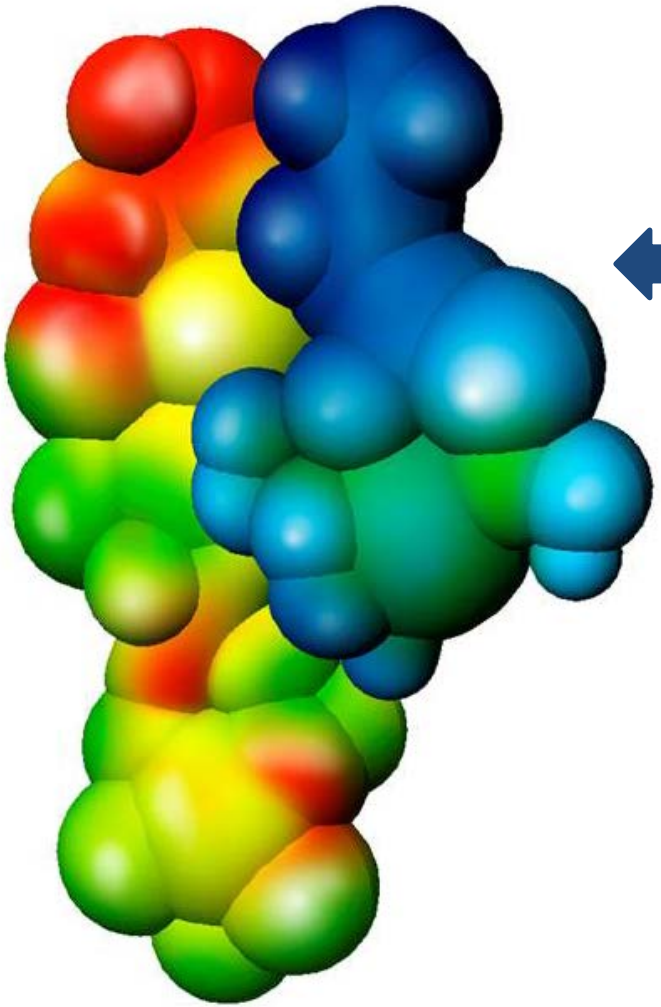
    HR = 1,87 (95% CI, 2.11, 3.80) P<.001

  - **Je možné dosiahnuť redukciu vzniku ICHS meranú Framinghamskou škálou o 27%†**

    †RRR=0,73 (95% CI, -31.71,-22.48) P<0.001

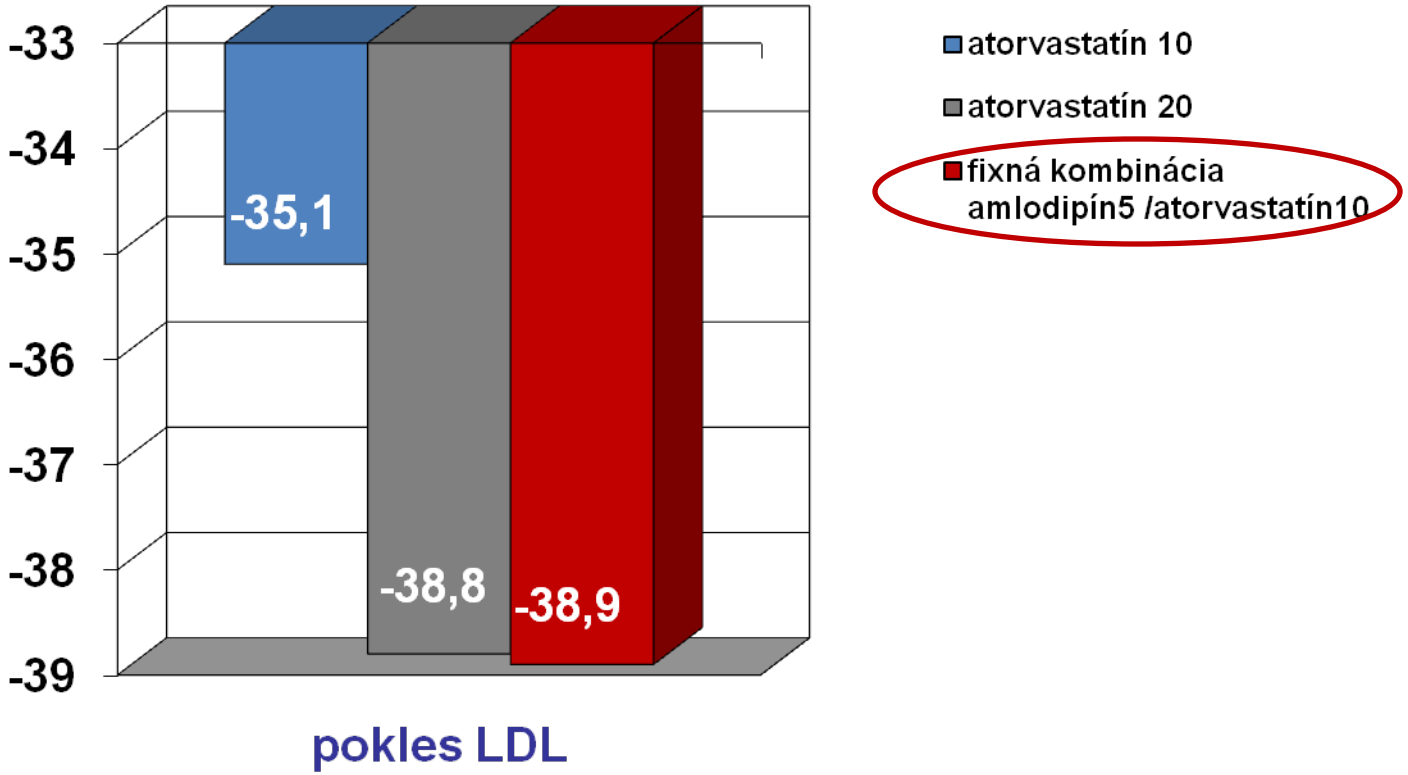
Synergický efekt molekúl amlodipínu a atorvastatínu

Atorvastatín
Negatívny náboj



Amlodipín
Pozitívny náboj

Synergický efekt originálnej fixnej kombinácie amlodipínu s atorvastatínom na LDL-C



Fixná kombinácia amlodipín 5 mg / atorvastatín 10 mg znižuje LDL-C na úrovni 20 mg atorvastatínu

Preston RA, The Respond Trial. J Clin Pharmacol 2007;47:1555-1569

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Manažment tlaku

Recommendations on blood pressure

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Lifestyle measures such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy products are recommended in all patients with hypertension and in individuals with high normal BP.	I	B	Strong	274, 285, 390–393
All major antihypertensive drug classes (i.e. diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and beta-blockers) do not differ significantly in their BP-lowering efficacy and thus should be recommended for the initiation and maintenance of antihypertensive treatment.	I	A	Strong	394
Beta-blockers and thiazide diuretics are not recommended in hypertensive patients with multiple metabolic risk factors increasing the risk of new-onset diabetes.	III	A	Strong	395, 396
In patients with diabetes, an ACE inhibitor or a renin–angiotensin receptor blocker is recommended.	I	A	Strong	397–399
Risk stratification using the SCORE risk chart is recommended as a minimal requirement in each hypertensive patient.	I	B	Strong	45, 400
In patients with grade 1 or 2 hypertension and at moderate total cardiovas… ug treatment may be delayed for several weeks, and in grade 1 hypertensive pa… months while trying lifestyle measures.	IIb	C	Weak	401
Systolic BP should be lowered to <140 mmHg (and diastolic BP <90 mmHg) in all hypertensive patients.	IIa	A	Strong	402–404
All hypertensive patients with established cardiovascular disease, or with type 2 diabetes, or with an estimated 10-year risk of cardiovascular death ≥5% (based on the SCORE chart) should be considered for statin therapy.	IIa	B	Strong	4…
Antiplatelet therapy, in particular low-dose aspirin, is recommended for hypertensive patients with cardiovascular events.	I	A	Strong	398
Antiplatelet therapy may be considered in hypertensive patients without a history of cardiovascular disease, but with reduced renal function or at high cardiovascular risk.	IIb	A	Weak	406–408

Statín patrí do liečby hypertenzie!

- CHD
- DM2
- SCORE>5

Manažment lipidov

Recommendations on management of hyperlipidaemia

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
The recommended target levels are <5 mmol/L (less than ~190 mg/dL) for total plasma cholesterol and <3 mmol/L (less than ~115 mg/dL) for LDL cholesterol for subjects at low or moderate risk.	I	A	Strong	457,458
In patients at high CVD risk, an LDL cholesterol goal <2.5 mmol/L (less than ~100 mg/dL) is recommended.	I	A	Strong	459–461
In patients at very high CVD risk, the recommended LDL cholesterol target is <1.8 mmol/L (less than ~70 mg/dL) or a ≥50% LDL cholesterol reduction when the target level cannot be reached.	I	A	Strong	459, 462, 463
All patients with familial hypercholesterolaemia must be recognized as high-risk patients and be treated with lipid-lowering therapy.	I	A	Strong	464, 465
In patients with an ACS, statin treatment in high doses has to be initiated while the patients are in hospital.	I	A	Strong	466–468
Prevention of non-haemorrhagic stroke: treatment with statins must be started in all patients with established atherosclerotic disease and in patients at high risk for developing CVD. Treatment with statins must be started in patients with a history of non-cardioembolic ischaemic stroke.	I	A	Strong	469, 470
Occlusive arterial disease of the lower limbs and carotid artery disease are CHD risk-equivalent conditions and lipid-lowering therapy is recommended.	I	A	Strong	471, 472
Statins should be considered as the first-line drugs in transplant patients with dyslipidaemia.	IIa	B	Strong	473
Chronic kidney disease (stages 2–5, i.e. GFR <90 mL/min/1.73 m^2) is acknowledged as a CHD risk-equivalent and the LDL cholesterol target in these patients should be adapted to the degree of renal failure.	IIa	C	Strong	474

ACS = acute coronary syndrome; CHD = coronary heart disease; CVD, cardiovasular disease; GFR = glomerular filtration rate; LDL = low-density lipoprotein.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

- Cieľom liečby je redukcia LDL
- Liekom voľby je statín

ESC odporúča: zlepšiť adherenciu pacientov - znížením počet tabliet

Recommendations on patients adherence

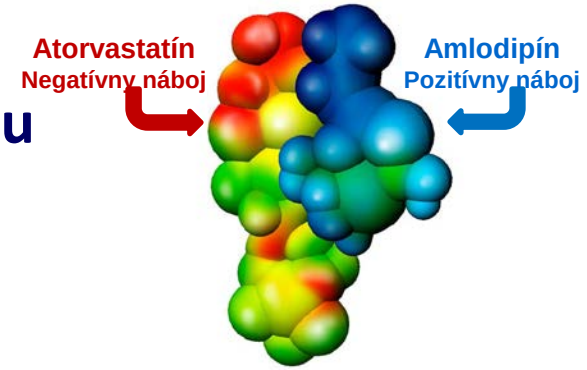
Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Physicians must assess adherence to medication, and identify reasons for non-adherence in order to tailor further interventions to the individual needs of the patient or person at risk.	I	A	Strong	518–520
In clinical practice, reducing dosage demands to the lowest acceptable level is recommended. In addition, repetitive monitoring and feedback should be implemented. If feasible, multisession or combined behavioural interventions should be offered in the case of persistent non-adherence.	IIa	A	Strong	520

ESC 2012
hlavné odkazy pre KV prevenciu

- **Zaistiť farmakoterapiu, ktorá zníži mortalitu**
- **Zahrnúť statín do liečby hypertenzie**
- **Zvýšiť adherenciu k liečbe zjednodušením liečebného režimu**

Existuje liečba, ktorá zahŕňa všetky tieto parametre ?

Originálna fixná kombinácia amlodipínu s atorvastatínom spĺňa tieto náročné kritériá pre KV prevenciu podľa ESC



- Zaistiť farmakoterapiu, ktorá zníži mortalitu
  - Dôkaz v štúdii ASCOT 2x2
- Zahrnúť statín do liečby hypertenzie
  - Fixná kombinácia antihypertenzíva a statínu
- Zvýšiť adherenciu k liečbe zjednodušením liečebného režimu
  - Dokázaná lepšia adherencia a dosahovanie cieľových hodnôt (štúdia Crucial)

ĎAKUJEM VÁM ZA POZORNOSŤ