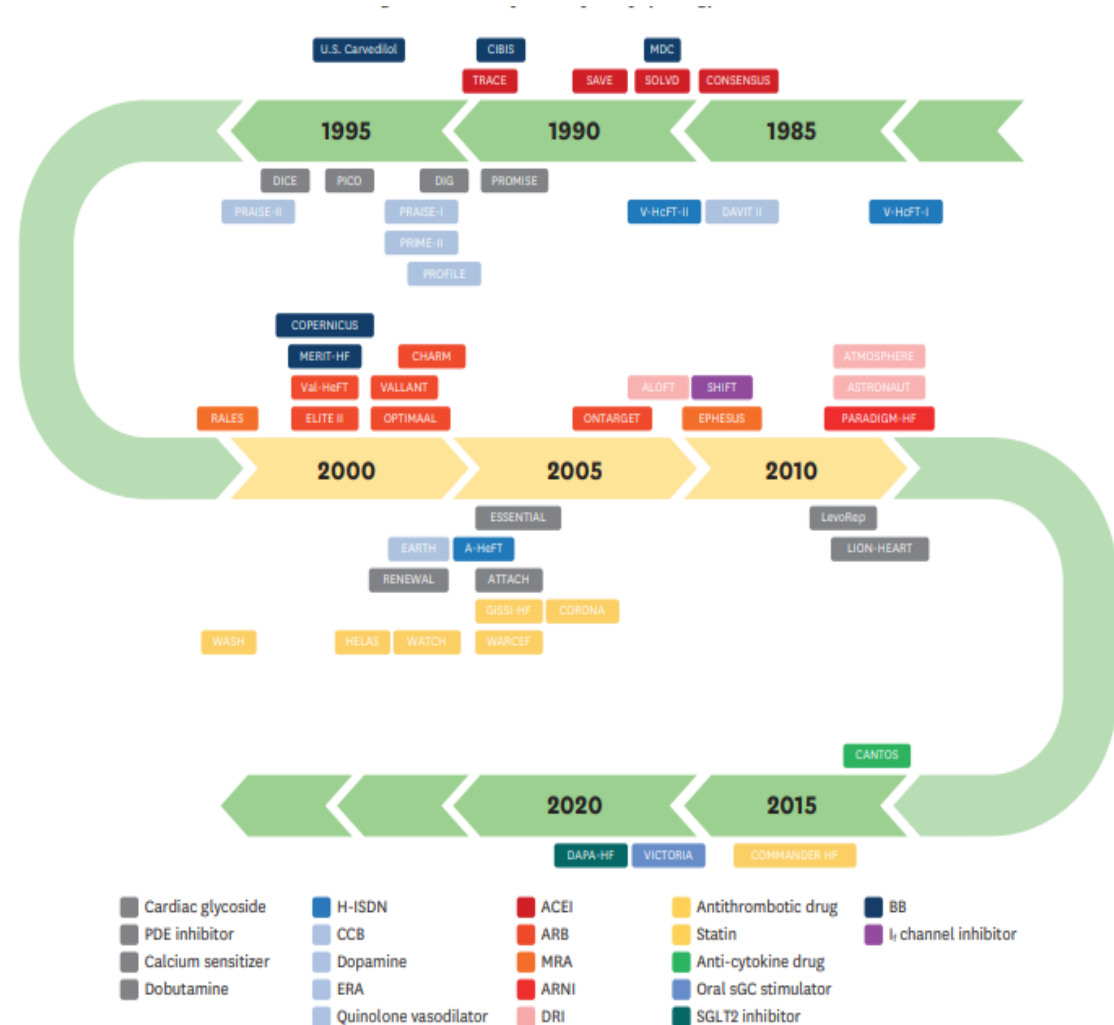


**Uloga kombinacije ramiprila i bisoprolola u
primarnoj i sekundarnoj prevenciji
kardiovaskularnih bolesti**

Istorijat primene kardiovaskularnih lekova



Zajedničko za ACE inhibitore i beta blokatore

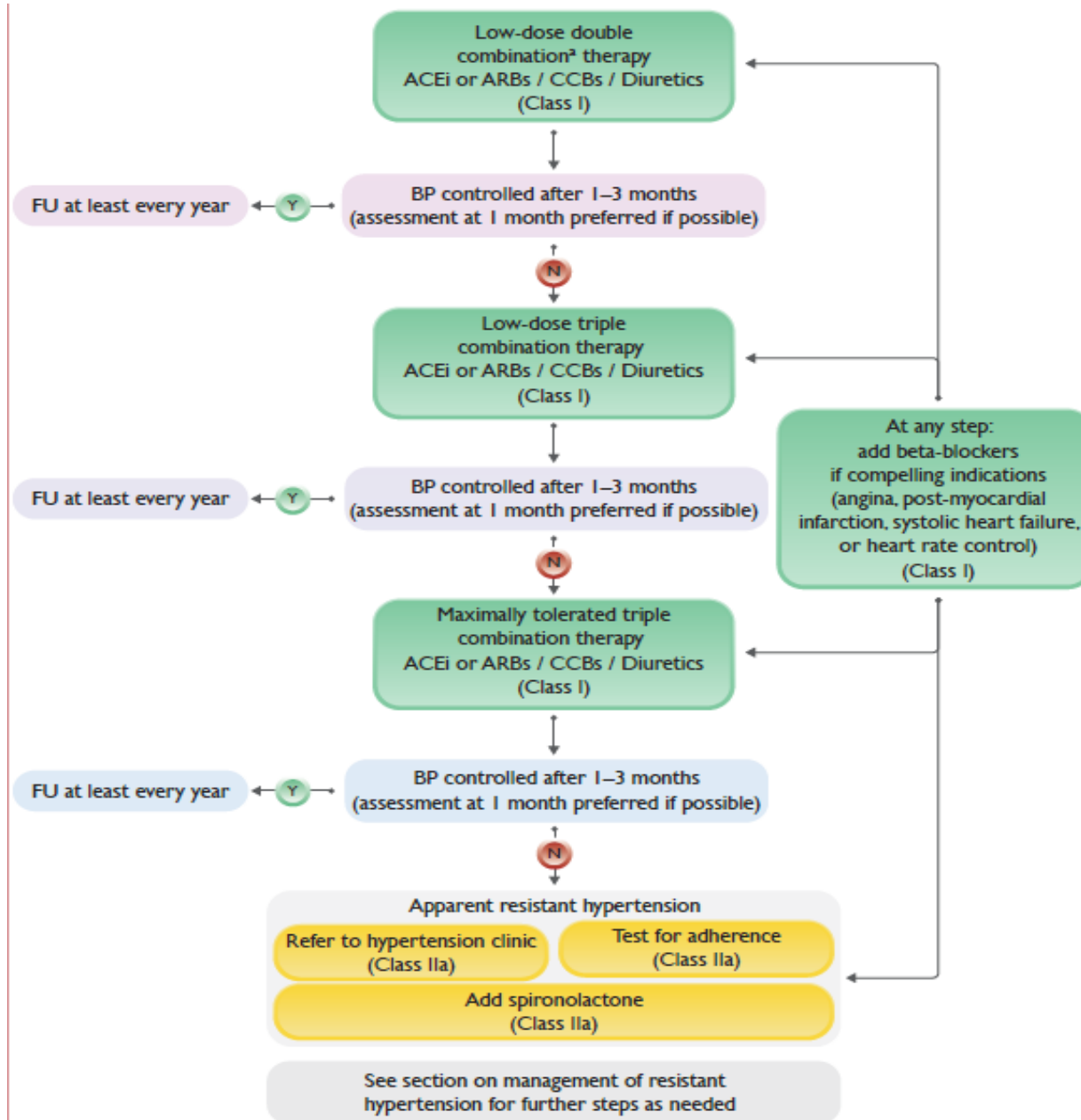
- Neuroendokrina terapija
- Efikasni u lečenju
 - ✓ Arterijske hipertenzije
 - ✓ Koronarne bolesti
 - ✓ Srčane insuficijencije

Farmakološko lečenje arterijske hipertenzije

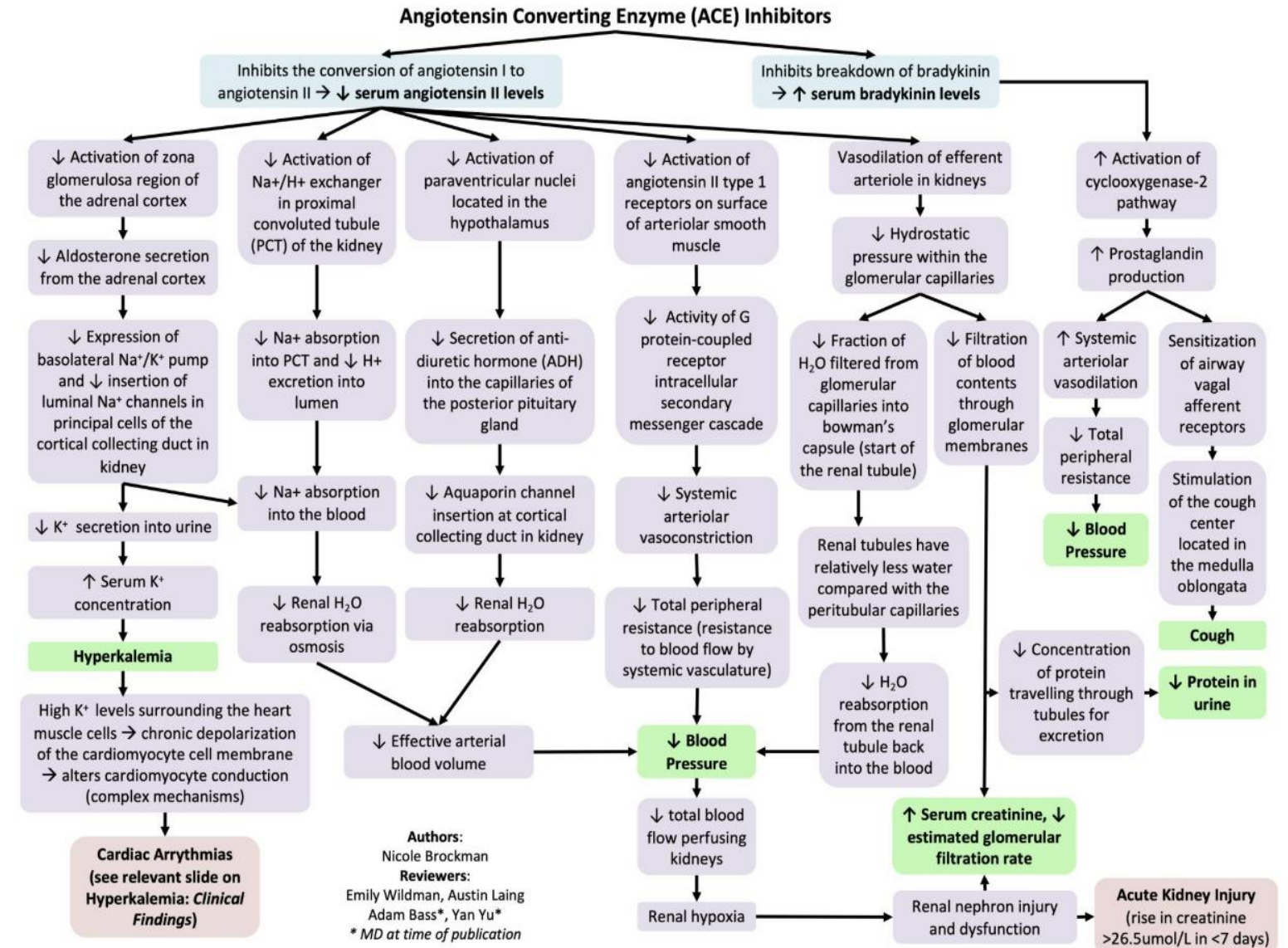
^aInitial monotherapy preferred

- Elevated BP category (120/70–139/89 mmHg)
- Moderate-to-severe frailty
- Symptomatic orthostatic hypotension
- Age ≥85 years

Ako pacijenti loše tolerišu dostignutu ciljnu vrednost 120-129 mmHg ili je nije moguće dostići potrebno je dostizanje najniže moguće (**as low as reasonably achievable ALARA principle**)



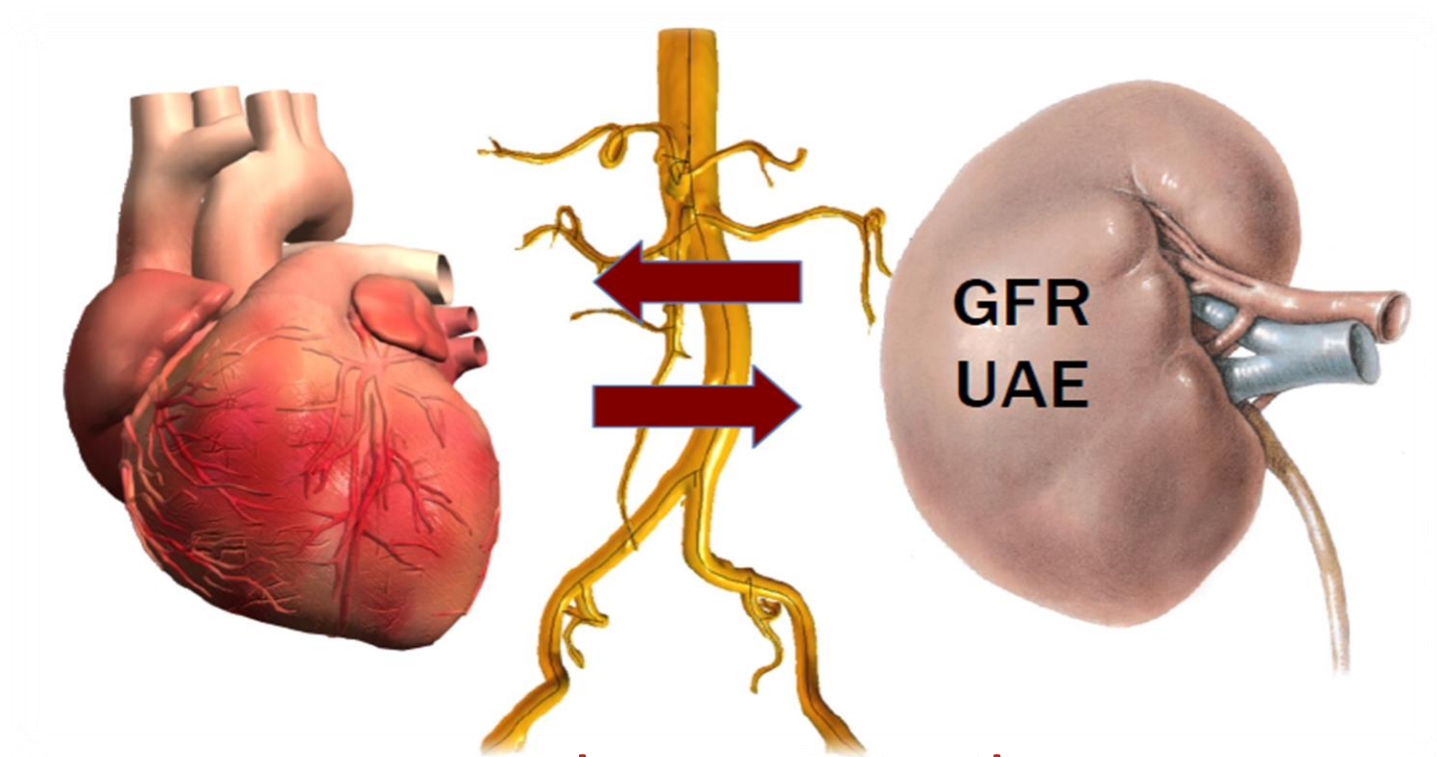
Mehanizmi delovanja ACE inhibitora



Efikasnost ramiprila u lečenju arterijske hipertenzije

11000 pacijenata sa blagom-umerenom esencijalnom hipertenzijom (7027 sa sistolno dijastolnom i 1881 pacijent sa ISH)

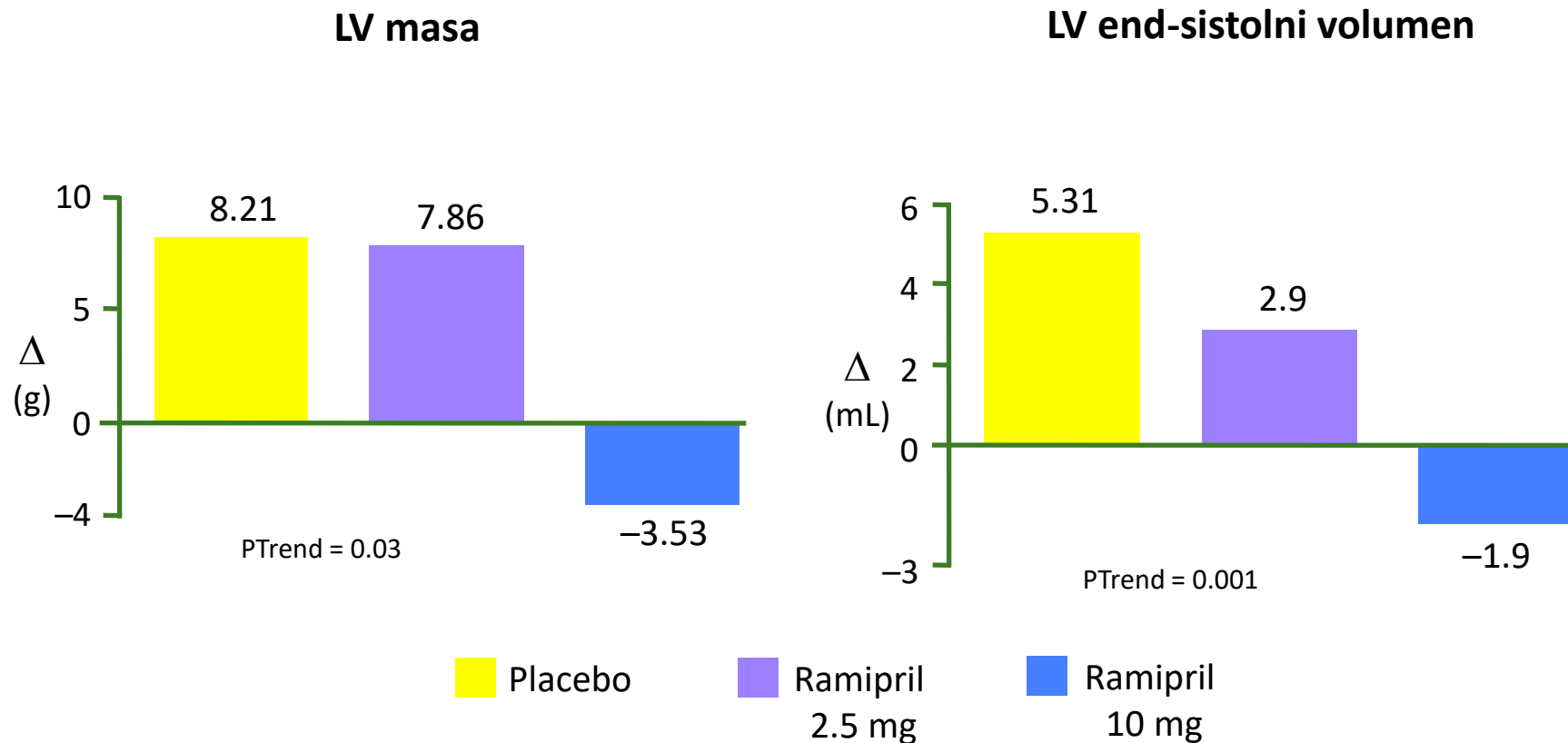
	Sistolno/dijastolna	Izolovana sistolna
Redukcija vr pritiska		
sistolni	-21,9	-17.8
dijastolni	-13.8	-3.3
Pacijenti koji su odgovorili na terapiju (%)		
sredovečni	86	71,8
stariji	87	64



Uloga ramiprila
u regresiji oštećenja ciljnih organa

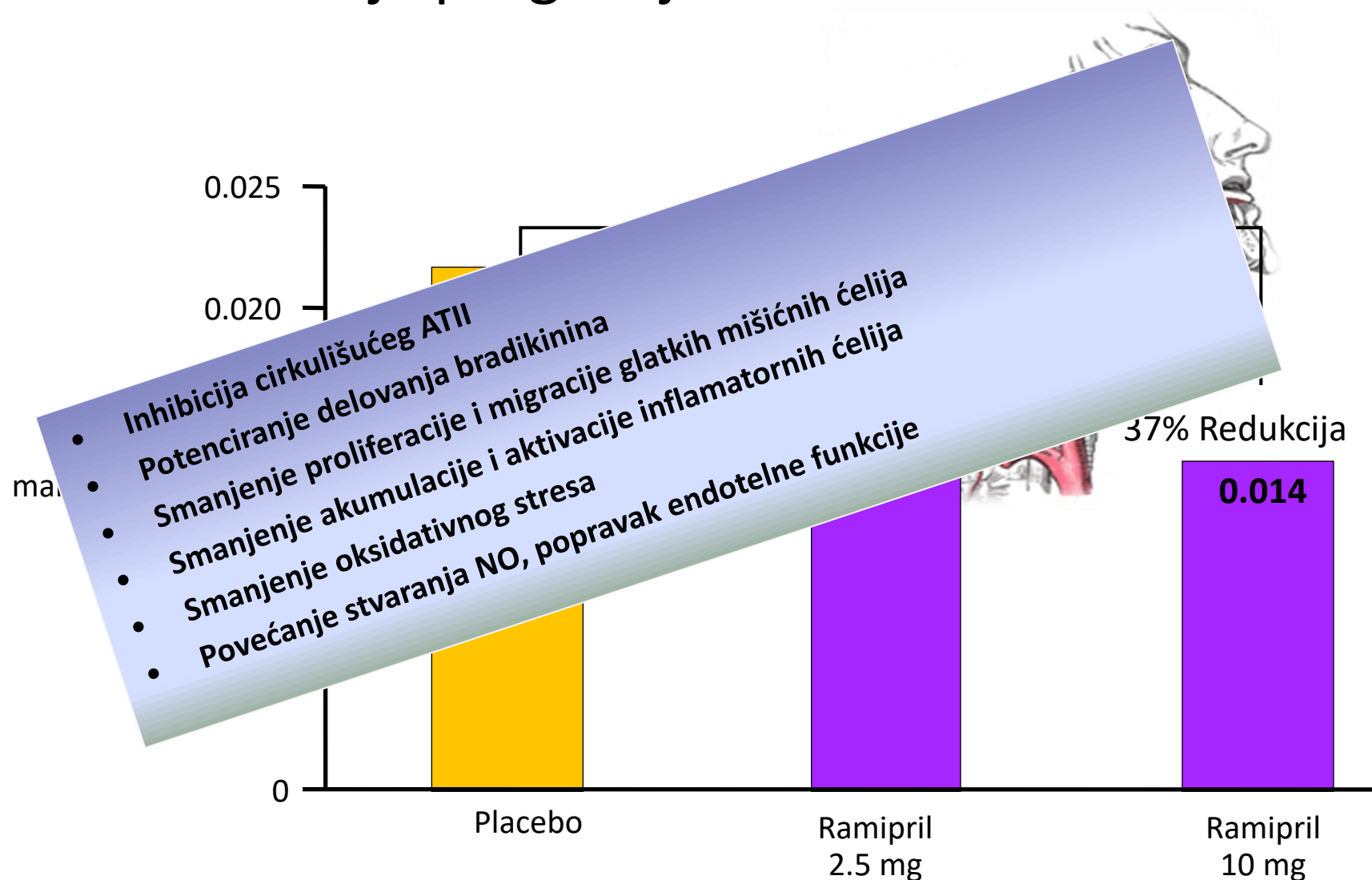
HOPE: dozno zavistan uticaj na masu i funkciju leve komore

N = 446 pts, 4 godine

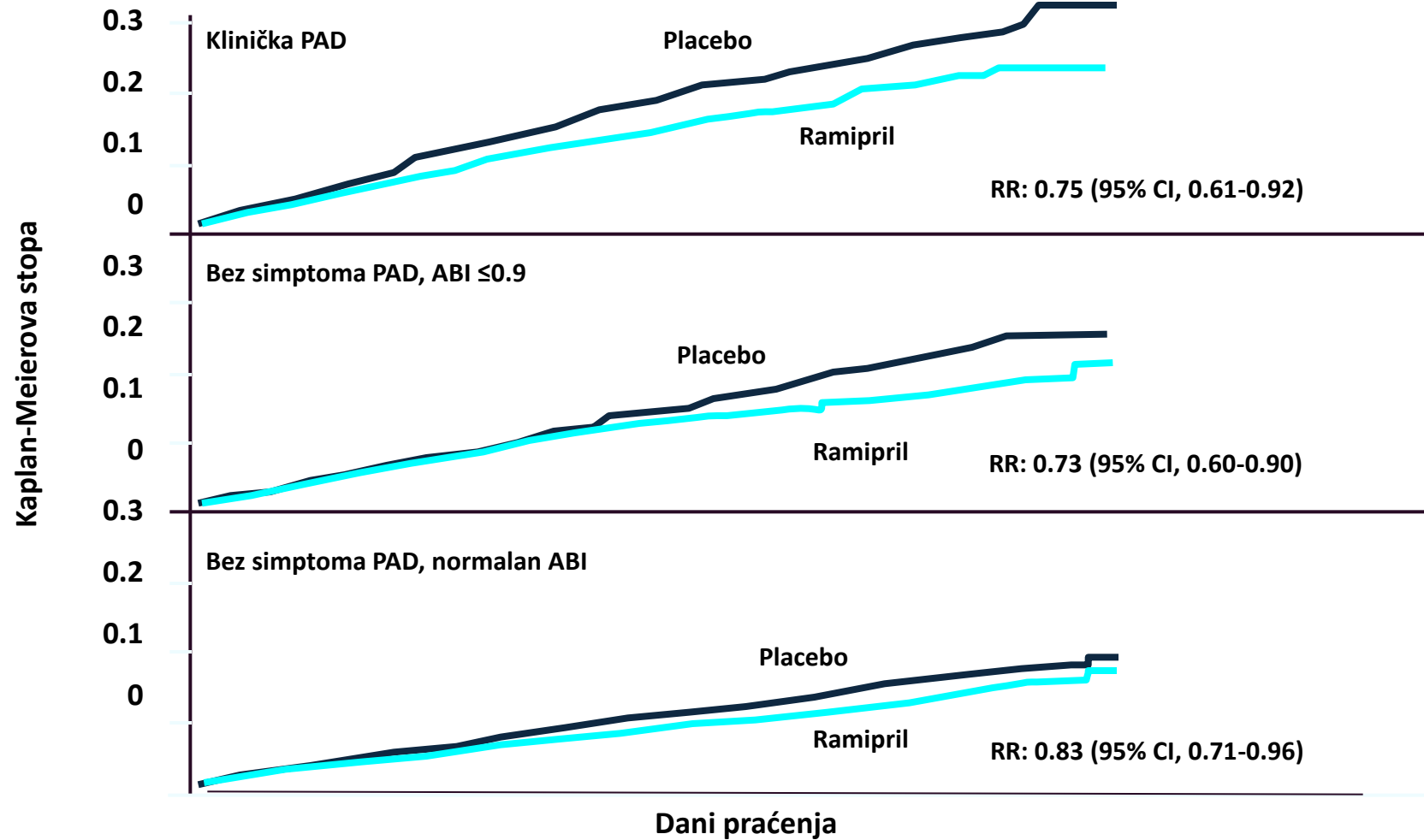


SECURE

Redukcija progresije ateroskleroze



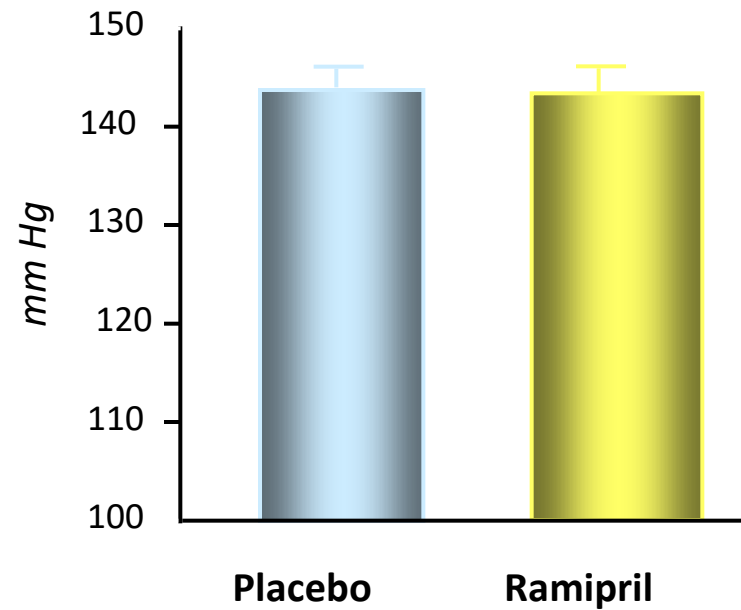
HOPE



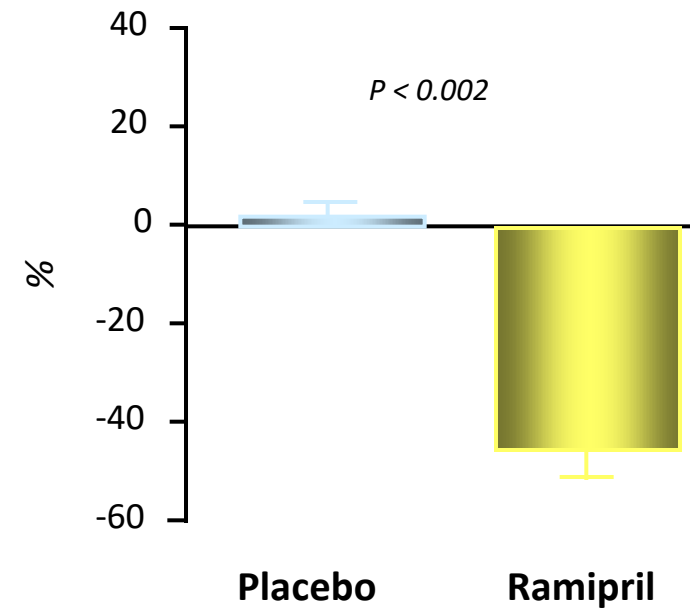
REIN CORE: *Stratum 2*

Renoprotekcija je udružena sa redukcijom proteinurije

Sistolni krvni pritisak



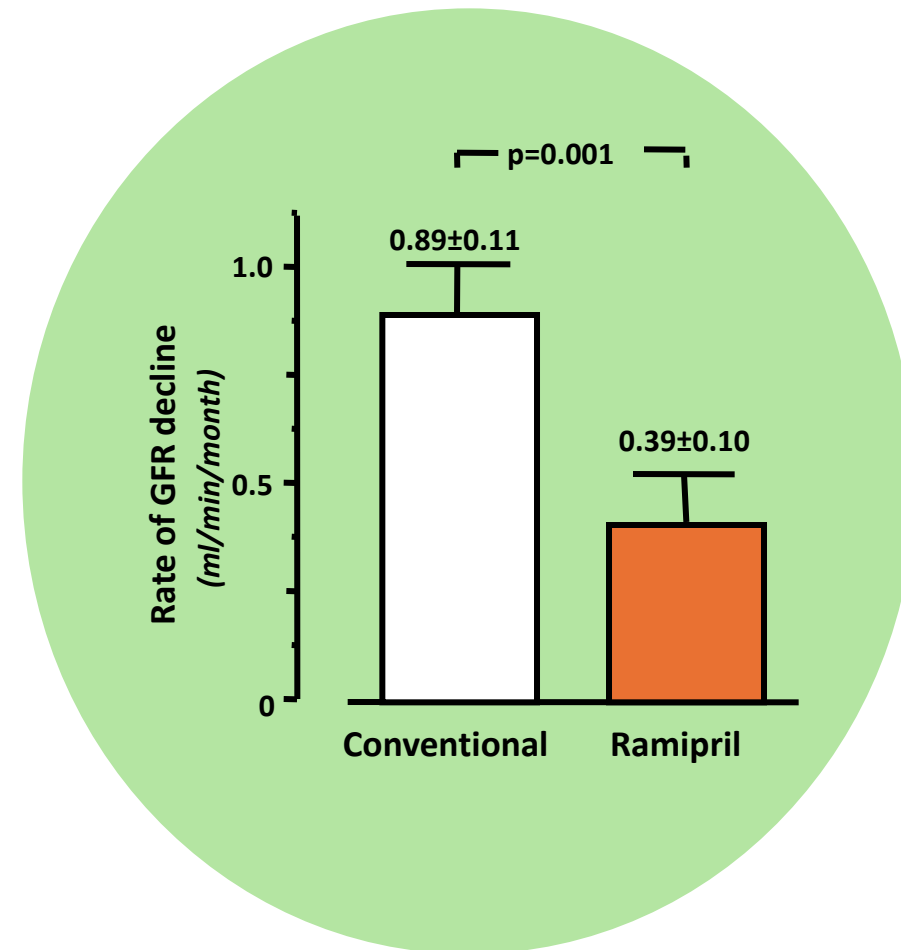
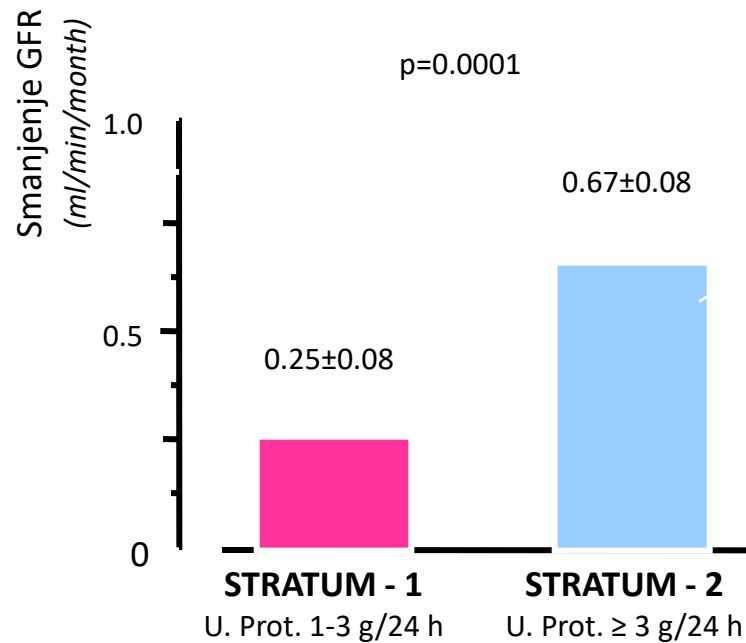
Redukcija proteinurije u odnosu na bazalne vr



REIN CORE:

Nivo opadanja GFR usaglašeno bazalnoj proteinuriji

177 pacijenata



“Preživljavanje bubrega”

konvencionalno 54 %

Ramipril 77 %

Mehanizam delovanja beta blokatora

- Redukuju srčanu frekvencu i minutni volumen
- Inhibiraju oslobadjanja renina
- Imaju inhibitorno centralno dejstvo
- Redukuju venski priliv i plazma volumen
- Popravljaju vaskularnu komplijansu
- Popravljaju baroreceptorsku senzitivnost
- Redukuju osnabadjanja NE
- Atenuirju presorni odgovor kateholamina na opterećenje
- Redukuju periferni vaskularni otpor (lekovi sa intrizičkom simpatikomimetskom aktivnošću alfa/beta blokatori ili oni sa vazodilatatornim delovanjem)

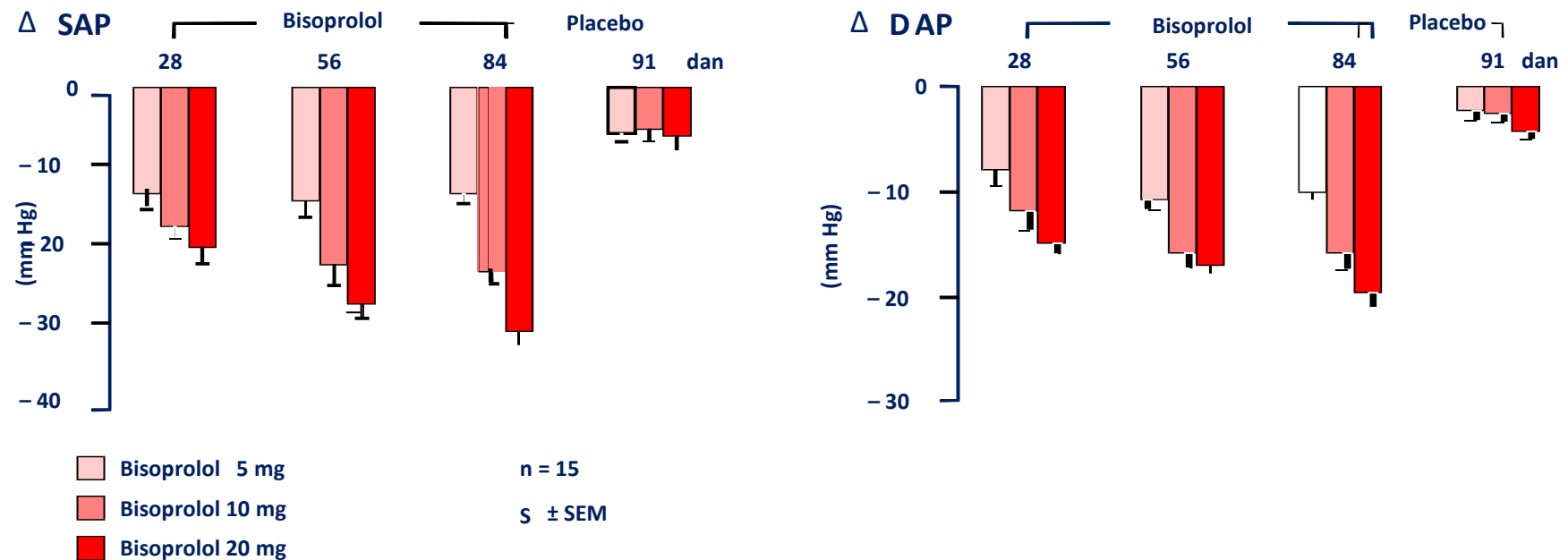
BB u arterijskoj hipertenziji i

- Hroničnom koronarnom sindromu
- Postinfarktno: aritmije, angina, nekompletna revaskularizacija, srčana insuficijencija
- Akutni koronarni sindrom
- HFrEF i HFpEF uz koronarnu bolest, aritmiju ili tahikardiju
- Atrialna fibrilacija: prevencija, kontrola ritma, kontrola frekvence
- Reproductivni period žena
- Hipertenzija u trudnoći

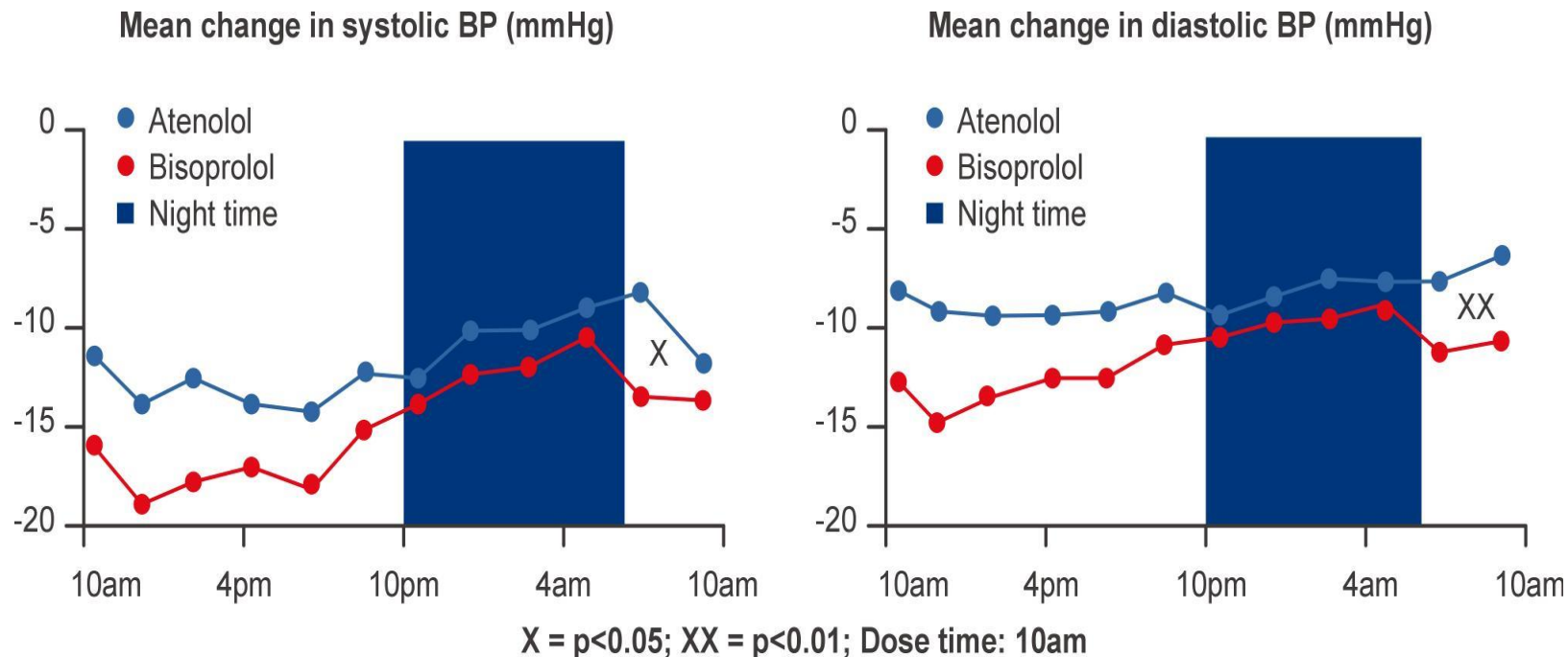
BB u arterijskoj hipertenziji i

- Ubrzanoj srčanoj radnji >80/min
- Hitnim hipertenzivnim stanjima
- Perioperativnoj hipertenziji
- Velikoj nekardijalnoj hirurgiji
- Ekscesnom prresornom odgovoru na opterećenje
- Hiperkinetskom sndromu
- Posturalnoj ortostatskoj hipertenziji sa tahikardijom
- Ortostatskoj hipertenziji
- OSA
- Perifernoj arterijskoj bolesti
- HOBP
- Portnoj hipertenziji, cirozi sa variksimi i ponavljanim krvarenjem
- Glaukomu
- Tireotoksikozi i hipertireozi
- Hiperparatiroidizmu u uremiji
- Migreni
- Esencijalnom tremoru
- Anksioznosti
- Psihijatrijskim bolestima

Bisoprolol - dozno zavisna redukcija krvnog pritiska kod hipertenzivnih pacijenata



Efikasna 24-časovna kontrola krvnog pritiska uz bisoprolol u poredjenju sa atenololom

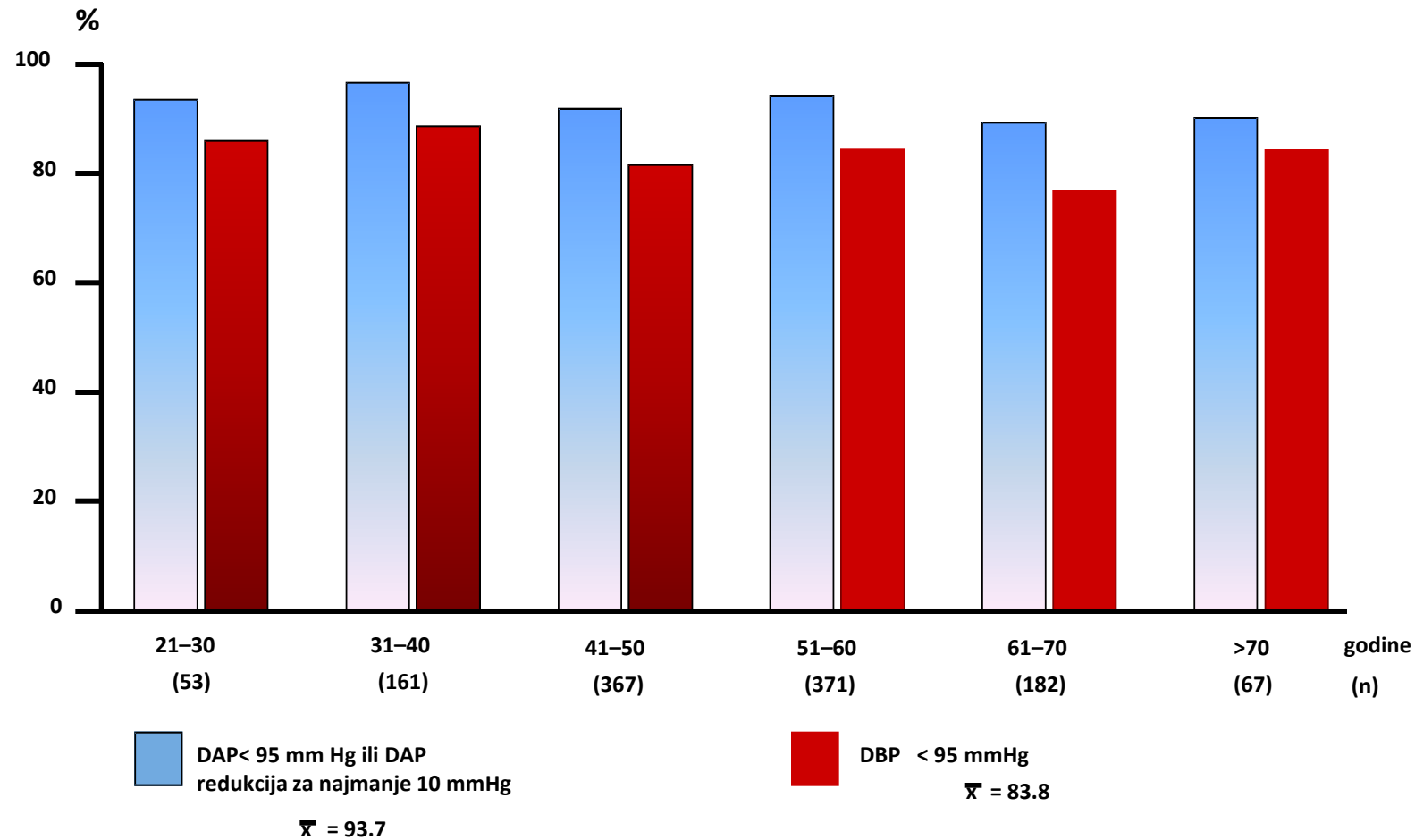


Bisoprolol je značajno efikasnije redukovao SAP ($p < 0.05$) i DAP ($p < 0.01$) tokom poslednja 4 od 24 časa.

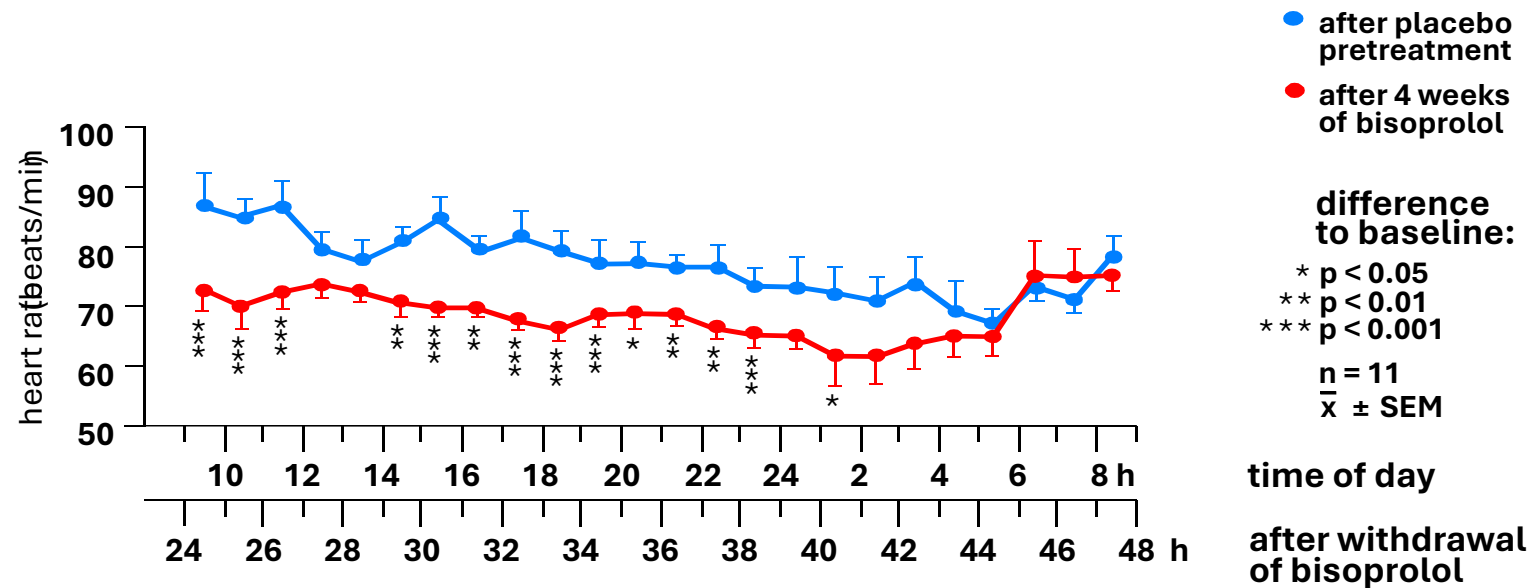
Bisoprololom je ostvarena za 33% veća redukcija pritiska tokom 24 časa, a srednjeg DAP za 11.6 vs 8.7 mmHg, $p < 0.01$

Randomizirana dvostruko slepa studija u koju je uključeno 659 pacijenata sa blagom do umerenom arterijskom hipertenzijom (starosti od 21 do 84 godine). 24-časovni ABPM je odradjen 8 nedelja od početka lečenja (bisoprolol 10 mg, $n=336$, atenolol 50 mg, $n=323$)

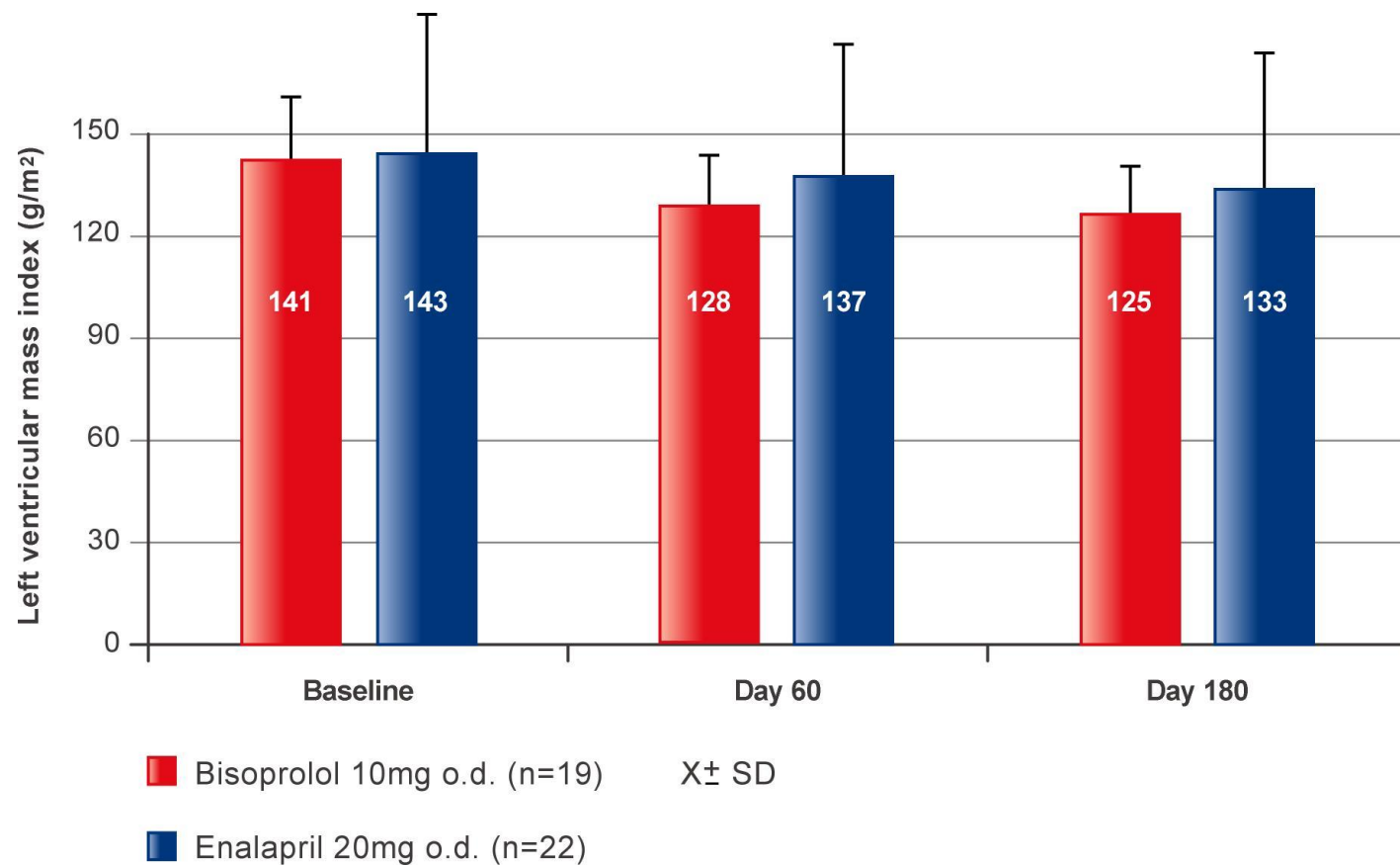
Odgovornost na bisoprolol u zavisnosti od životnog doba



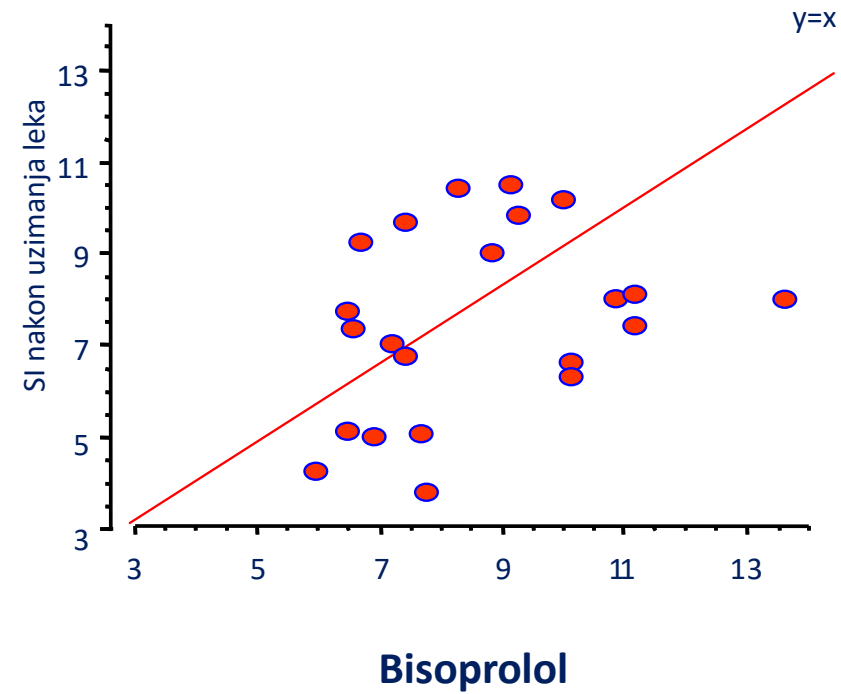
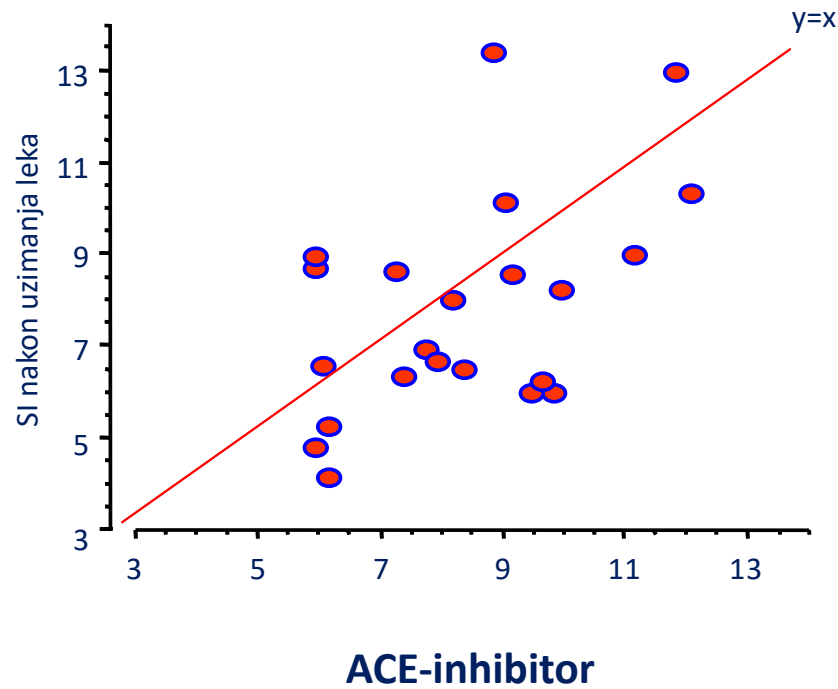
Bisoprolol:redukcija frekvence



Bisoprolol slično enalaprilu redukuje masu leve komore

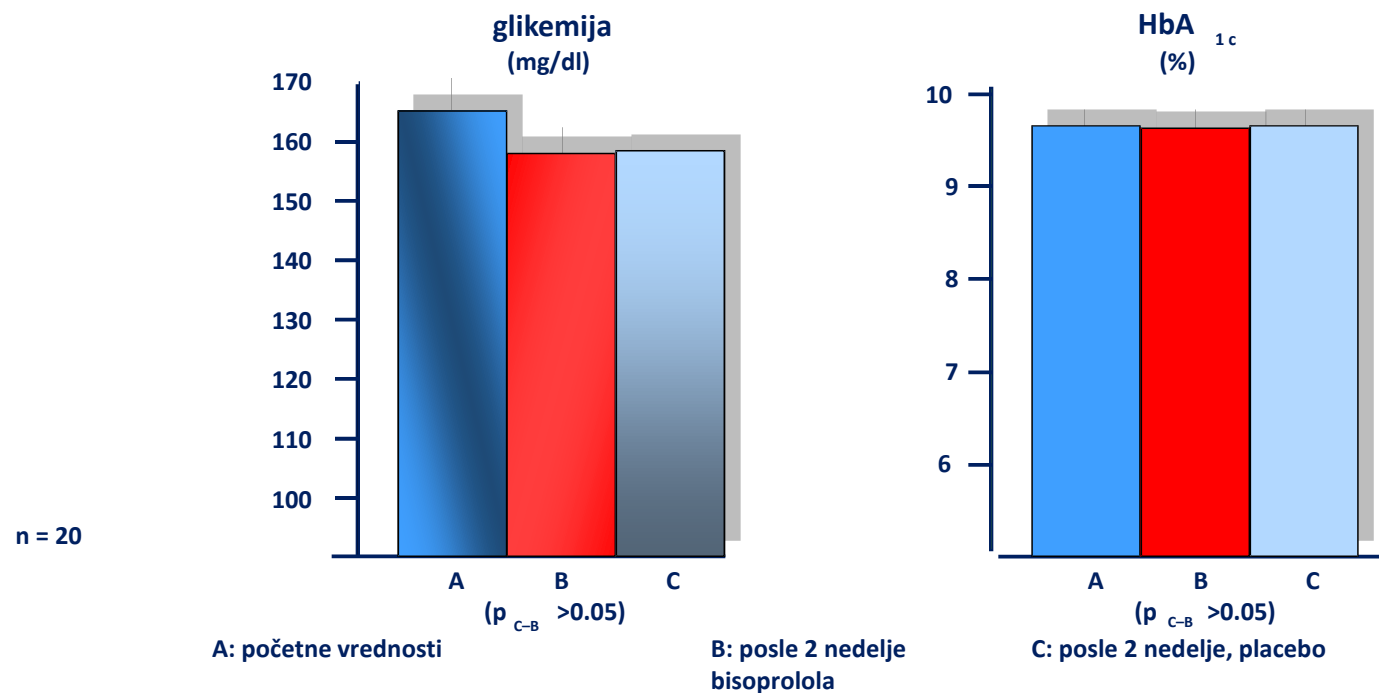


Uticaj bisoprolola i ACE inhibitora na insulinsku senzitivnost



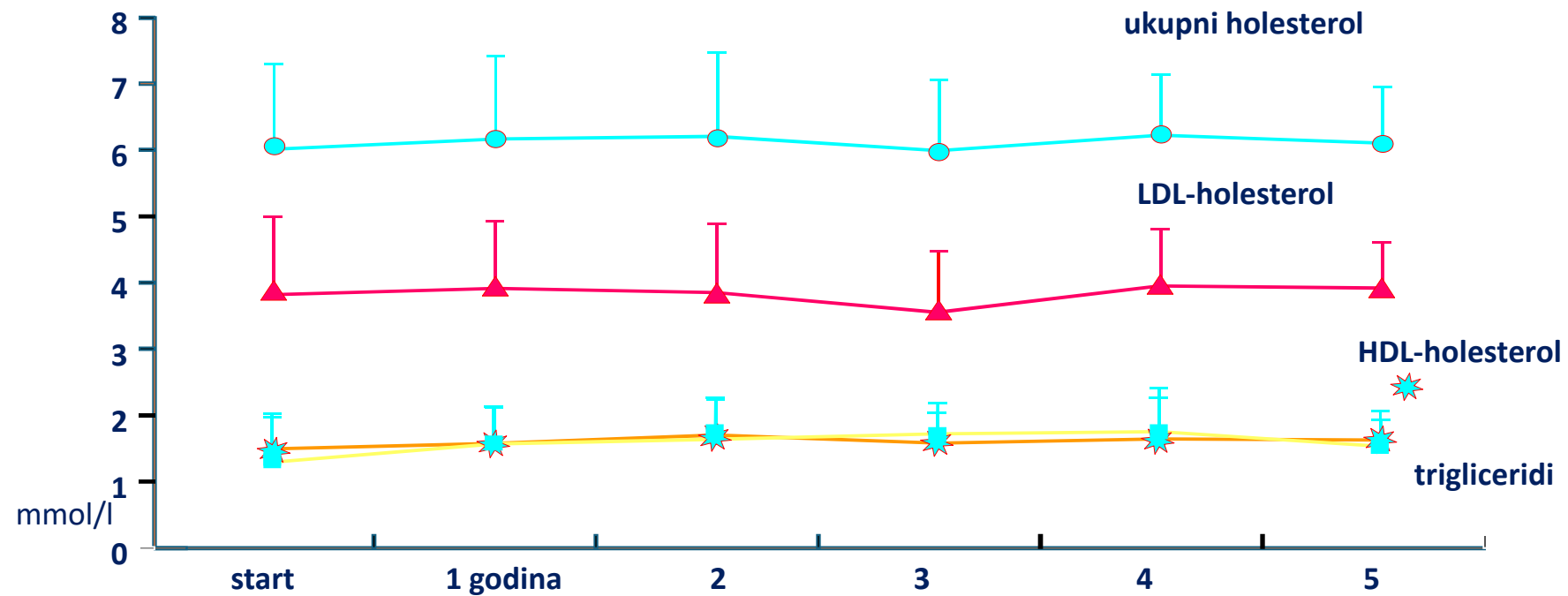
* Insulin indeks senzitivnosti

Bisoprolol: β_1 -selektivnost i metabolizam glukoze kod bolesnika sa diabetes melitusom

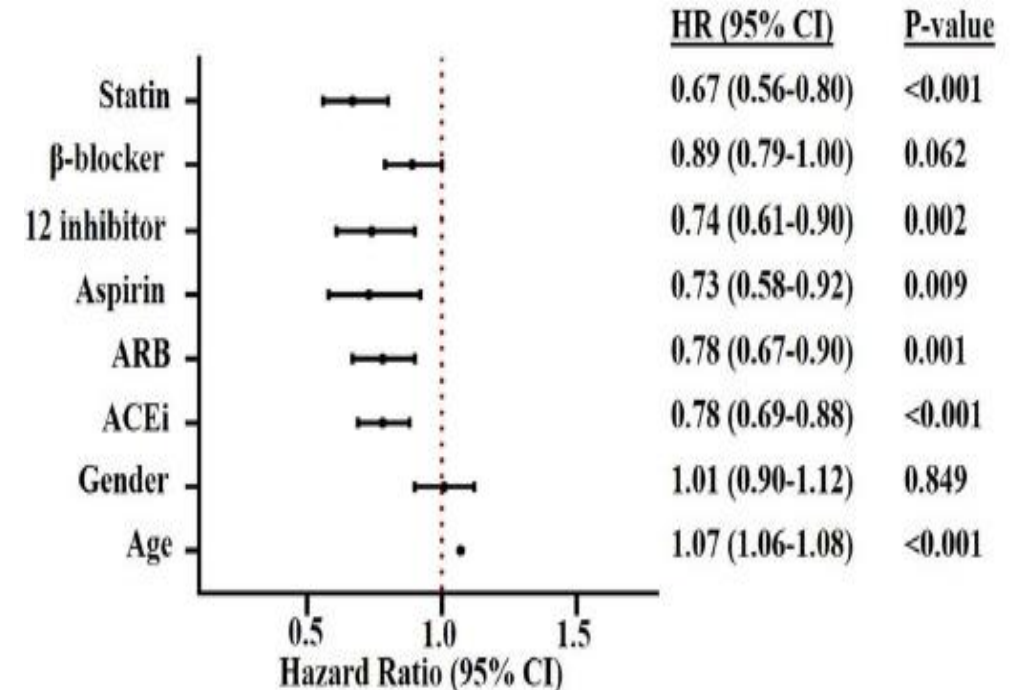
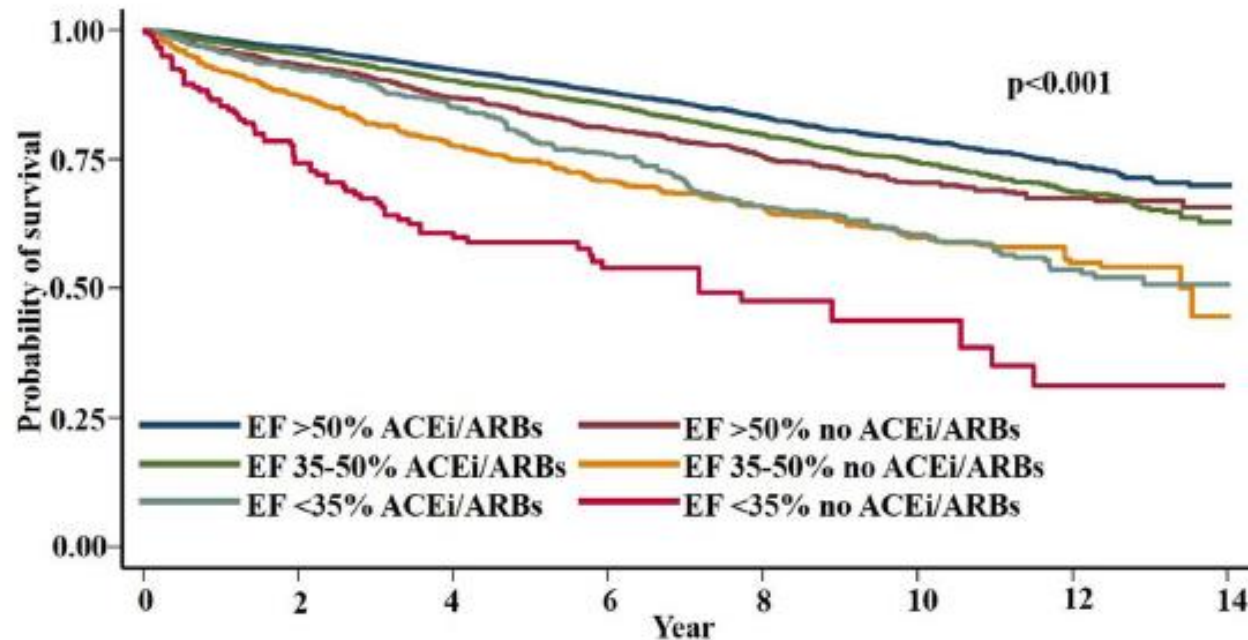


-bisoprolol ne menja nivo glikemije i HbA_{1c}
-bez hipoglikemijskih incidenata

Bisoprolol: β_1 -selektivnost i metabolizam lipida



Uticaj blokatora SRAA na preživljavanje nakon STEMI ili NSTEMI





Role of renin–angiotensin system antagonists on long-term mortality post-percutaneous coronary intervention in reduced and preserved ejection fraction

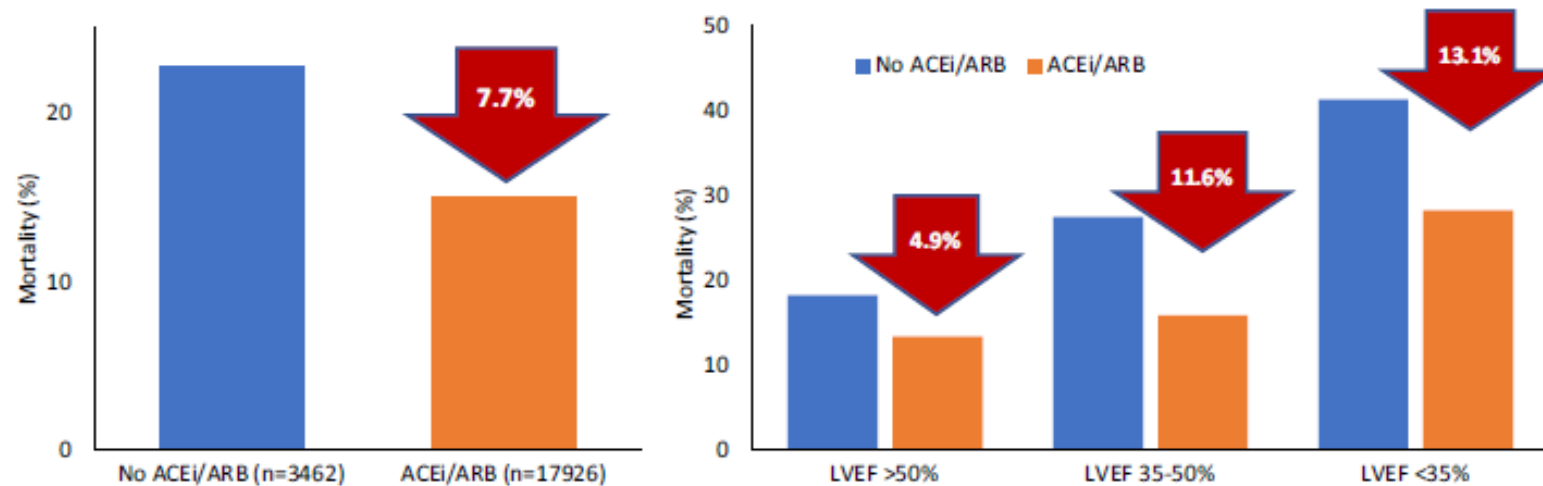
Hamish C. Prosser^{1,2} · Kah Yong Peck^{1,2} · Diem Dinh³ · Louise Roberts^{1,2} · Jaya Chandrasekhar^{1,2} · Angela Brennan³ · Stephen J. Duffy^{3,4} · David Clark⁵ · Andrew E. Ajani⁶ · Ernesto Oqueli^{7,10} · Martin Sebastian⁸ · Christopher M. Reid^{9,3} · Melanie Freeman¹ · Jithin K. Sajeev^{1,2} · Andrew W. Teh^{1,2,5}

ACEi/ARB therapy post PCI for NSTEMI/STEMI is associated with lower long-term mortality

21,388 patients post PCI for NSTEMI and STEMI

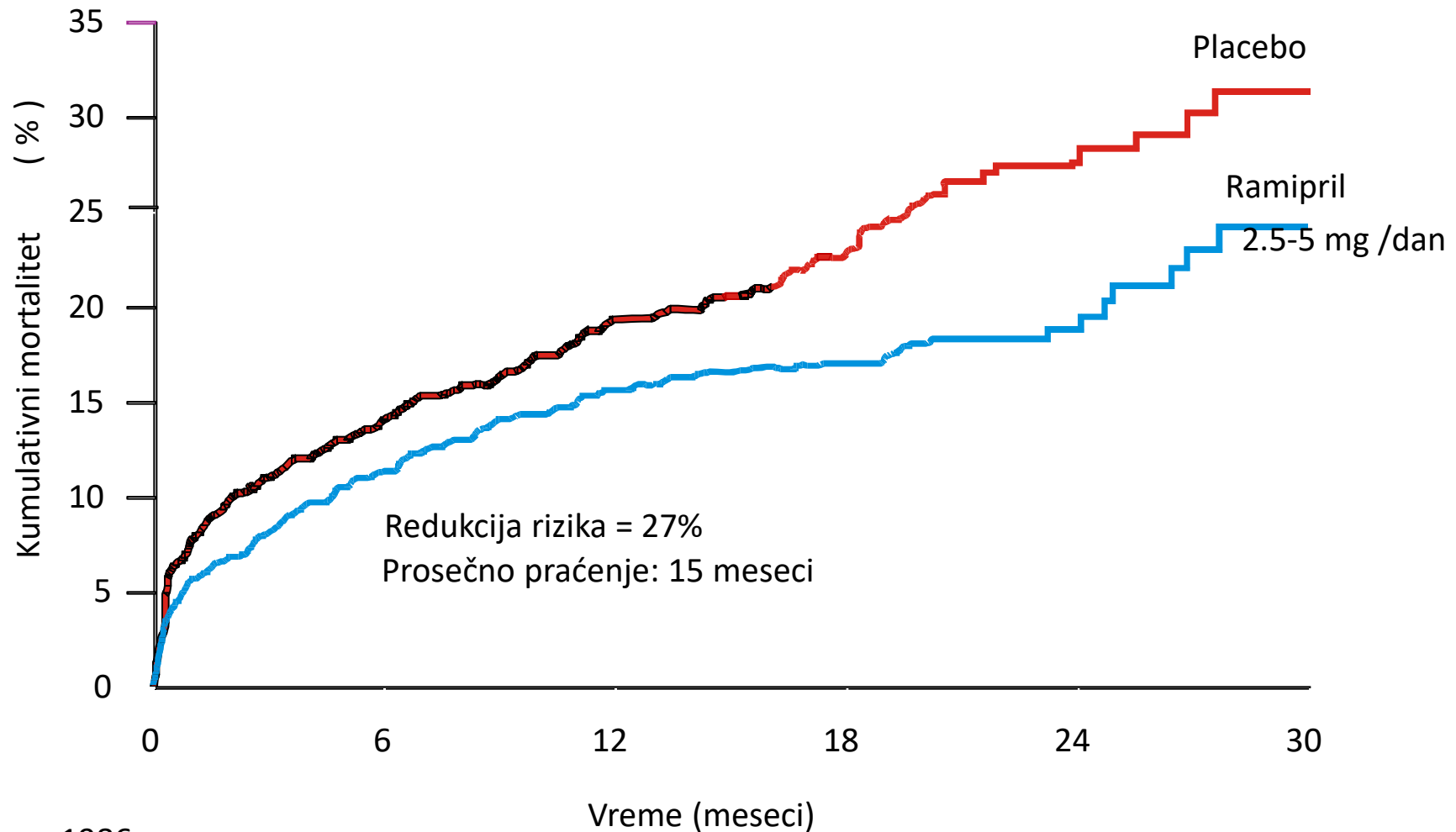
ACEi/ARB used in 83.8% of patients

Mean follow-up 5.58 years

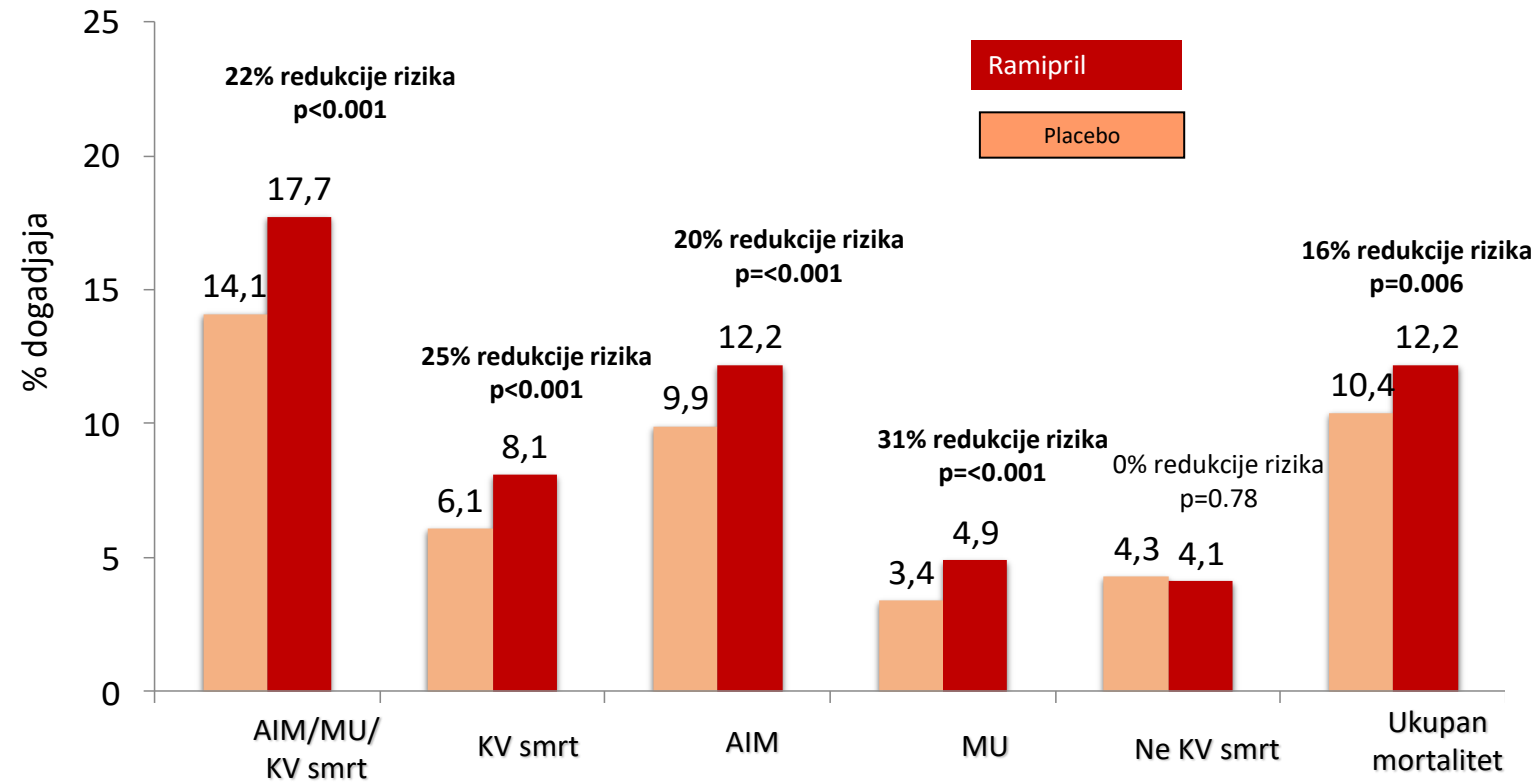


Abbreviations: LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, Non-STEMI

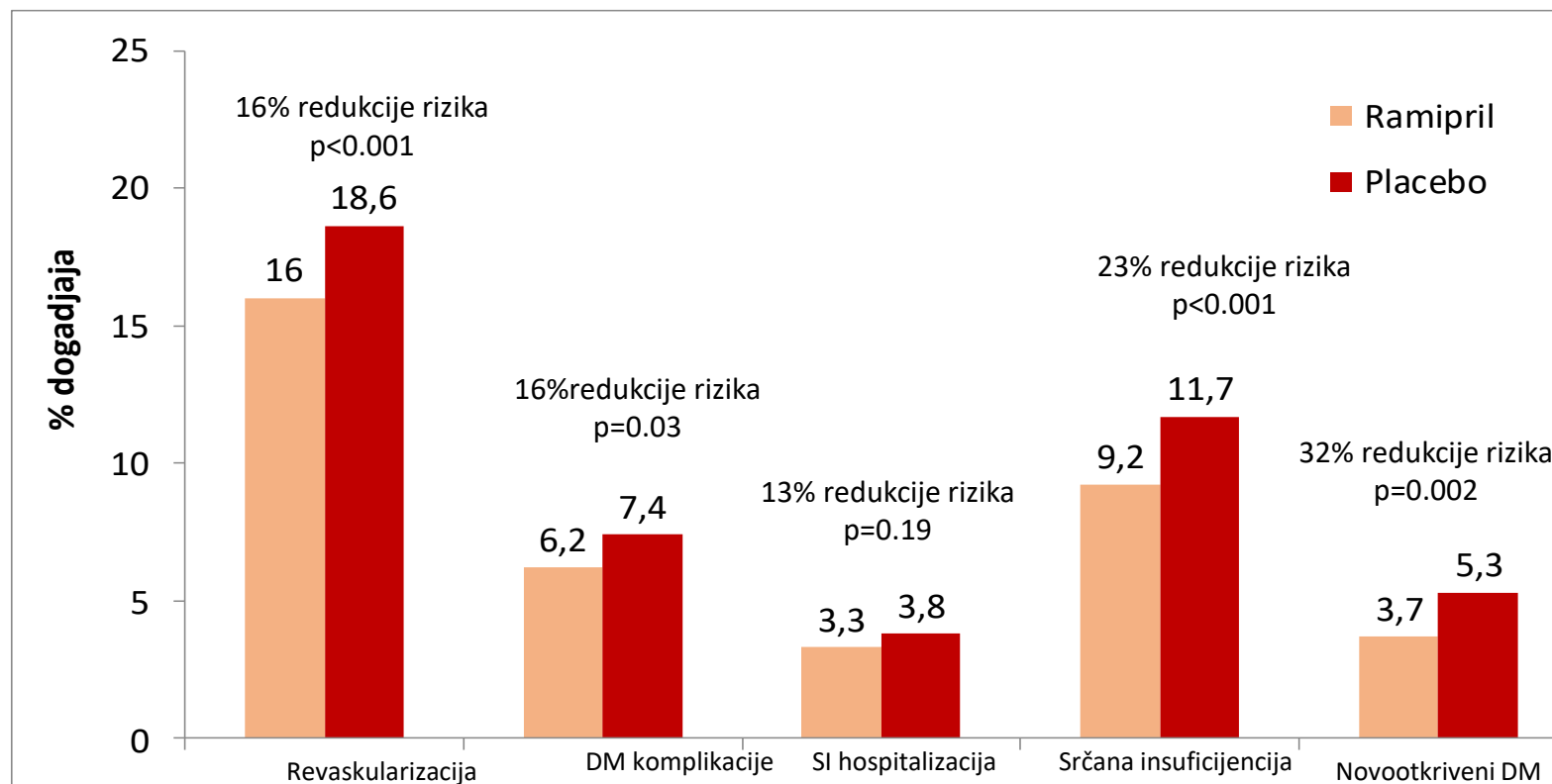
AIRE Study (Acute Infarction Ramipril Efficacy)



HOPE – primarni cilj

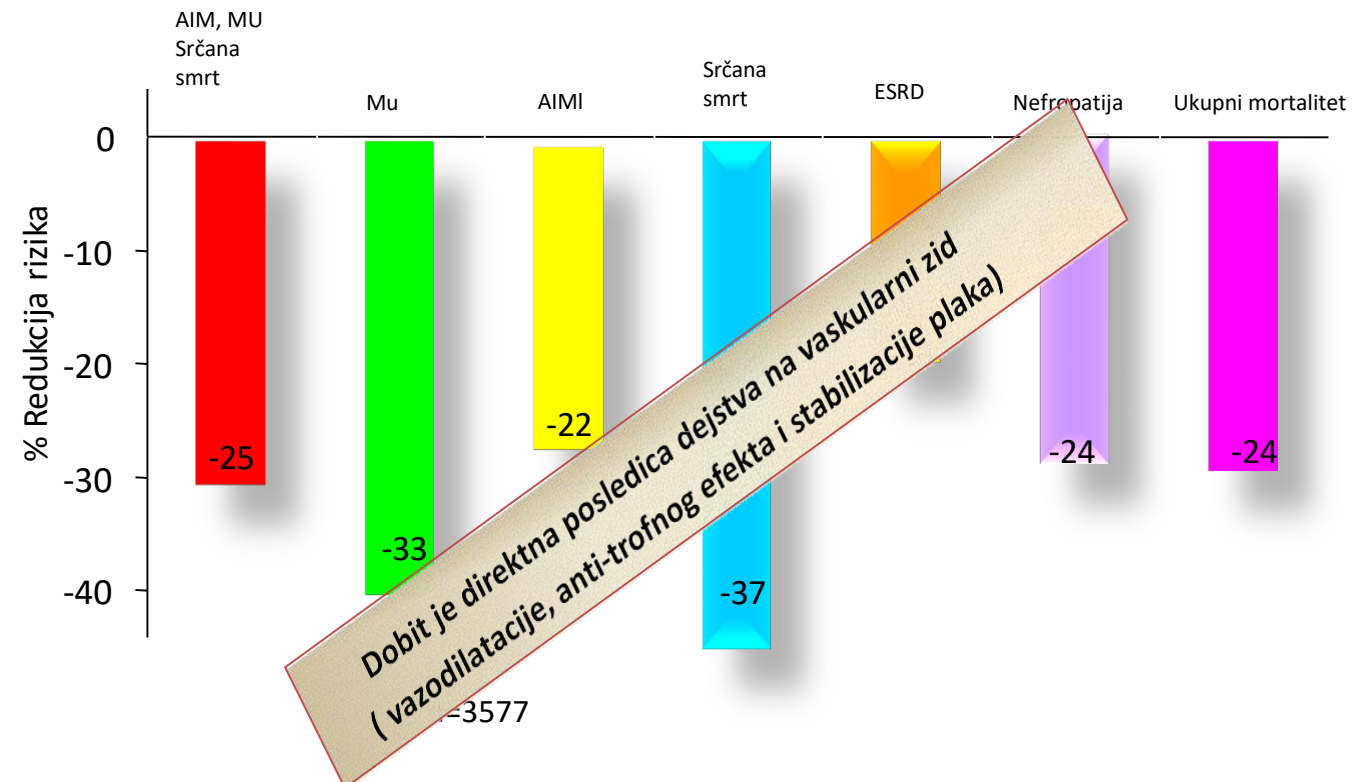


HOPE – sekundarni ciljevi

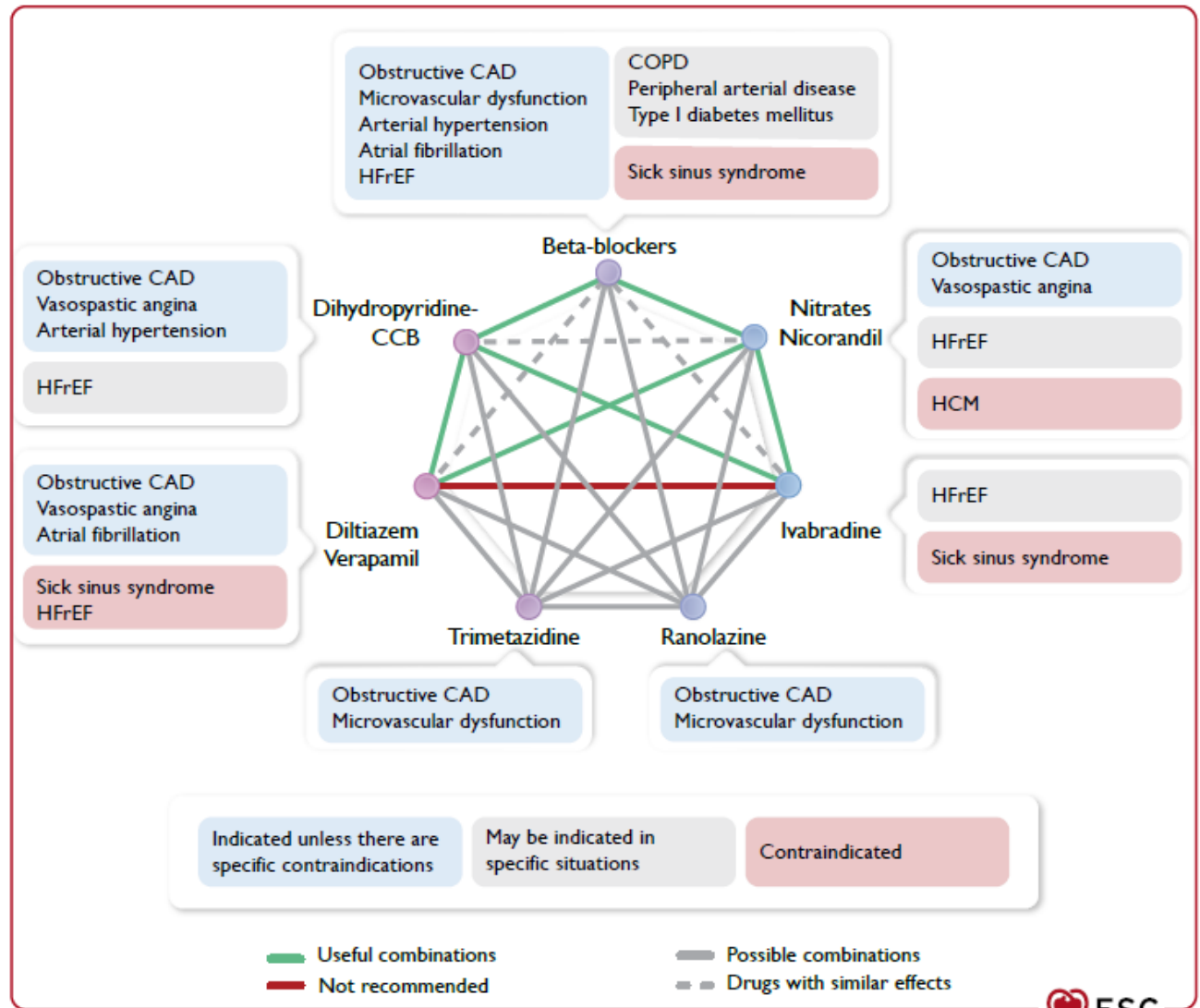


MICRO-HOPE Study

Pacijenti sa DM tip 2

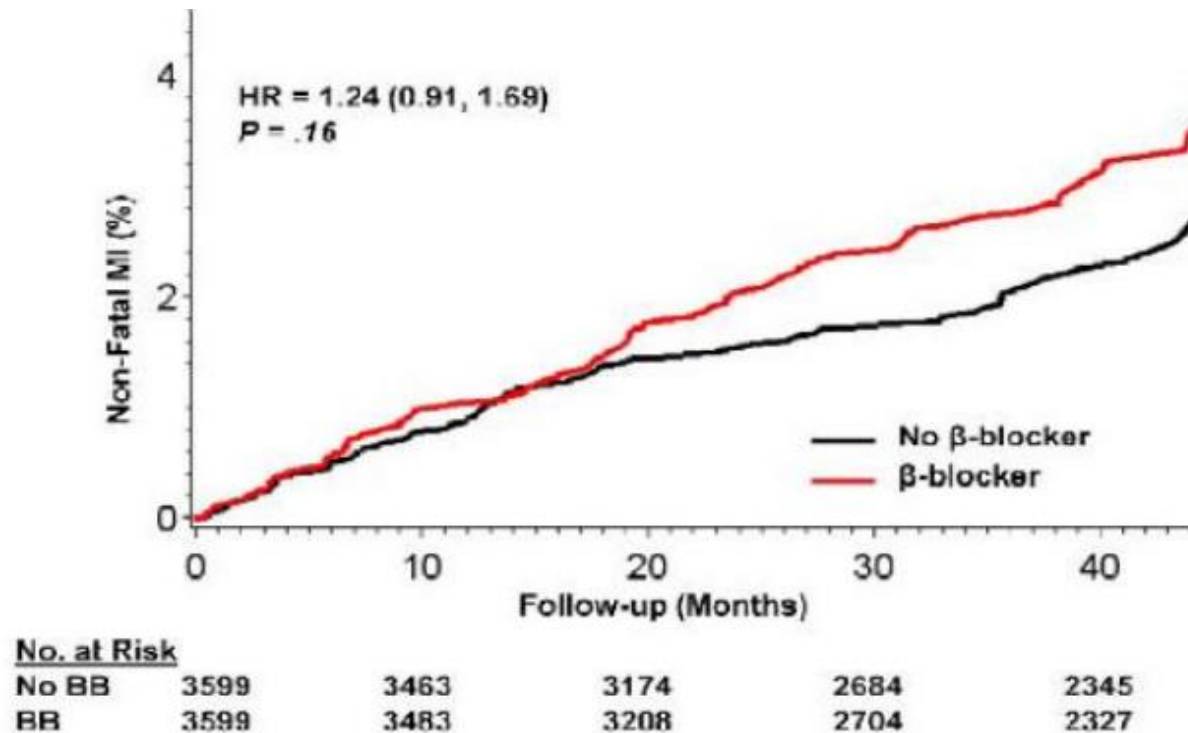


Uloga BB u lečenju hroničnog koronarnog sindroma

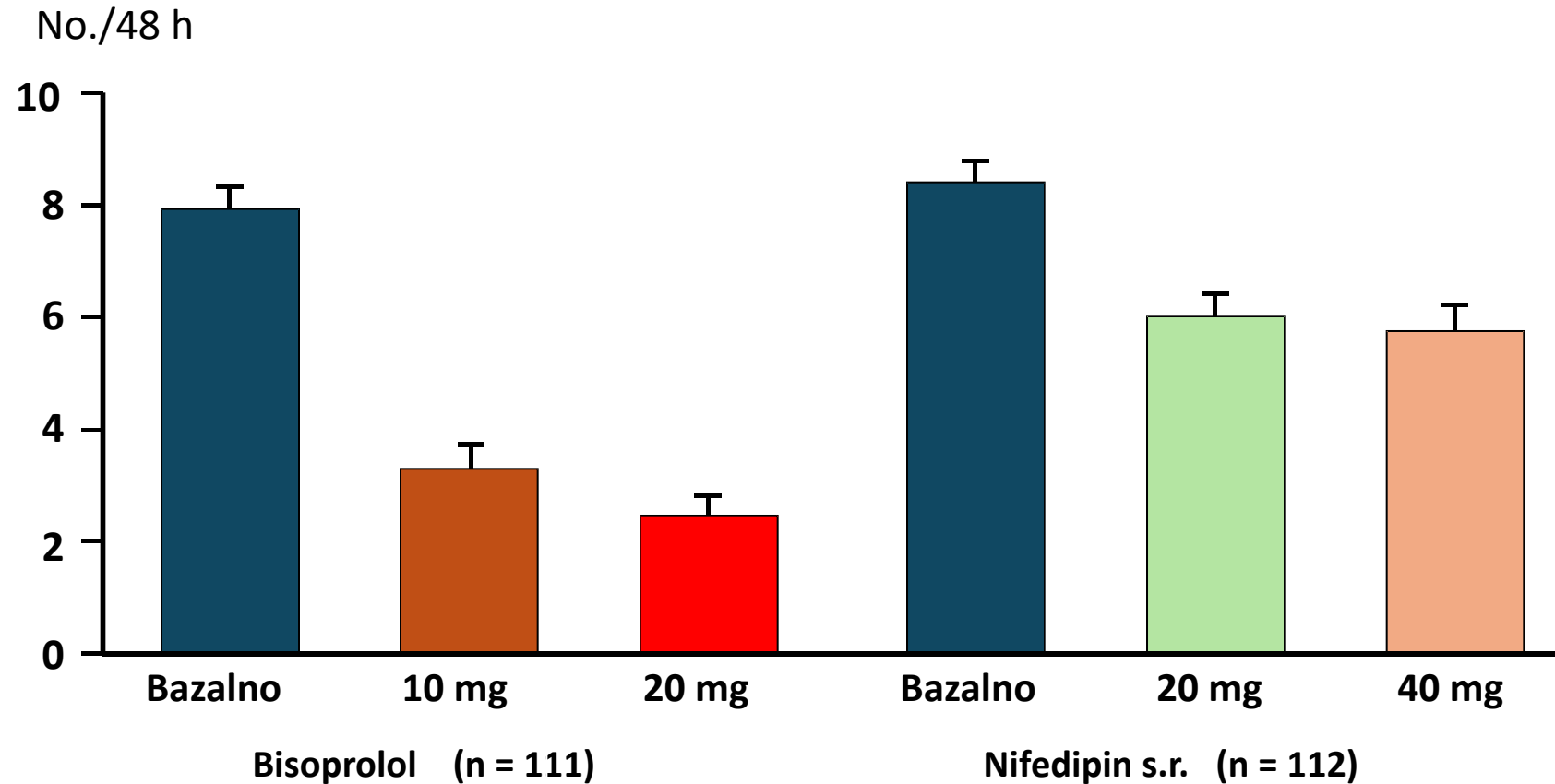


Beta blokatori u angini pektoris bez prethodnog infarkt miokarda

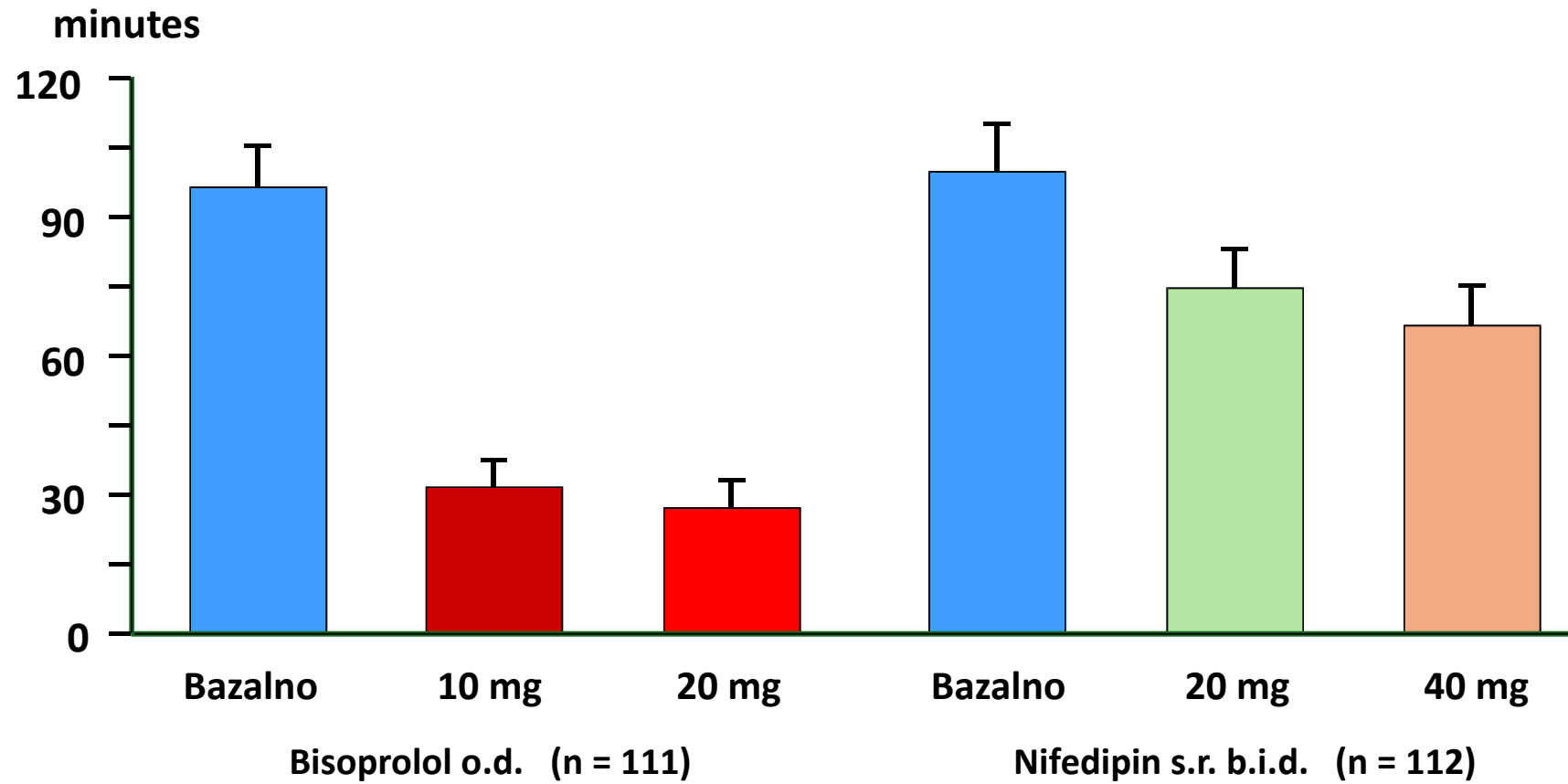
REACH registar



TIBBS – učestalost epizoda ishemije u zavisnosti od modaliteta lečenja

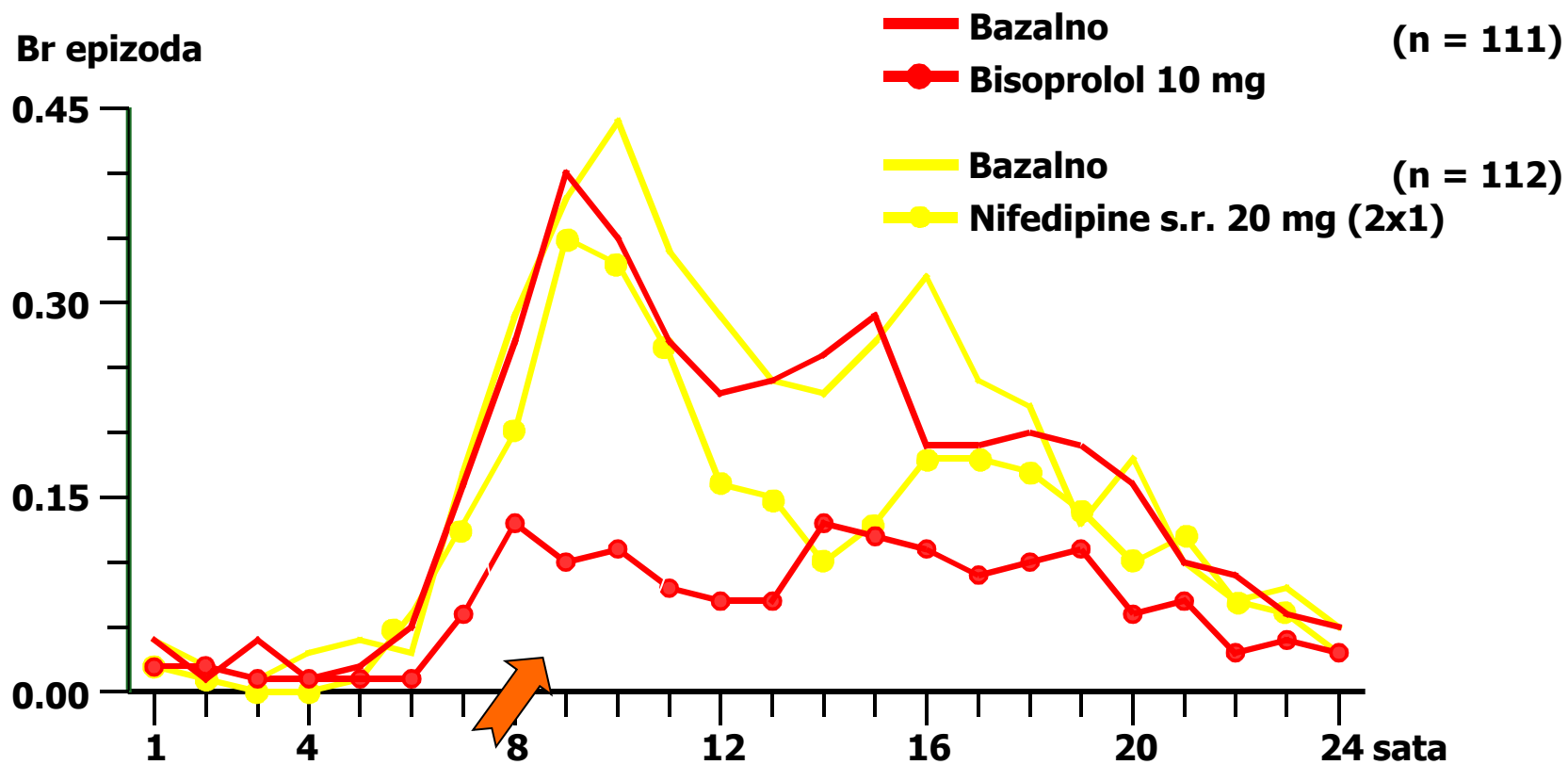


TIBBS - trajanje epizoda ishemije u zavisnosti od modaliteta lečenja



TIBBS

profil cirkadijalnih ishemijskih epizoda





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Pharmacological intervention in hypertension using beta-blockers: Real-world evidence for long-term effectiveness

Meritxell Sabidó^{a,*}, Thilo Hohenberger^a, Guido Grassi^{b,c}

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^b Clinica Medica, University of Milano-Bicocca, Milan, Italy

^c IRCCS Multimedica, Sesto San Giovanni, Milan, Italy

- Postoje (postojale su) razlike u stavovima o primeni beta blokatora u lečenju arterijske hipertenzije
- ESC /ESH preporuke su ukazale na prednosti primene beta blokatora u lečenju hipertenzije postinfarktno, u angini pektoris, srčanoj insuficijenciji i atrijalnoj fibrilaciji
- The current National Institute for Health and Care Excellence (NICE) preporuke su isključile beta blokatore kao prvu liniju terapije u hipertenziji
- Da li su beta blokatori inferiorniji od drugih klasa antihipertenziva u smanjenju ukupnog mortaliteta kardiovaskularnih događaja, moždanih udara?

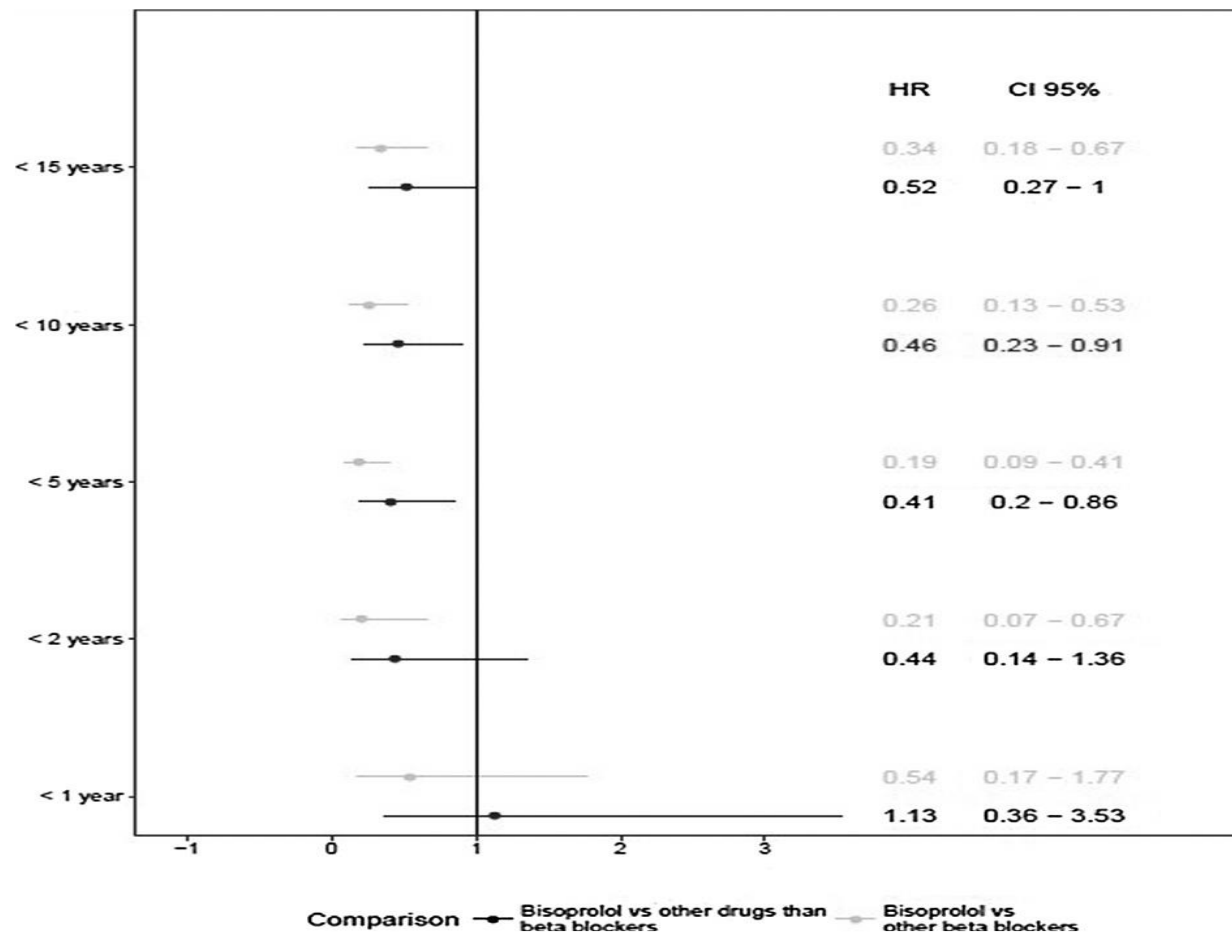
Izvor podataka

- The UK Clinical Practice Research Datalink (CPRD) database, 2000-2014
- CPRD uključuje 800 lekara UK i 5000000 pacijenata
- Uključeno 8,5% ukupne populacije koji predstavljaju reprezentativni uzorak opšte populacije sa sličnom distribucijom po polu i godinama
- Ispitivani su pacijenti sa novootkrivenom arterijskom hipertenzijom ≥ 18 god

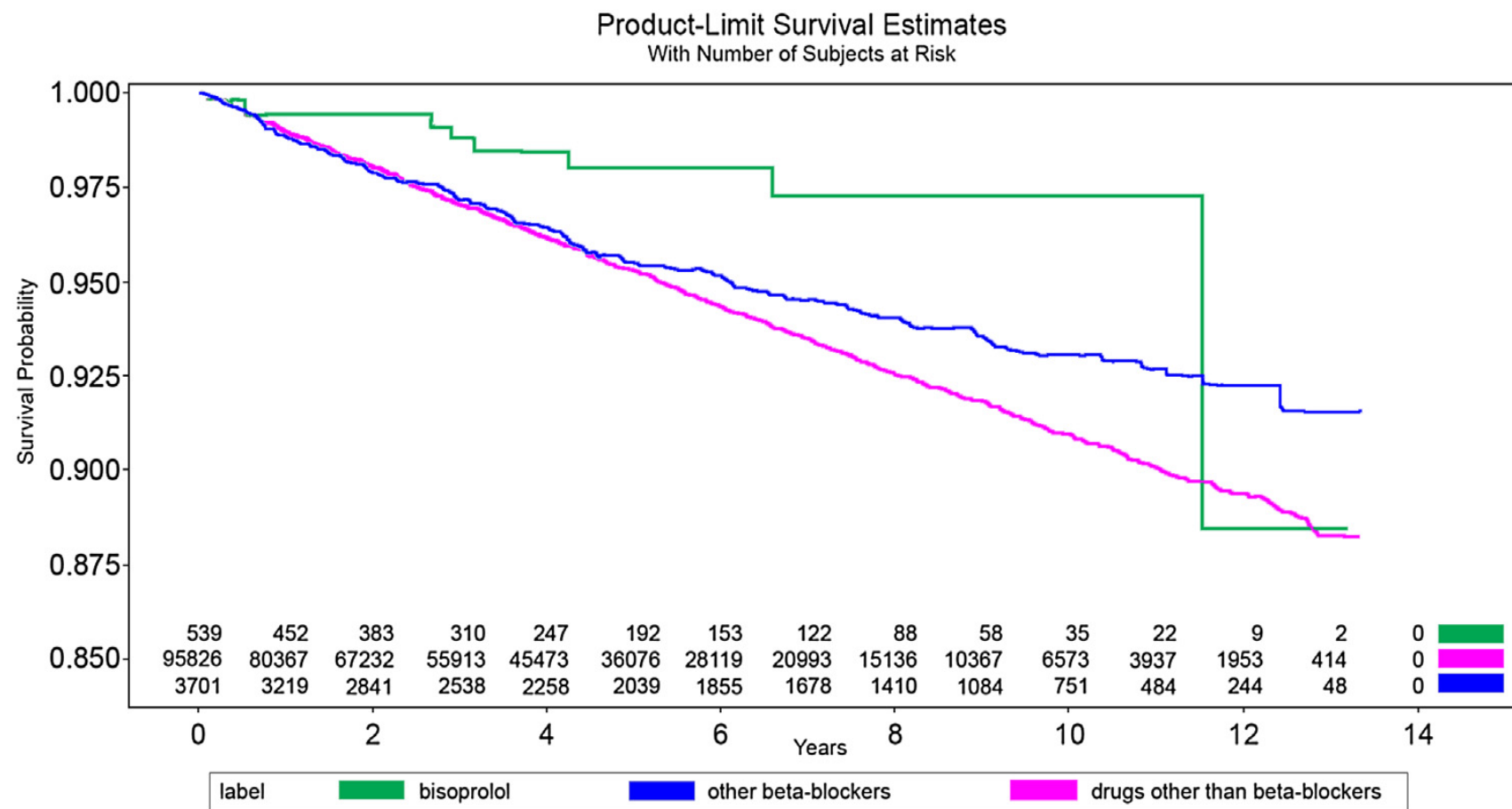
Ciljevi

- Primarni cilj – uticaj modaliteta lečenja na mortalitet
- Sekundarni cilj – uticaj lečenja na KV dogadjaje, nefatalne IM, nefatalne moždane udare, nefatalne aritmije, embolizam i epizode angine
- Drugi ciljevi- uticaj na visinu SAP i DAP

Redukcija mortaliteta: bisoprolol vs drugi beta blokatori i bisoprolol vs drugi antihipertenzivi



Kaplan- Meier kriva preživljanja



Bisoprolol vs drugi beta blokatori i bisoprolol vs drugi antihipertenzivi

	Adjusted HR (95% CI)				
	<1 year	<2 years	<5 years	<10 years	Total (≤14 years)
Bisoprolol vs other β-blockers					
Arrhythmia	0.67 (0.34–1.32)	0.57 (0.32–1.03)	0.60 (0.36–1.00)	0.85 (0.52–1.38)	1.09 (0.67–1.78)
Embolism	0.16 (0.02–1.36)	0.20 (0.04–0.98)	0.23 (0.04–1.11)	0.46 (0.12–1.74)	0.60 (0.16–2.29)
Stroke	0.68 (0.18–2.55)	0.62 (0.19–2.04)	0.72 (0.26–1.98)	0.92 (0.35–2.44)	1.20 (0.45–3.20)
Angina	0.58 (0.49–0.68)	0.48 (0.41–0.56)	0.43 (0.37–0.50)	0.50 (0.43–0.58)	0.58 (0.50–0.68)
MI	0.44 (0.25–0.78)	0.39 (0.23–0.69)	0.45 (0.27–0.75)	0.66 (0.40–1.11)	0.84 (0.50–1.42)
Bisoprolol vs drugs other than β-blockers					
Arrhythmia	0.55 (0.32–0.94)	0.61 (0.37–0.99)	0.61 (0.40–0.93)	0.78 (0.52–1.16)	0.92 (0.61–1.37)
Embolism	0.18 (0.02–1.38)	0.33 (0.08–1.39)	0.23 (0.05–0.94)	0.37 (0.12–1.19)	0.45 (0.14–1.44)
Stroke	0.50 (0.17–1.45)	0.41 (0.16–1.04)	0.38 (0.17–0.82)	0.45 (0.21–0.97)	0.54 (0.25–1.17)
Angina	0.71 (0.61–0.88)	0.65 (0.56–0.74)	0.61 (0.54–0.70)	0.70 (0.62–0.80)	0.77 (0.68–0.88)
MI	0.19 (0.12–0.31)	0.20 (0.12–0.31)	0.22 (0.15–0.35)	0.30 (0.19–0.45)	0.34 (0.23–0.52)

5. Conclusions

Overall, this study showed that bisoprolol had a sustained benefit on survival in patients with hypertension versus other β -blockers and versus drugs other than β -blockers, and therefore provides long-term evidence for the bisoprolol use in patients with hypertension within primary care. With β -blockers possessing differing pharmacological properties, and given the lack of long-term studies of β -blockers for the treatment of hypertension, the advantages observed in this study with bisoprolol over other β -blockers support reconsideration of its use in the treatment of hypertension in a broader patient spectrum.

.... The present study therefore provides valuable insight, indicating prolonged survival benefits of bisoprolol compared with other beta -blockers and drugs other than beta blockers...

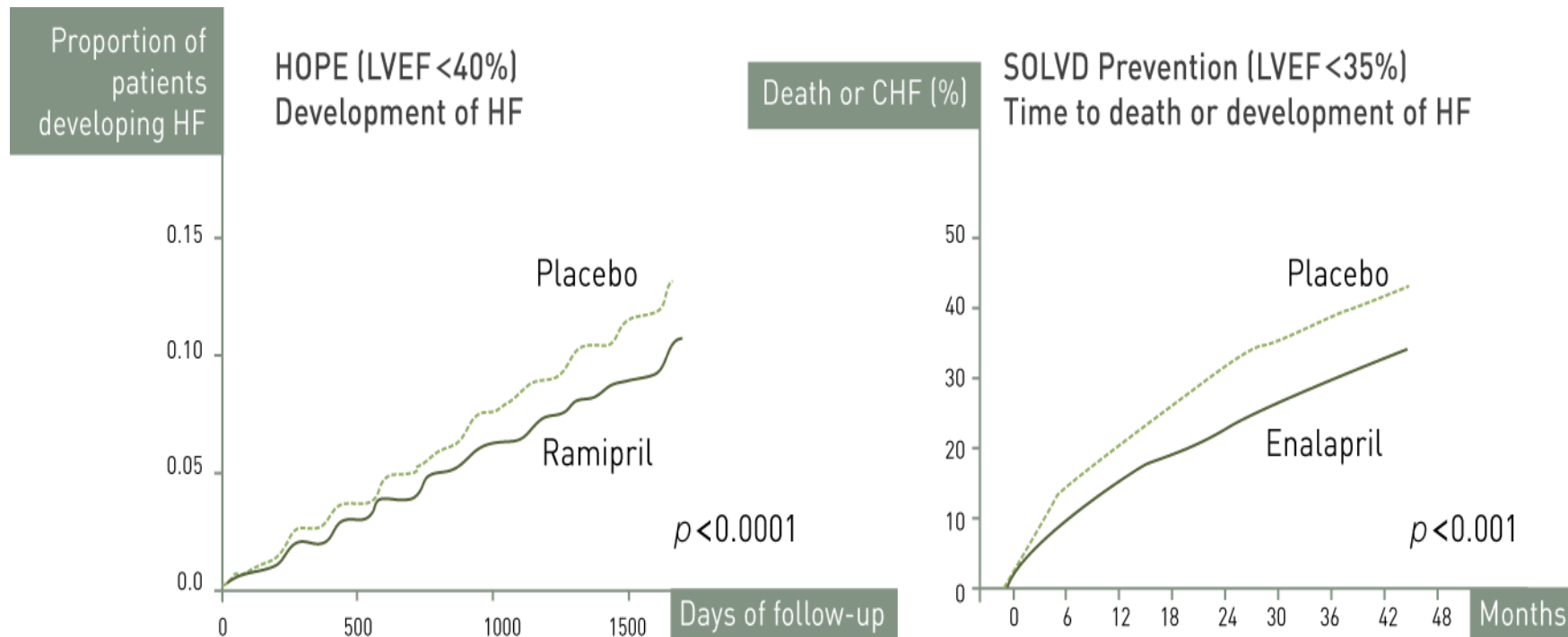
...the long-term protective effect of bisoprolol provides
....supporting its use as first-line hypertension monotherapy in a wider range of patients.

Dobit od primene ACE inhibitora u lečenju srčane insuficijencije

- Smanjuju remodelovanje leve komore
- Redukuju postinfarktne ishemijske događaje
- Popravljaju endotelnu funkciju, parasimpatički tonus i neurohumoralni balans
- Redukuju oksidativni stres
- Atenuiraju simpatički odgovor
- Smanjuju insulinsku rezistenciju i popravljaju kontrolu glikemije

ACE inhibitori u srčanoj insuficijenciji

ACE inhibitori deluju preventivno na razvoj SI kod visoko rizičnih pacijenata



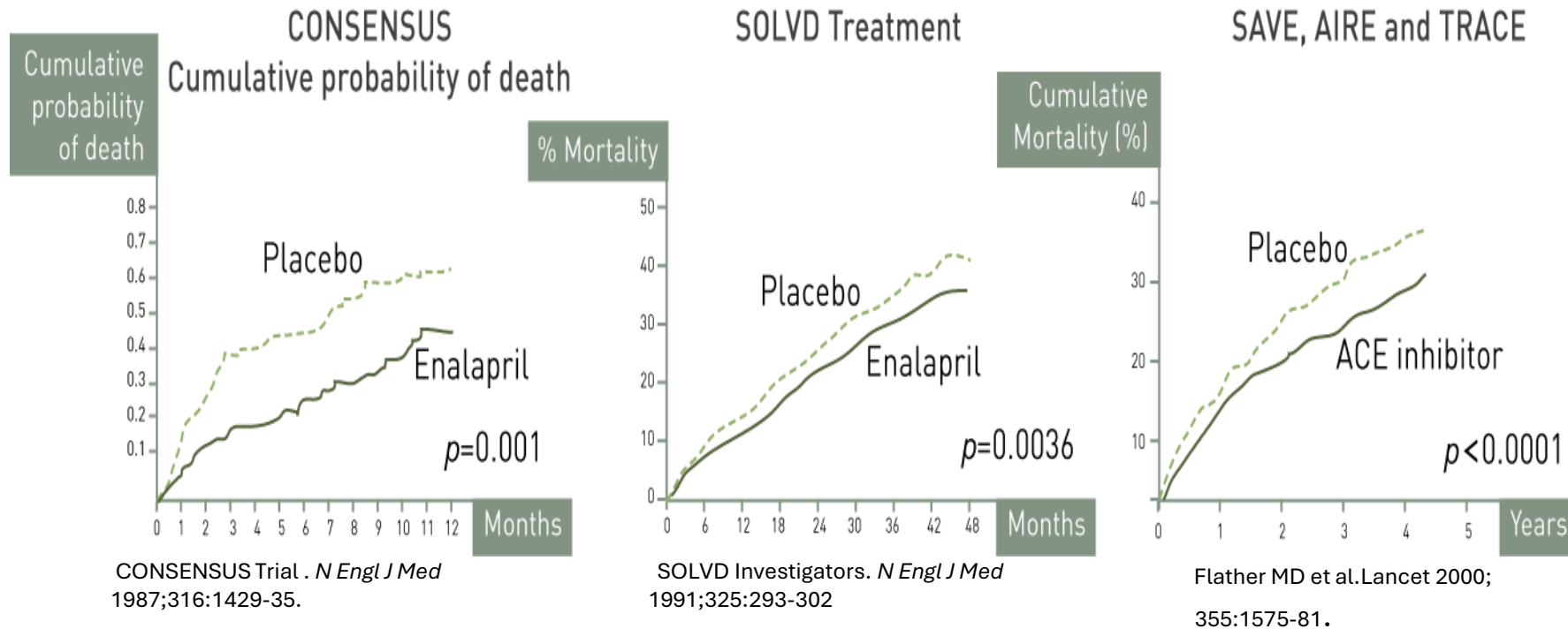
Arnold JMO et al. *Circulation* 2003;107:1284-90.

SOLVD Investigators. *N Engl J Med* 1992;327:685-91.

Arnold JMO, Liu P et al. *Can J Cardiol* 2006;22(1):23-45.

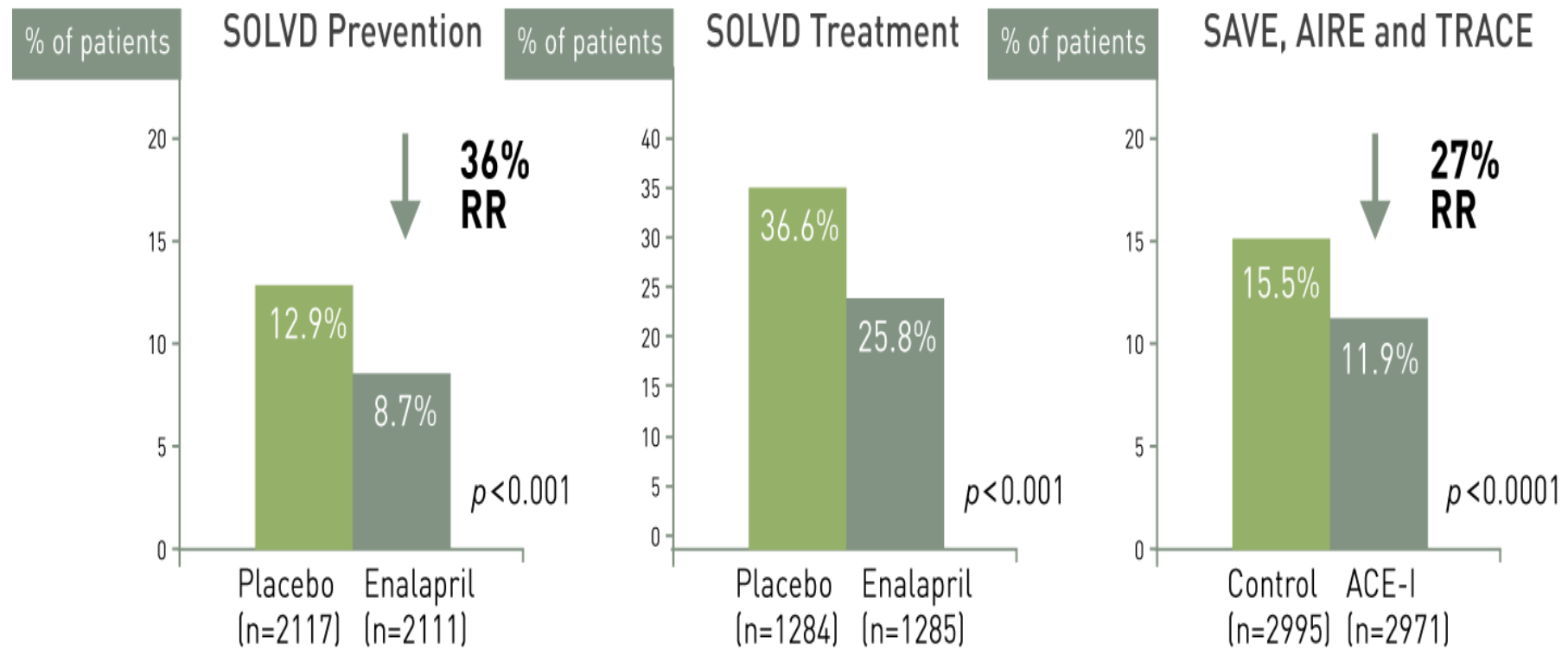
ACE inhibitori u srčanoj insuficijenciji

Indikovni kod svih pacijenata sa HFrEF uz beta blokator ako ne postoje kontraindikacije radi smanjenja mortaliteta

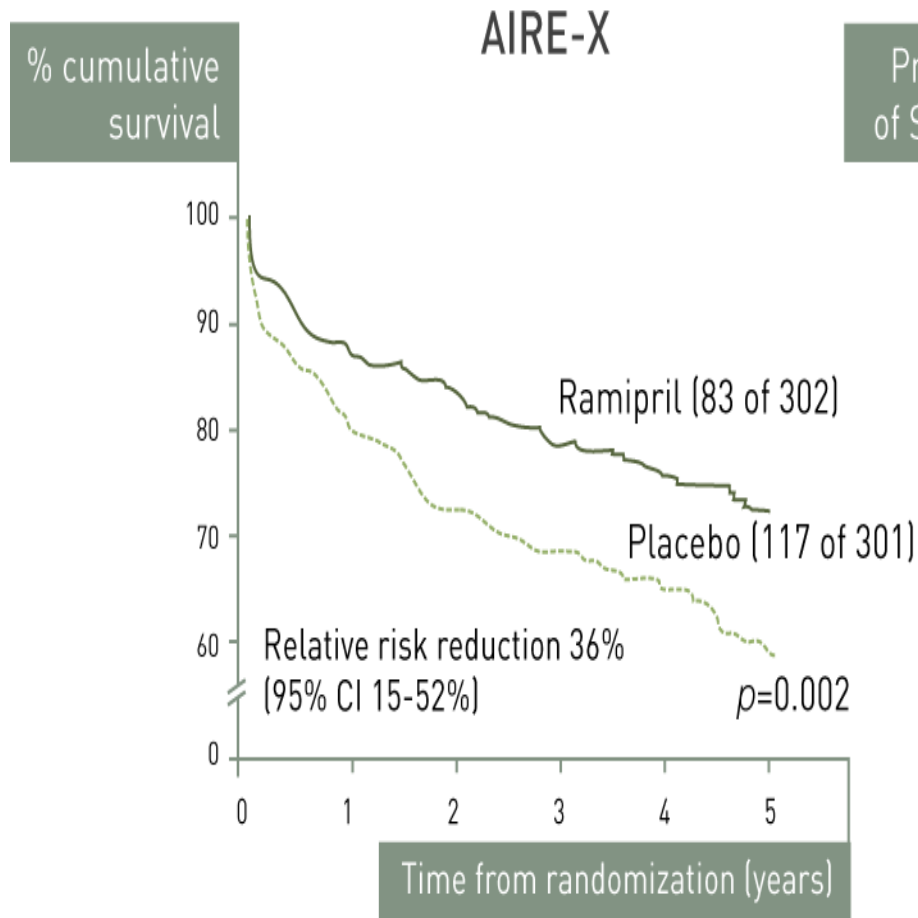


Ove studije se odnose na primenu ACE I u SI sa i bez koronarne bolesti

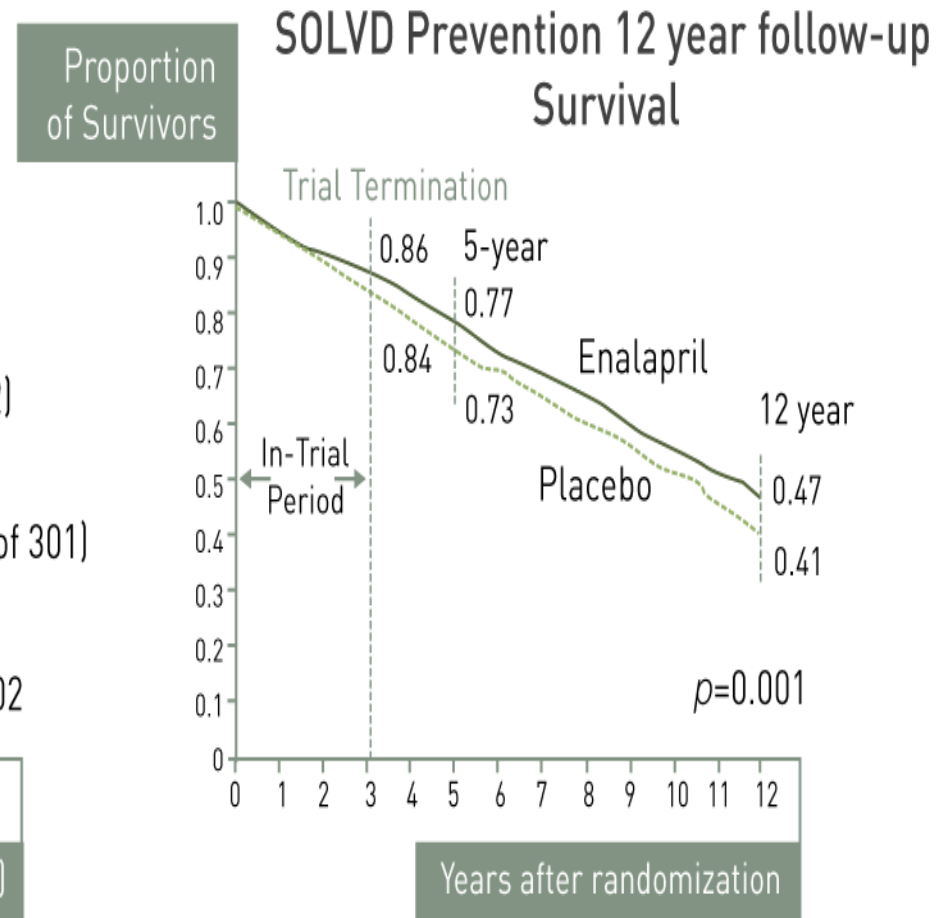
ACE Inhibitori – redukcija hospitalizacije zbog srčane insuficijencije



ACE inhibitori uticaj na preživljavanje

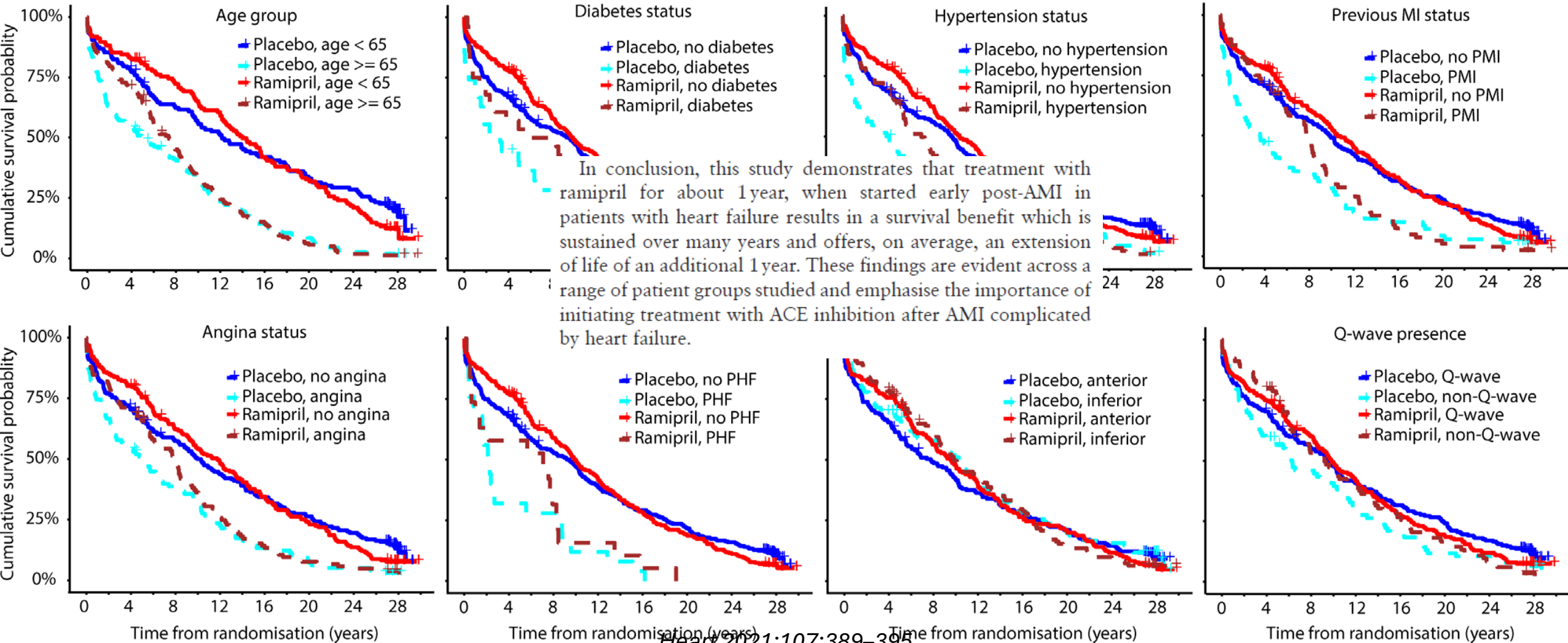


Hall AS et al. *Lancet* 1997;349:1493-7.



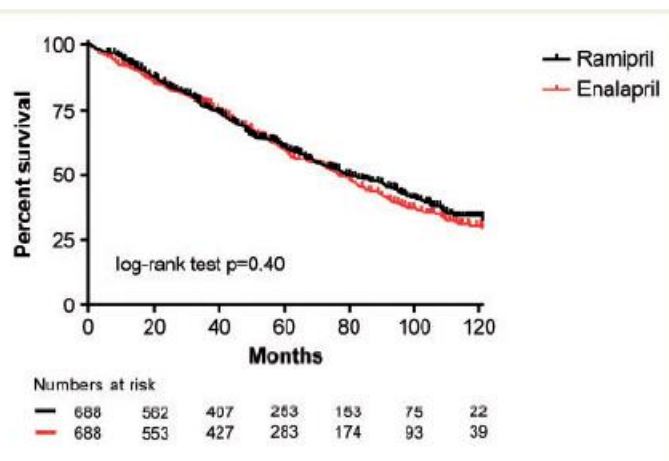
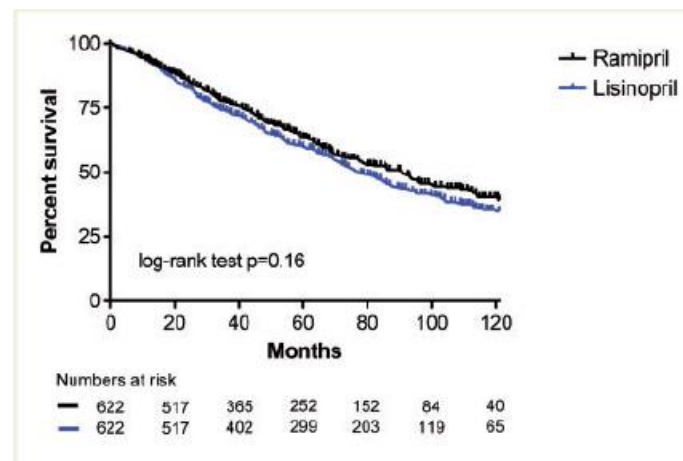
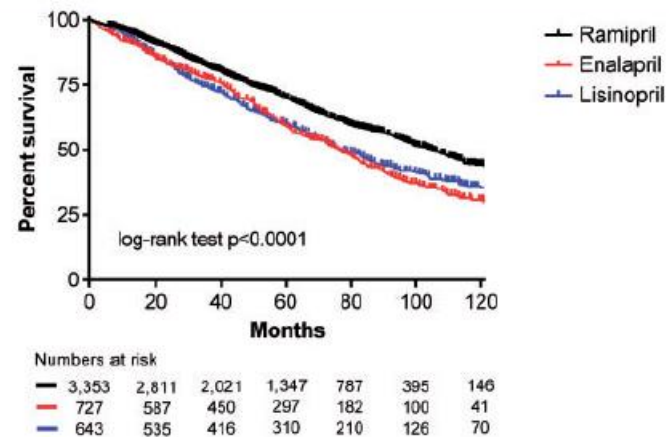
Jong P et al. *Lancet* 2003;361:1843-8.

Long-term survival benefit of ramipril in patients with acute myocardial infarction complicated by heart failure

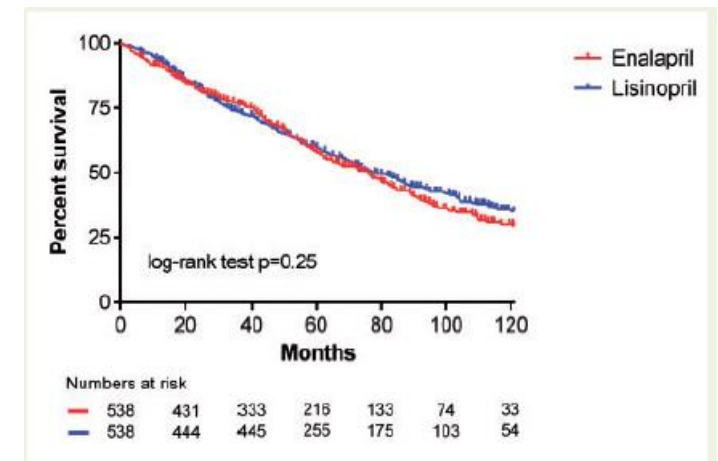


Comparative effectiveness of enalapril, lisinopril, and ramipril in the treatment of patients with chronic heart failure: a propensity score-matched cohort study

Kv mortalitet

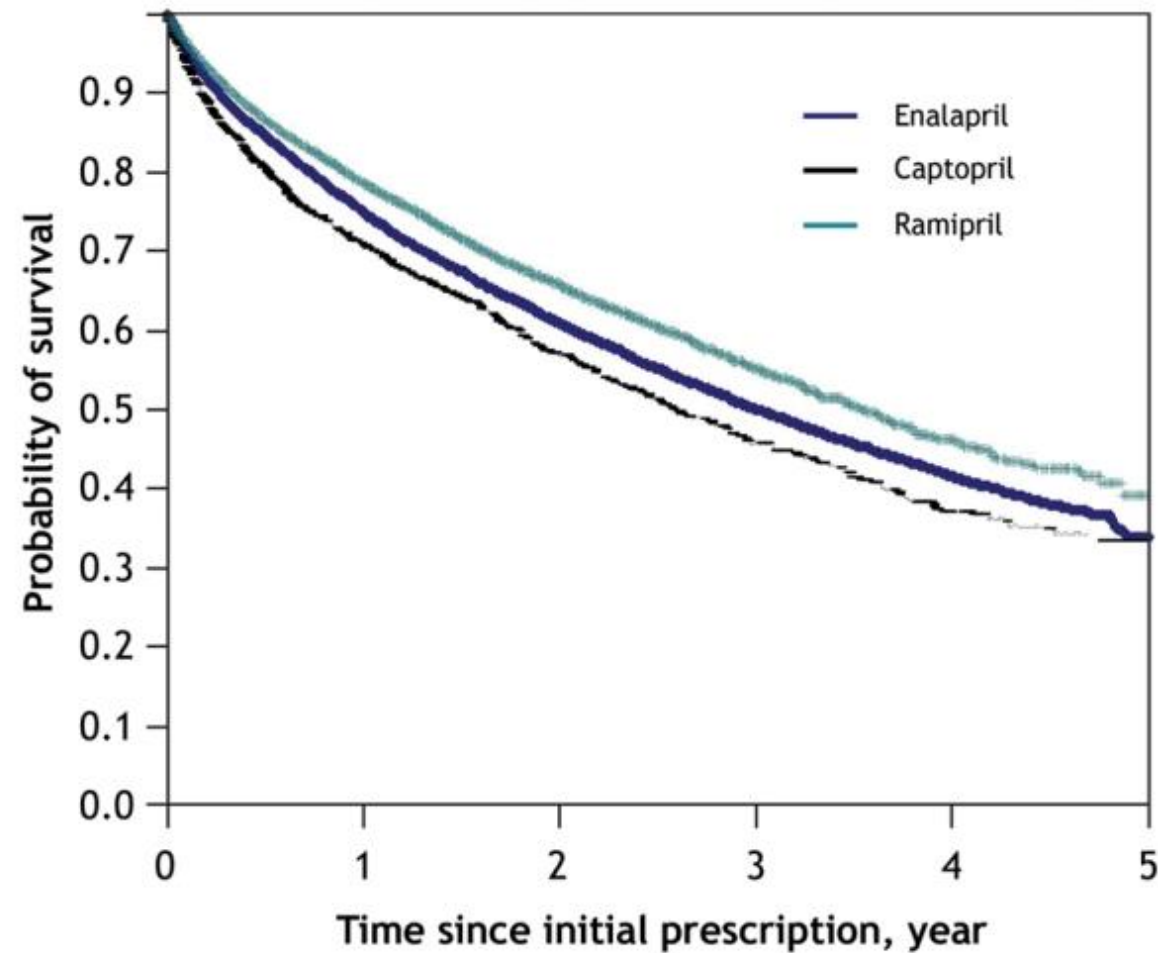


Ukupni mortalitet



Effect of different angiotensin-converting-enzyme inhibitors on mortality among elderly patients with congestive heart failure

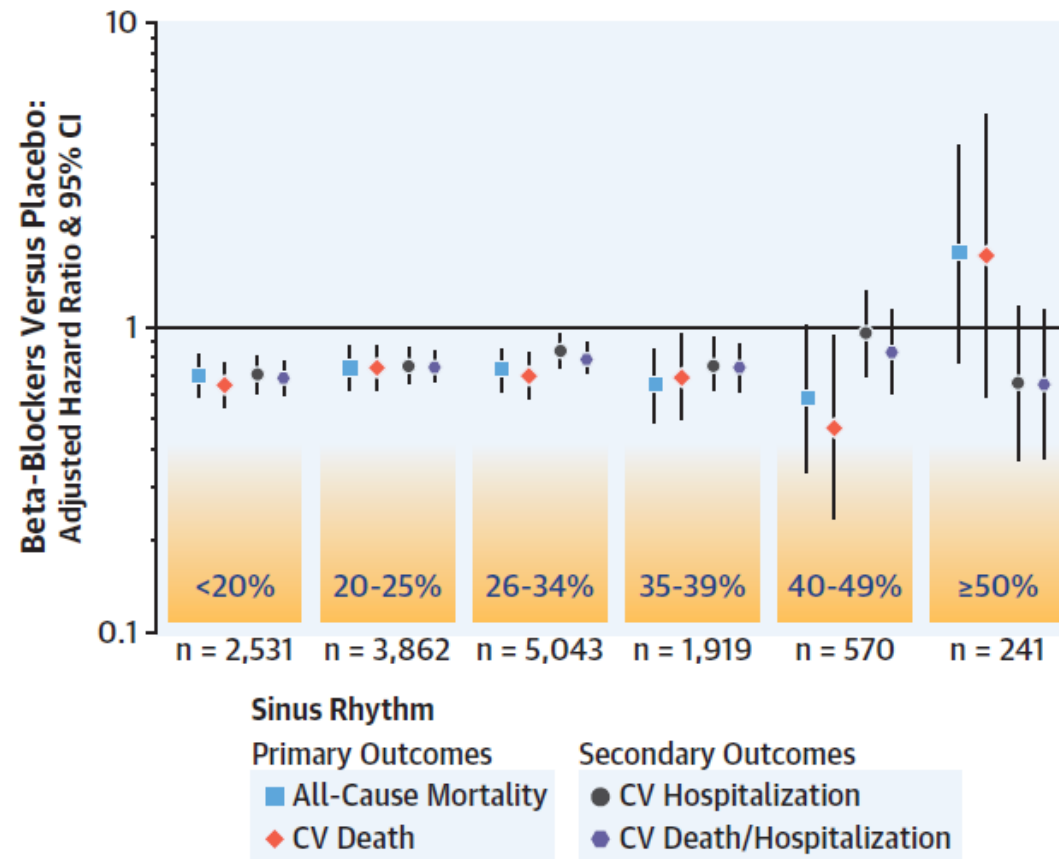
Louise Pilote MD PhD, Michal Abrahamowicz PhD, Mark Eisenberg MD MPH, Karin Humphries DSc, Hassan Behlouli MSc PhD, Jack V. Tu MD PhD



Uloga beta blokatora u srčanoj insuficijenciji

Cardiac Disease	Effects of β -Blockers Based on RCTs	Recommendations
Heart failure with reduced ejection fraction	• Reduces mortality • Reduces hospitalizations	• Use widely
Heart failure with mid-range or preserved ejection fraction	• Insufficient data on major adverse cardiac outcomes	• No data to support use without a secondary indication (i.e., atrial fibrillation, hypertension) • Large RCTs needed
Post ACS	Immediate effect: • Reduces mortality (pre-reperfusion era data) • Reduces re-infarction • Can increase risk of heart failure and cardiogenic shock (mainly observed in patients at higher risk) Longer-term effect: • Reduces mortality (pre-reperfusion era data)	• Initiate post-ACS in patients without a low blood pressure or clinical evidence of decompensated heart failure • Start at low doses, and titrate gradually to avoid adverse effects • Continue treatment for up to 3 years (or permanently if heart failure with reduced ejection fraction) • Large contemporary RCTs in progress to study long-term effect in patients without left ventricular dysfunction
Stable CAD (without recent ACS, and with normal left ventricular function)	• Insufficient data on major adverse cardiac outcomes	• Use for angina • No data to support routine use • Large RCTs needed

Efikasnost BB u zavisnosti od EF



CIBIS I: bisoprolol u lečenju srčane insuficijencije

- Redukcija mortaliteta sa bisoprololom

... ukupno (n = 641)	– 20%	p = 0.22
... bez IM	– 47%	p = 0.01
... sa dilatativnom CMP	– 53%	p = 0.01
... Sa komorskim odgovorom preko 80 otk/min	– 42%	p < 0.05

- Redukcija za jednu NYHA klasu kod bolesnika koji su primali ...

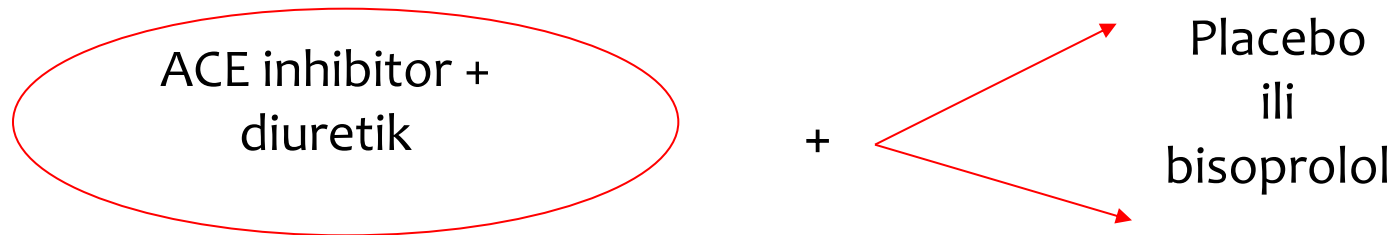
... bisoprolol	21%	p = 0.04
... placebo	15%	

- Redukcija u pogledu dekompenzacije
koja zahteva hospitalizaciju

– **32%** p < 0.01

- uz izvanrednu toleranciju beta blokade

CIBIS II: bisoprolol u lečenju srčane insuficijencije (NYHA III + IV)

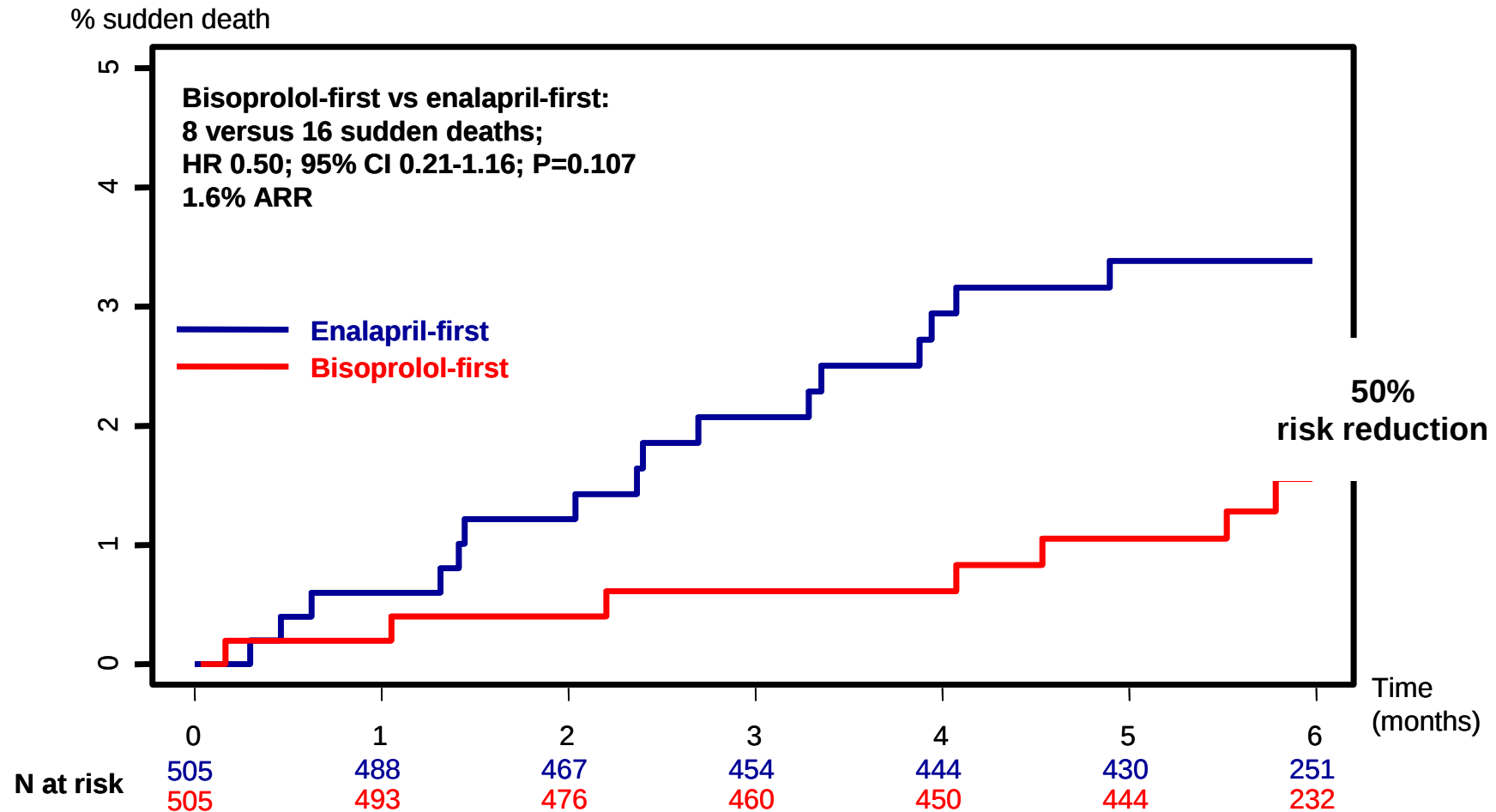


U bisoprolol grupi došlo je do značajne redukcije u

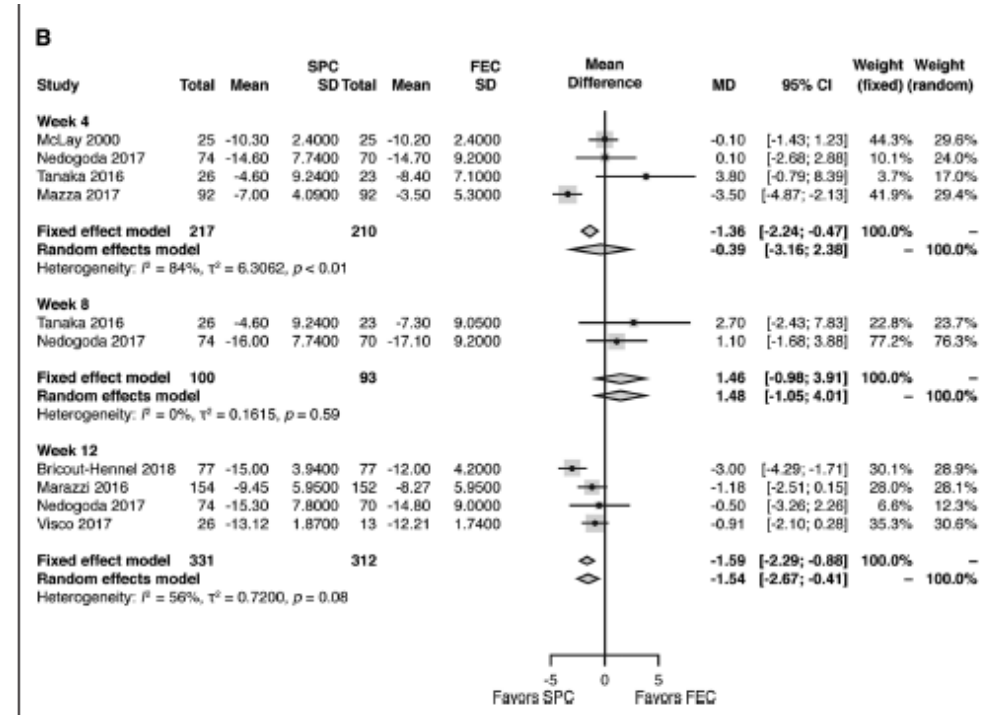
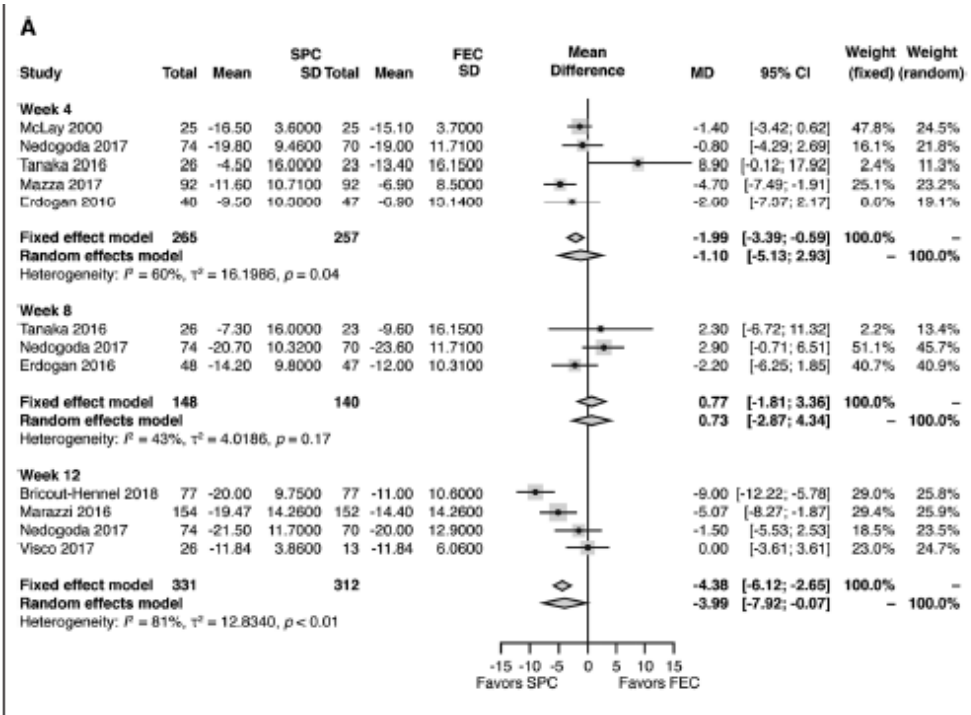
Mortalitetu (nezavisno od etiologije) za	34% (p<0.0001)
Iznenadne smrti za	44% (p<0.0011)
Hospitalizacija za	20% (p<0.0006)
Hospitalizacija zbog pogoršanja HSS za	36% (p<0.0001)

CIBIS III studija

NAGLA SMRT – MONOTERAPIJSKA FAZA



Dobit od fiksnih kombinacija u regulaciji sistolnog i dijastolnog pritiska



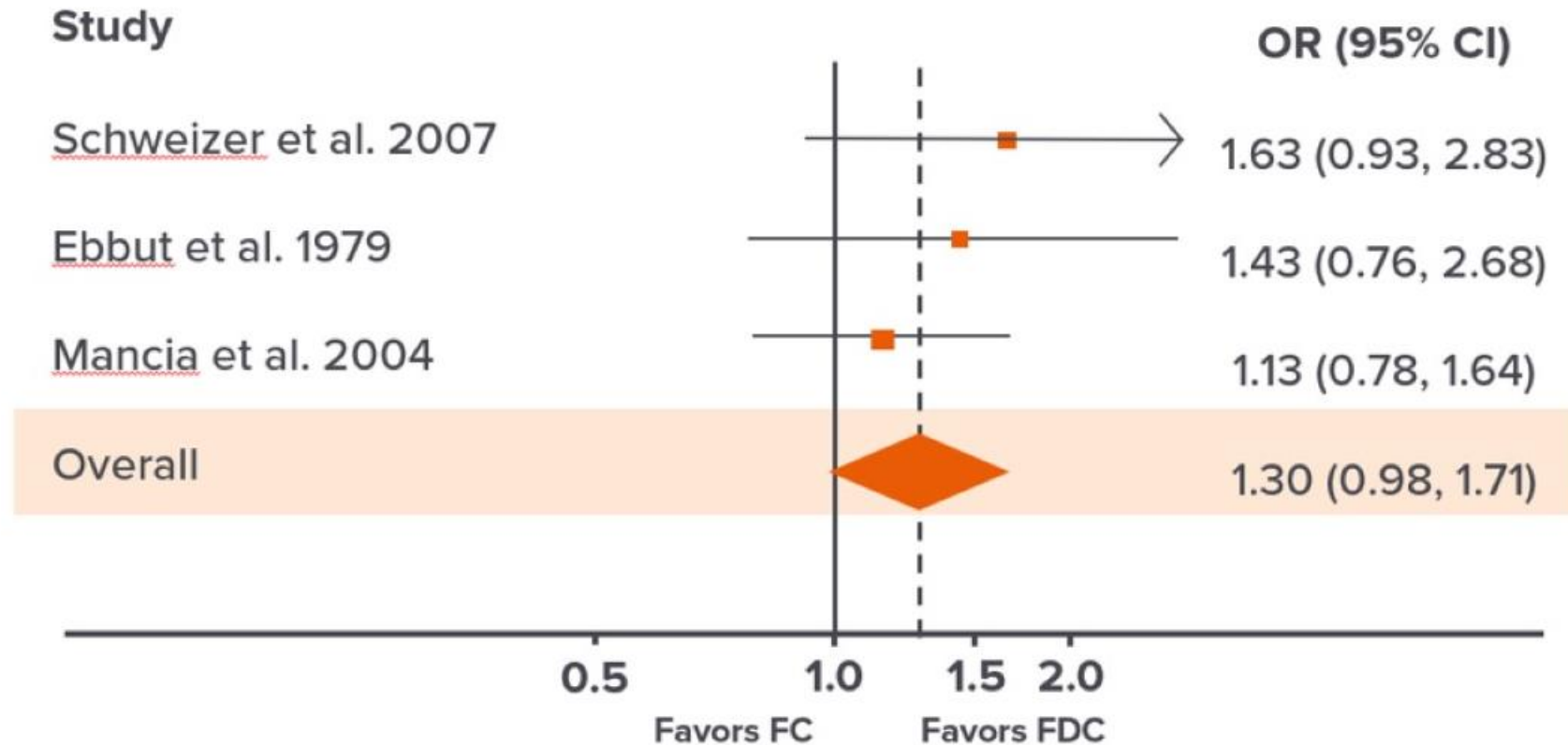
Summary

Single-pill combination therapy leads to improved medication adherence and persistence compared with free-equivalent combination therapy and may lead to better blood pressure control in patients with hypertension.

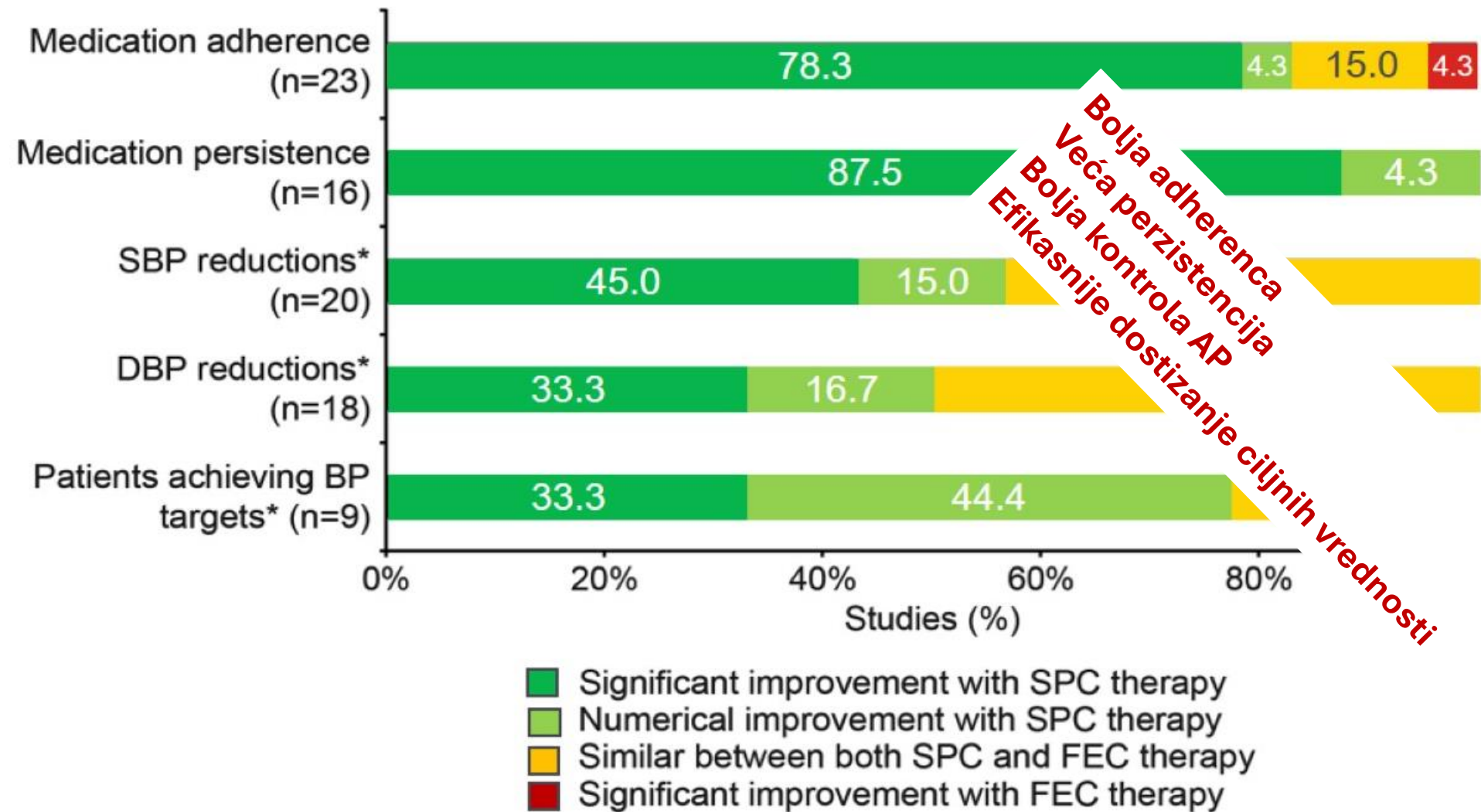
Započinjanje lečenja fiksnim kombinacijama bolje redukuje KV događaje

SBP and DBP Normalization Ratios

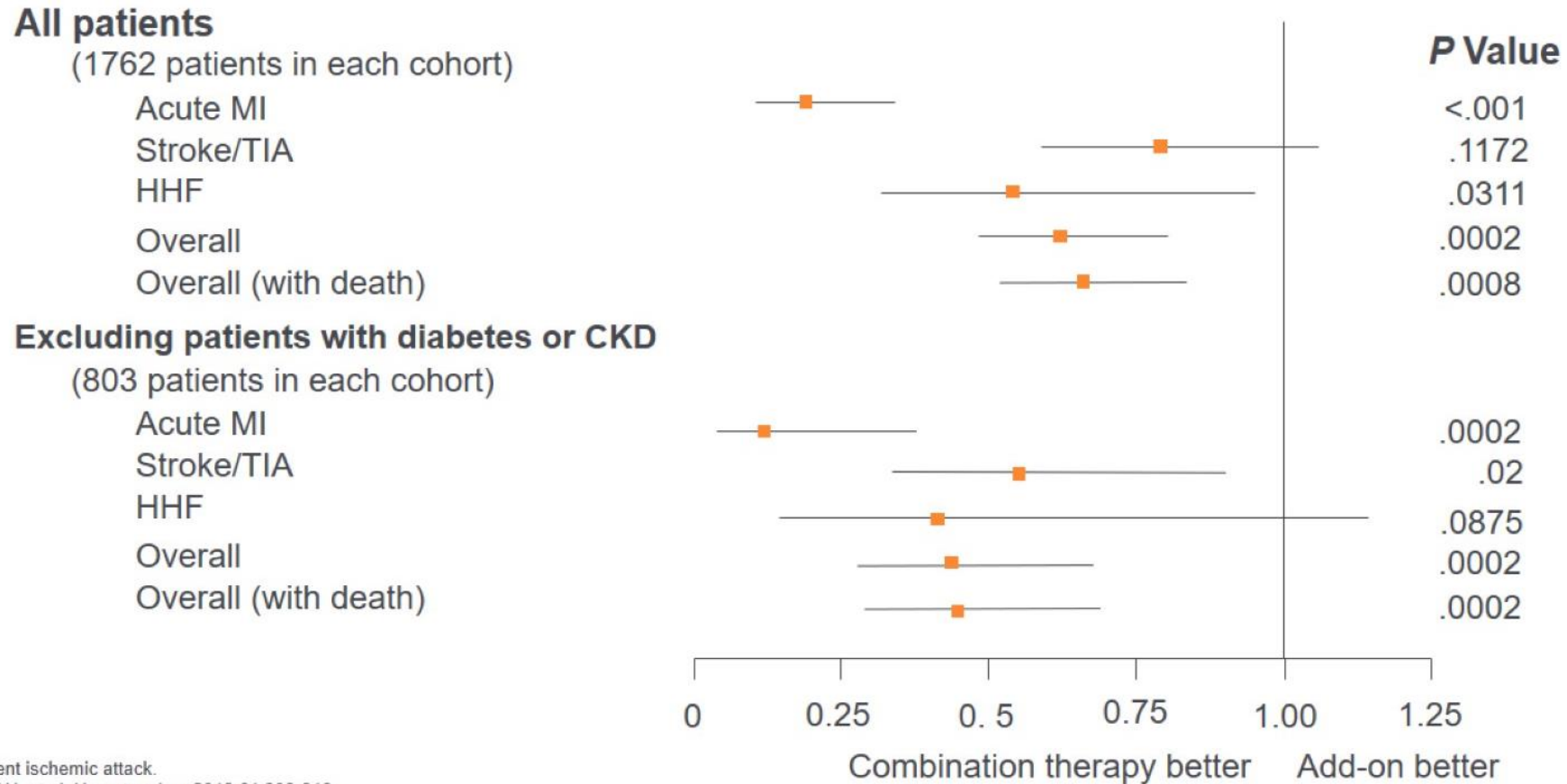
Three studies including 653 patients



Prednost fiksnih kombinacija



Započinjanje lečenja fiksnim kombinacijama redukuje KV događaje kod hipertenzivnih pacijenata



Inicijalna primena fiksnih kombinacija i redukcija KV događaja

Podaci iz realnog života - Lombardija

44534 ispitanika
Započinjanje monoterapije
(37078) i započinjanje
lečenja fiksnim
kombinacijama (7456

Evaluacija rizika od KV
događaj

Primena fiksnih kombinacija
rezultovala je efikasnijom
KV protekcijom

Outcome	HR (95% CI)	P Value
Any CV event	0.85 (0.74, 0.97)	.02
Ischemic heart disease	0.73 (0.56, 0.95)	.02
Cerebrovascular disease	0.83 (0.61, 1.14)	.26
Heart failure	0.9 (0.54, 1.51)	.69
Atrial fibrillation	0.63 (0.42, 0.94)	.02