



PRAVA MERA  
ZA DOBAR HOLESTEROL  
I ZDRAVE KRVNE SODOVE

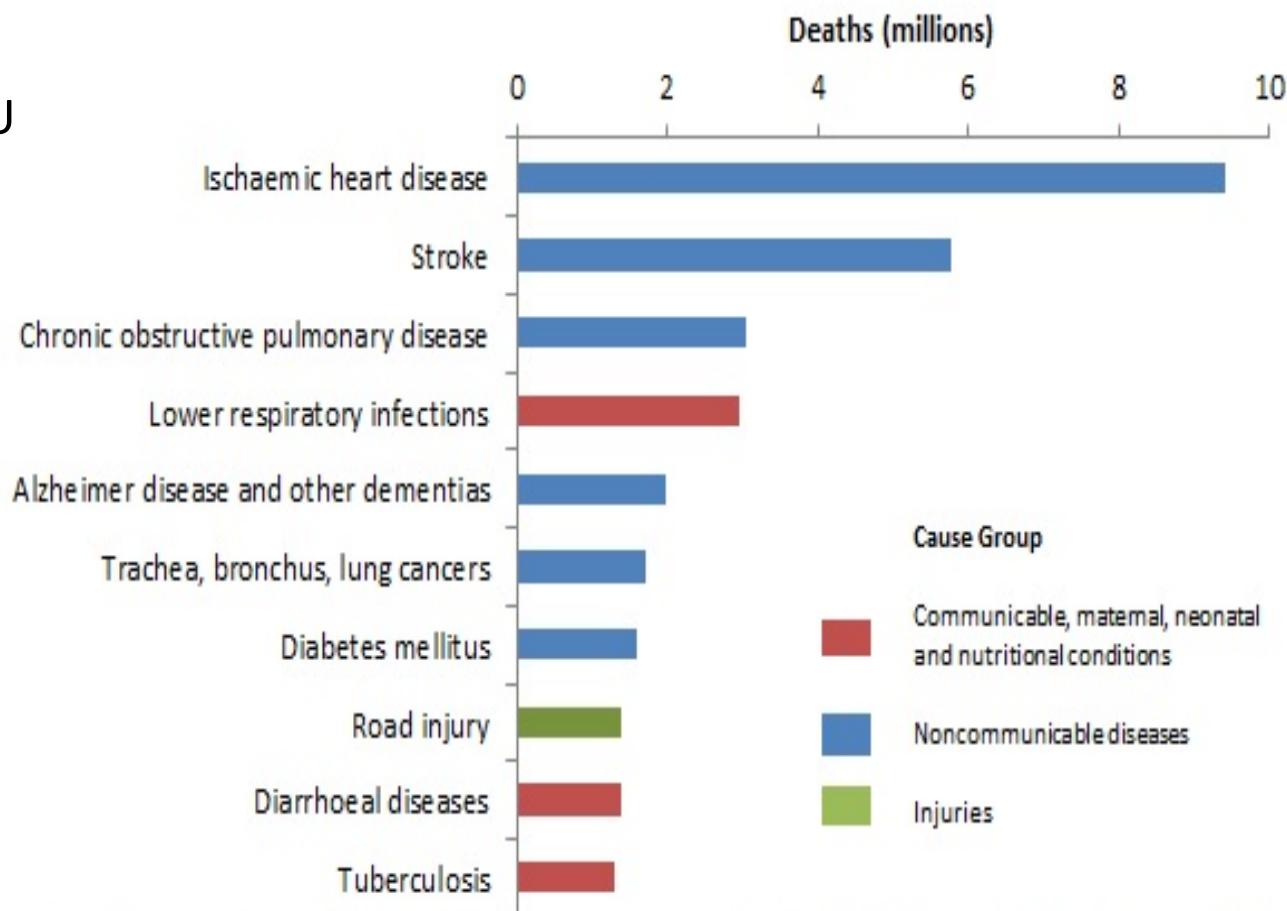
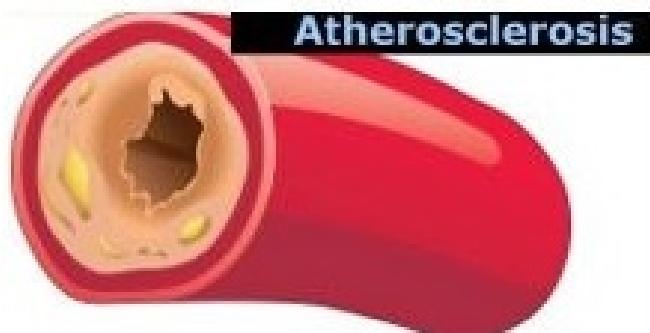


# SVET

## Top 10 global causes of deaths, 2016

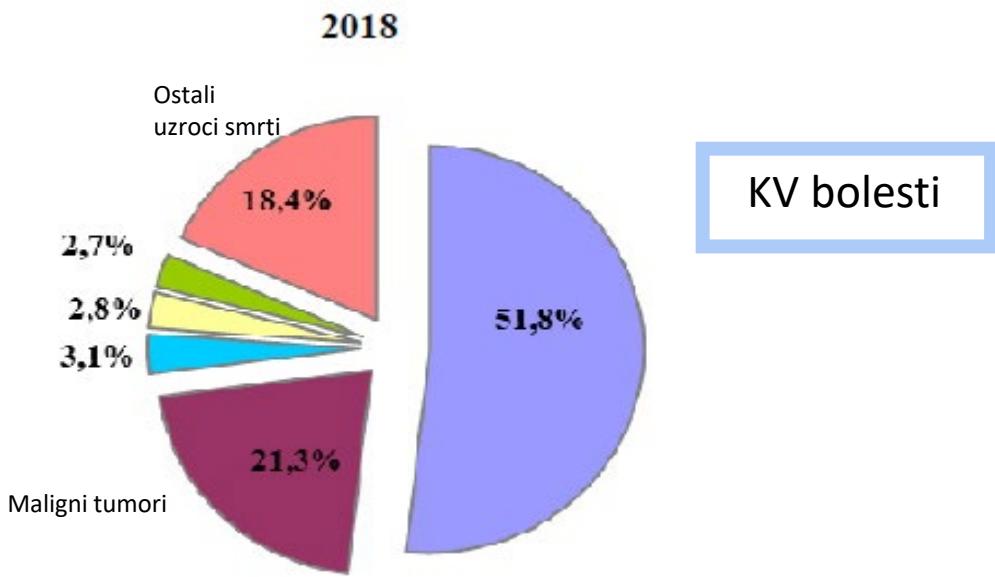
- KVB VODEĆI UZROČNIK SMRTNOSTI U SVETU
- SITUACIJA JE ISTA VEĆ 15 GODINA

**15.2 milion od IBS i MU**

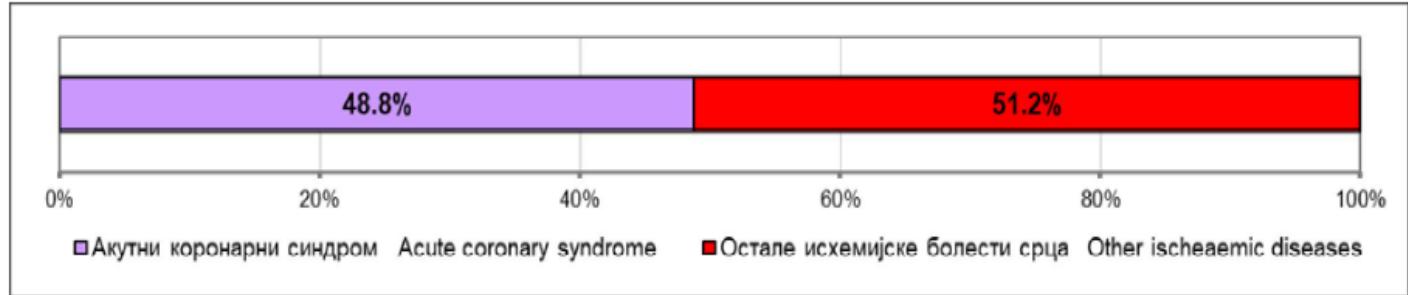


Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

# SRBIJA-epidemiologija, statistika



KV bolesti



Struktura umiranja (%) od ishemijskih bolesti srca, Republika Srbija, 2018.

Stopa mortaliteta (na 100.000 stanovnika) od vodečih nezaraznih bolesti, Republika Srbija, 2018.

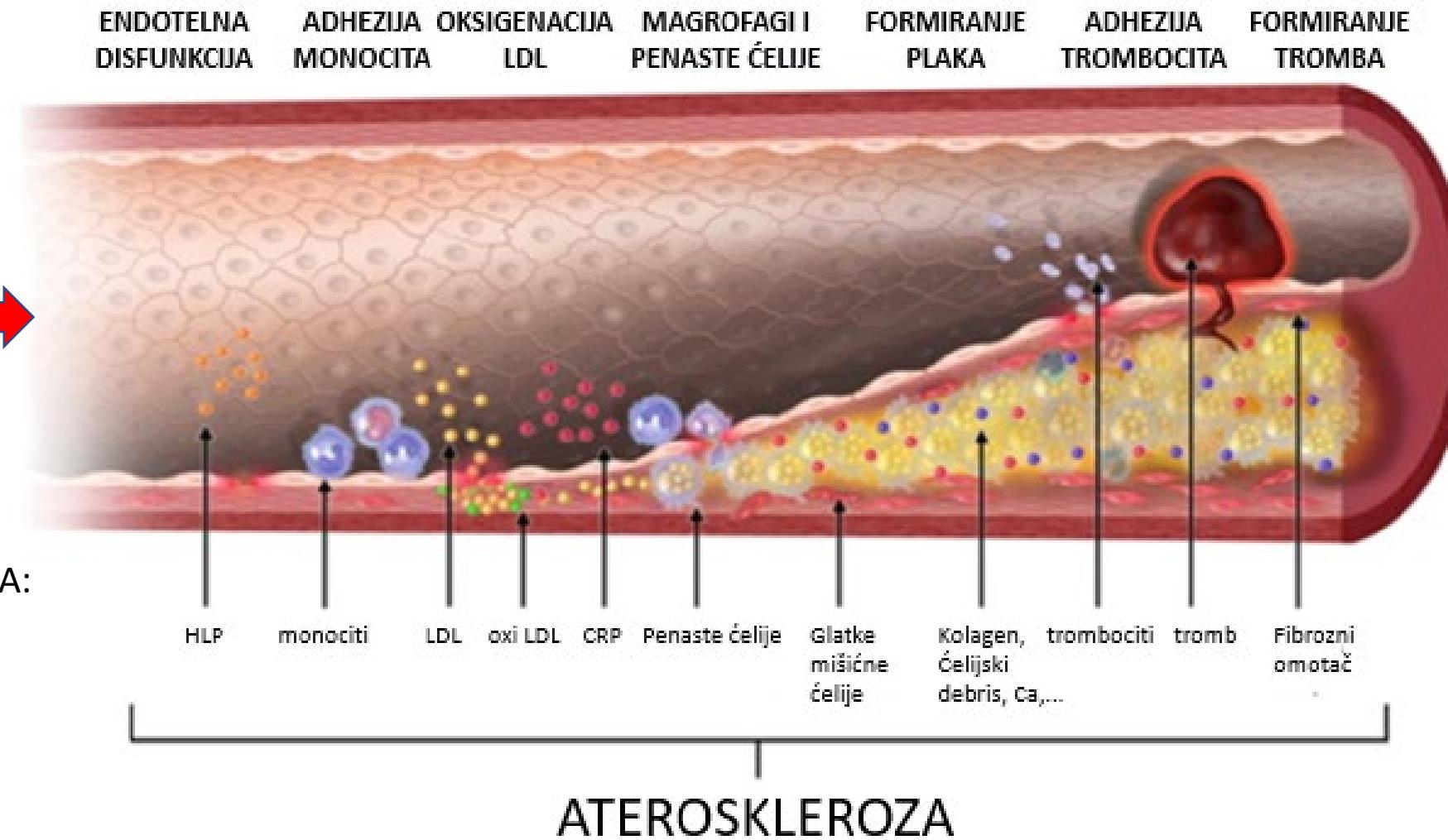
U Srbiji u proseku 36000 godišnje oboli MU i IM  
1 događaj na svakih 15min  
1 smrt na svakih sat vremena

# MEHANIZAM NASTANKA

1. DISLIPIDEMIJA
2. HIPERTENZIJA
3. PUŠENJE CIGARETA
4. HIPERGLIKEMIJA
5. OKSIDATIVNI STRES
6. HIPERHOMOCISTEINEMIJA
7. INFEKTIVNI AGENSI

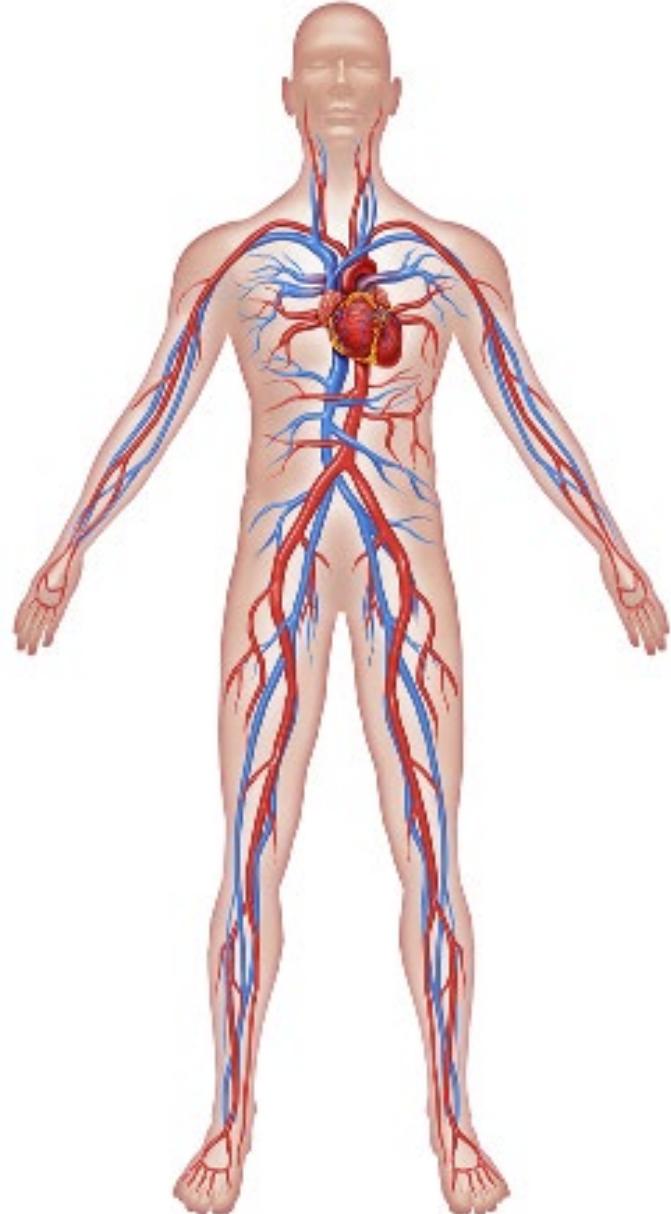
NEPROMENLJIVI FAKTORI RIZIKA:

- NASLEĐE
- POL
- GODINE



# GENERALIZOVANI PROCES

- Lumenska opstrukcija
- Akutni koronarni sindrom
- Moždani udar ili tranzitorni ishemijski atak
- Periferna arterijska bolest
- Visceralna ishemija
- Aneurizma aorte



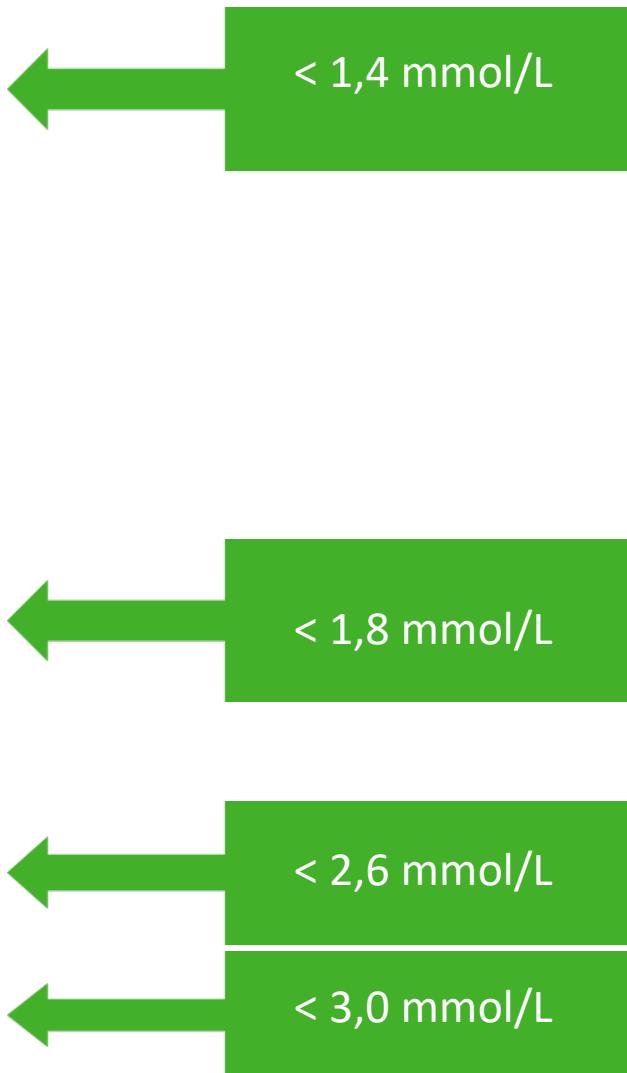
- Smatra se da je u većine ljudi oko **85. godine života** oko 60% koronarne cirkulacije prekriveno aterosklerotičnim plakovima, i to pod uslovom da u toku života nisu prisutni faktori rizika.
- U prisustvu faktora rizika kao što je **dislipidemija** takve promene na koronarnim krvnim sudovima se dostižu negde u **42. godini života**.

- Poremećaji lipida imaju fundamentalni značaj za aterogenezu
- Povišene vrednosti LDL holesterola, predstavljaju glavni faktor rizika.



Very-high-risk	<p>People with any of the following:</p> <p>Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having &gt;50% stenosis), or on carotid ultrasound.</p> <p>DM with target organ damage,<sup>a</sup> or at least three major risk factors, or early onset of T1DM of long duration (&gt;20 years).</p> <p>Severe CKD (eGFR &lt;30 mL/min/1.73 m<sup>2</sup>).</p> <p>A calculated SCORE ≥10% for 10-year risk of fatal CVD.</p> <p>FH with ASCVD or with another major risk factor.</p>
High-risk	<p>People with:</p> <p>Markedly elevated single risk factors, in particular TC &gt;8 mmol/L (&gt;310 mg/dL), LDL-C &gt;4.9 mmol/L (&gt;190 mg/dL), or BP ≥180/110 mmHg.</p> <p>Patients with FH without other major risk factors.</p> <p>Patients with DM without target organ damage,<sup>a</sup> with DM duration ≥10 years or another additional risk factor.</p> <p>Moderate CKD (eGFR 30—59 mL/min/1.73 m<sup>2</sup>).</p> <p>A calculated SCORE ≥5% and &lt;10% for 10-year risk of fatal CVD.</p>
Moderate-risk	<p>Young patients (T1DM &lt;35 years; T2DM &lt;50 years) with DM duration &lt;10 years, without other risk factors. Calculated SCORE ≥1 % and &lt;5% for 10-year risk of fatal CVD.</p>
Low-risk	<p>Calculated SCORE &lt;1% for 10-year risk of fatal CVD.</p>

# CILJNE VREDNOSTI ZA LDL za prevenciju KV oboljenja

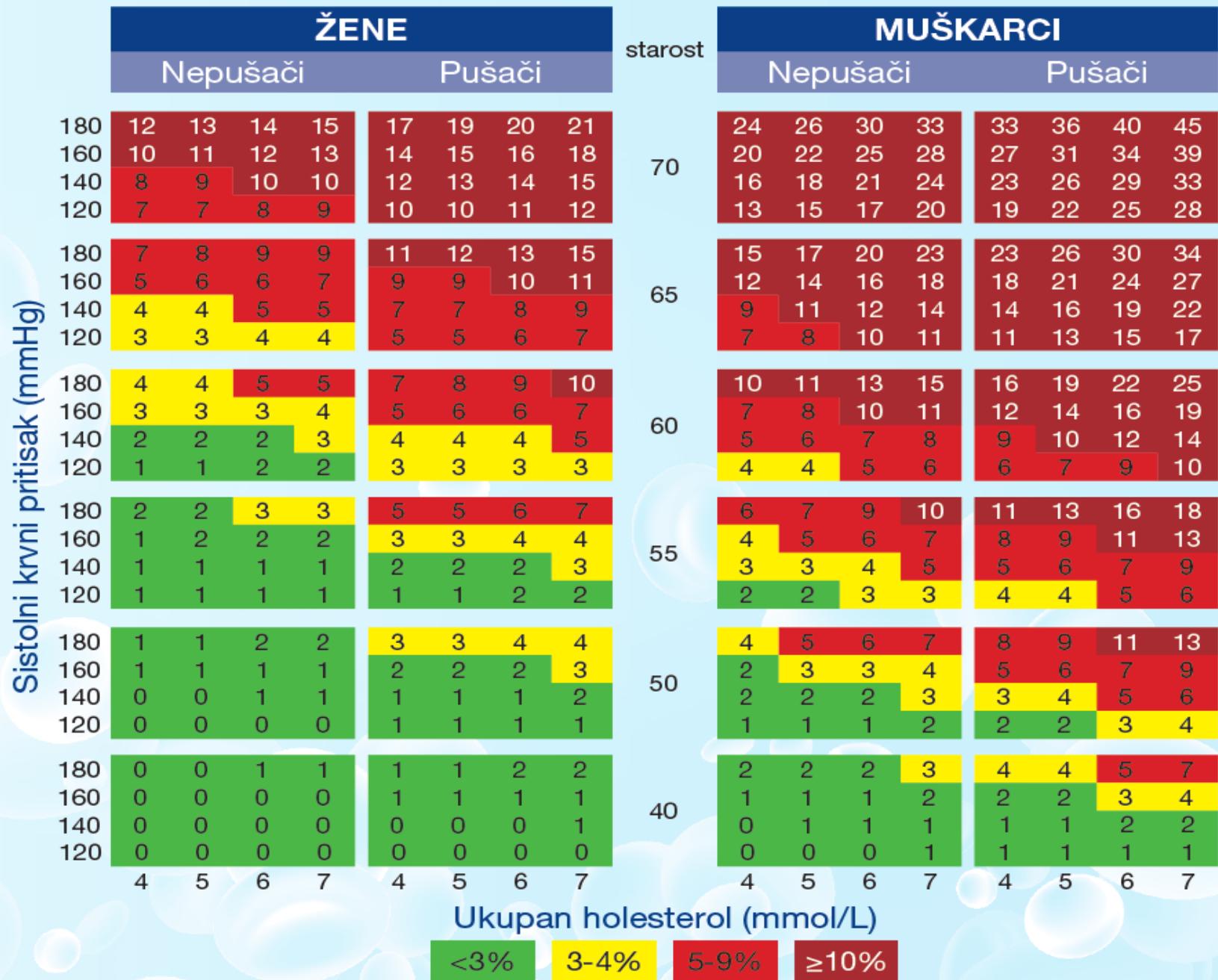


2019 ESC/EAS Guidelines for the management of dyslipidaemias

# SCORE tabela

10-godišnjeg rizika za fatalno kardiovaskularno oboljenje u populaciji sa visokim kardiovaskularnim rizikom<sup>1</sup>

## *2019 ESC/EAS Guidelines for the management of dyslipidaemias*



# ARTERINORM

JEDINSTVENI PROIZVOD NA TRZISTU koji reguliše

3 ključna mehanizma za nastanak aterosleroze.

Ekstrakt fermentisanog crvenog pirinča (monascus purpureus), standardizovan na 1,5% monakolina K	200,0 mg	Snižavaju nivo LDL holesterola, triglicerida i podižu nivo HDL holesterola u krvi
Alifatični alkoholi dugog lanca (polikozanol), standardizovani na 60% oktakozanola	10,0 mg	
<b>Vitamin B3 (niacin)</b>	27,0 mg	Snižavaju nivo homocisteina u krvi
<b>Folna kiselina</b>	300,0 µg	
<b>Vitamin B6</b>	2,0 mg	
<b>Vitamin B12</b>	1,0 µg	
<b>Vitamin E</b>	20,0 mg	Antioksidativna zaštita
<b>Ekstrakt čaja (Camellia sinensis)</b> standardizovan na 40% polifenola	144,0 mg	

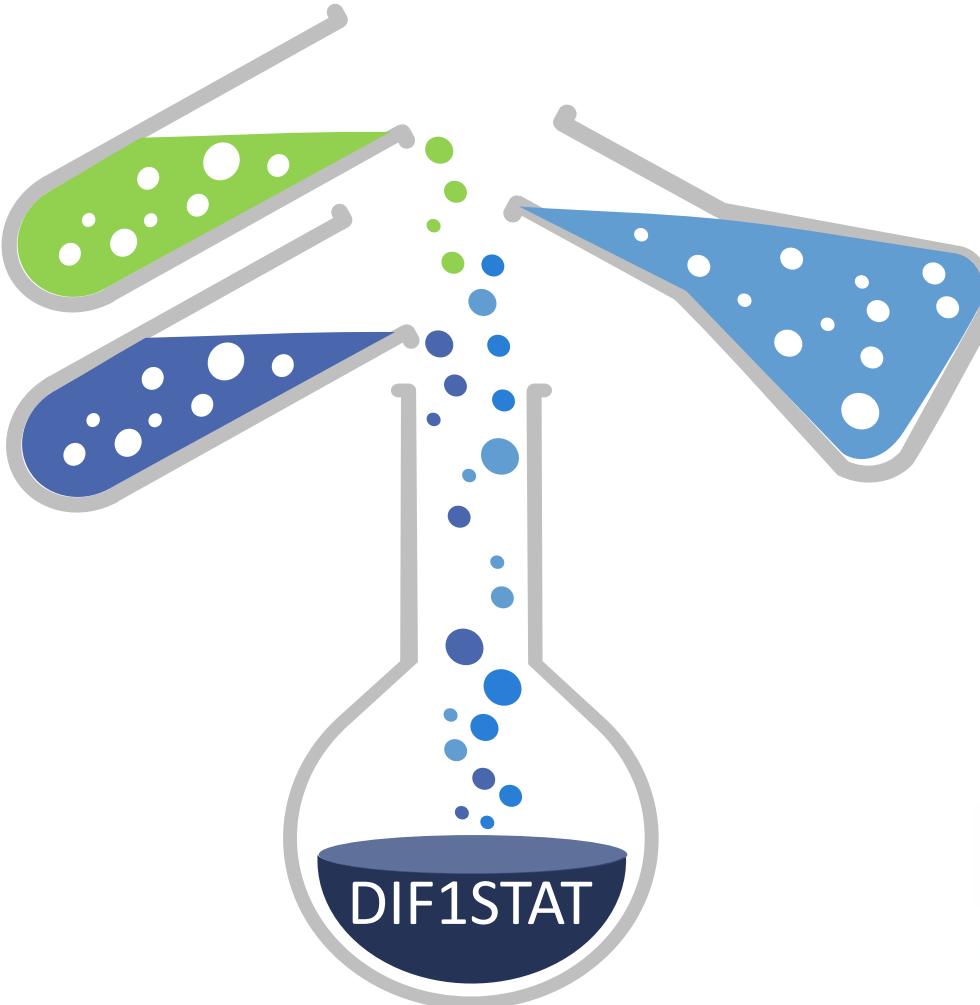
# HIPOLIPEMIJSKI EFEKAT – DIF1STAT

## SINERGIZAM BIOAKTIVNIH SUPSTANCI

POLIKOZANOLI

NIACIN

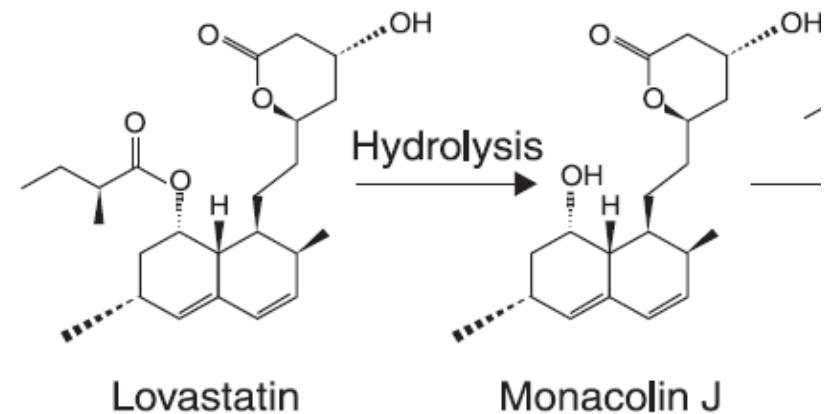
MONAKOLIN K



# Fermentisani crveni pirinač

Monakolin K dobija se fermentacijom belog  
pirinča pomoću plesni *Monascus purpureus*

Deluje istim mehanizmom kao i sintetski statini,  
tako što blokira endogenu produkciju  
holesterola u jetri inhibicijom HMG Co  
reduktaze, ključni enzim u procesu sinteze  
holesterola.



Delotvornost 2,5-10 mg Monakolina K dokazana je u više od 30 kliničkih studija dostupnih u bazi podataka PubMed.

Potvrda njegove efikasnosti je jasno definisana kroz aktuelne Evropske vodiče u lečenju dislipidemija 2019.



# Uticaj promene zivotnog stila na nivo lipida

**Table 8 Impact of specific lifestyle changes on lipid levels**

	Magnitude of the effect	Level
<b>Lifestyle interventions to reduce TC and LDL-C levels</b>		
Avoid dietary trans fats	++	A
Reduce dietary saturated fats	++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A
Use red yeast rice nutraceuticals	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B
<b>Lifestyle interventions to reduce TG-rich lipoprotein levels</b>		
Reduce excessive body weight	+	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrates	++	A
Use supplements of n-3 polyunsaturated fats	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fats with mono- or polyunsaturated fats	+	B
<b>Lifestyle interventions to increase HDL-C levels</b>		
Avoid dietary trans fats	++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fats	++	A
Modest consumption in those who take alcohol may be continued	++	B
Quit smoking	+	B

The magnitude of the effect (+++ = >10%, ++ = 5–10%, + = <5%) and the level of evidence refer to the impact of each dietary modification on plasma levels of a specific lipoprotein class.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

2019 ESC/EAS Guidelines for the management of dyslipidaemias



## **2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk***

**Primena monakolina K je opravdana kod pacijenata koji ne žele ili iz razloga pojave neželjenih dejstava ne mogu da koriste standardne statine. (15%)**

### **7.5.2 Monacolin and red yeast rice (RYR)**

In the only available RCT in patients with ASCVD, a partially purified extract of RYR reduced recurrent events by 45%. A clinically relevant hypocholesterolaemic effect (up to a 20 % reduction) has been observed with RYR preparations providing a once daily dose of 2.5-10 mg monacolin K. Nutraceuticals containing purified RYR may be considered in people with elevated plasma cholesterol concentrations who do not qualify for treatment with statins in view of their global CV risk.

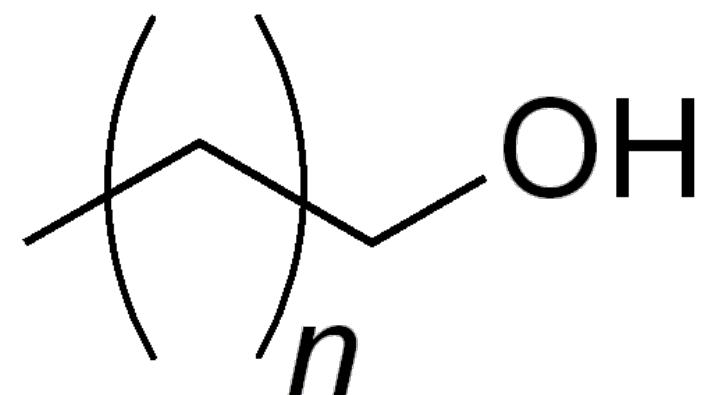
# Polikozanoli

Polikozanol je prirodni ekstrakt biljnih voskova u kom dominira oktakozanol (izolovan iz šećerne trske).

Imaju složeni mehanizam dejstva, najverovatnije dovode do  $\downarrow$  sinteze holesterola u jetri i  $\uparrow$  LDL katabolizma u krvi

Hipolipemski efekti su dokazani u preko 60 kliničkih studija radjenih na 3000 bolesnika

Smatra se da ima i antiagregaciono dejstvo (20mg = 100mg ASA)





[www.ahjonline.com](http://www.ahjonline.com)



TC      17%-21%



LDL-C    21%-29%



HDL-C    8%-15%

## Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent

Ioanna Gouni-Berthold, MD,<sup>a</sup> and Heiner K. Berthold, MD, PhD<sup>b</sup> Rotenburg an der Fulda and Bonn, Germany

**Background** Policosanol is a mixture of higher primary aliphatic alcohols isolated from sugar cane wax, whose main component is octacosanol. The mixture has been shown to lower cholesterol in animal models, healthy volunteers, and patients with type II hypercholesterolemia.

**Methods** We reviewed the literature on placebo-controlled lipid-lowering studies using policosanol published in peer-reviewed journals as well as studies investigating its mechanism of action and its clinical pharmacology.

**Results** At doses of 10 to 20 mg per day, policosanol lowers total cholesterol by 17% to 21% and low-density lipoprotein (LDL) cholesterol by 21% to 29% and raises high-density lipoprotein cholesterol by 8% to 15%. Because higher doses have not been tested up to now, it cannot be excluded that effectiveness may be even greater. Daily doses of 10 mg of policosanol have been shown to be equally effective in lowering total or LDL cholesterol as the same dose of simvastatin or pravastatin. Triglyceride levels are not influenced by policosanol. At dosages of up to 20 mg per day, policosanol is safe and well tolerated, as studies of >3 years of therapy indicate. There is evidence from *in vitro* studies that policosanol may inhibit hepatic cholesterol synthesis at a step before mevalonate generation, but direct inhibition of the hydroxy-methylglutaryl-coenzyme A reductase is unlikely. Animal studies suggest that LDL catabolism may be enhanced, possibly through receptor-mediated mechanisms, but the precise mechanism of action is not understood yet. Policosanol has additional beneficial properties such as effects on smooth muscle cell proliferation, platelet aggregation, and LDL peroxidation. Data on efficacy determined by clinical end points such as rates of cardiac events or cardiac mortality are lacking.

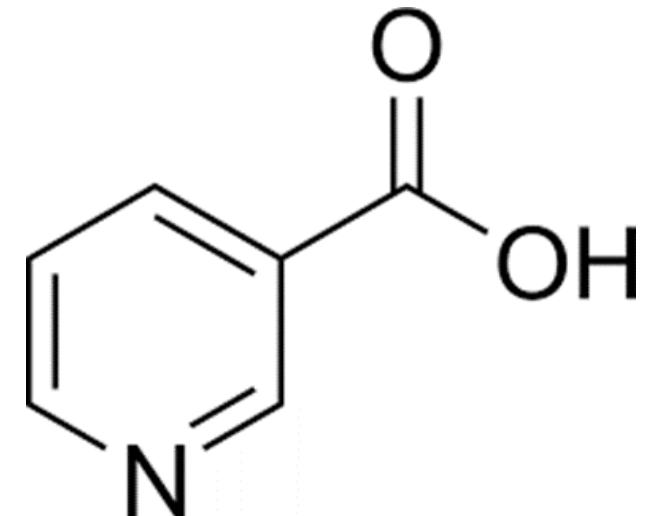
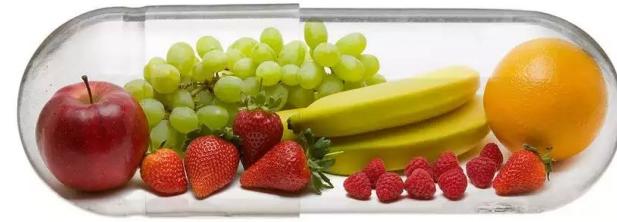
**Conclusions** Policosanol seems to be a very promising phytochemical alternative to classic lipid-lowering agents such as the statins and deserves further evaluation. (Am Heart J 2002;143:356-65.)

# Niacin

Vitamin B3 ili nikotinska kiselina

Neophodan je za metabolisanje šećera,  
masti i proteina

- Dovodi i do redukcije ukupnog i LDL holesterola
- Snižava trigliceride
- **Najefikasnije povećava HDL holesterol**



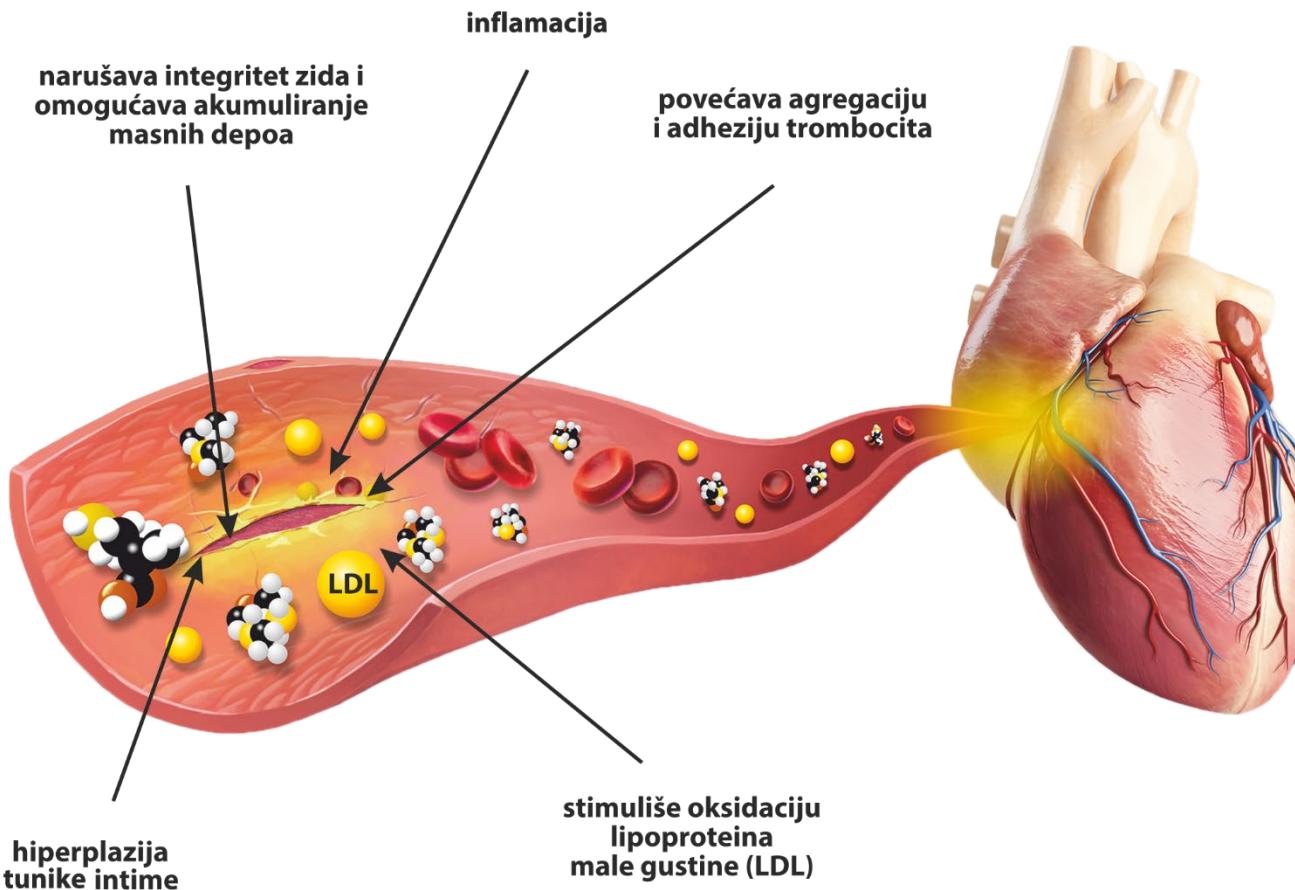


# 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

## 8.9 Nicotinic acid

Nicotinic acid has key action sites in both the liver and adipose tissue. In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 resulting in decreased secretion of VLDL particles, which is also reflected in reductions of plasma levels of both IDL and LDL particles.<sup>335</sup> Nicotinic acid primarily raises HDL-C and ApoA1 by stimulating ApoA1 production in the liver.<sup>335</sup> Two large randomized trials with nicotinic acid—one with extended-release niacin<sup>66</sup> and one with niacin plus laropiprant<sup>67</sup>—have shown no beneficial effect and an increased frequency of serious adverse effects. No medication con-

# HOMOCISTEIN - Samostalni faktor rizika za aterosklerozu

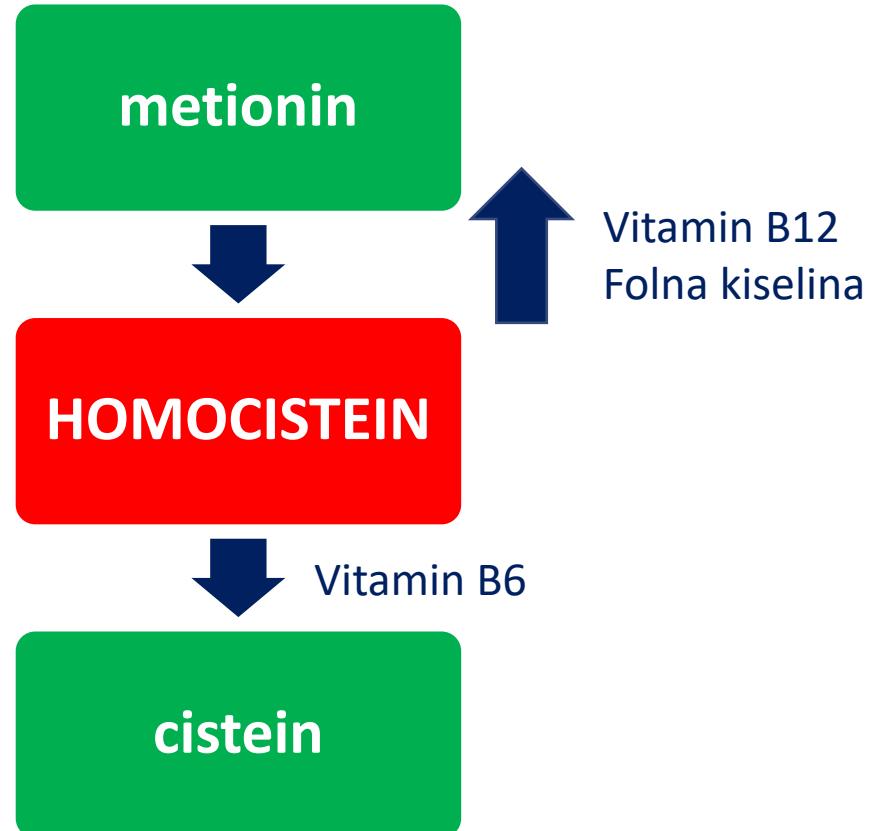


# HOMOCISTEIN

Proizvodi se u organizmu

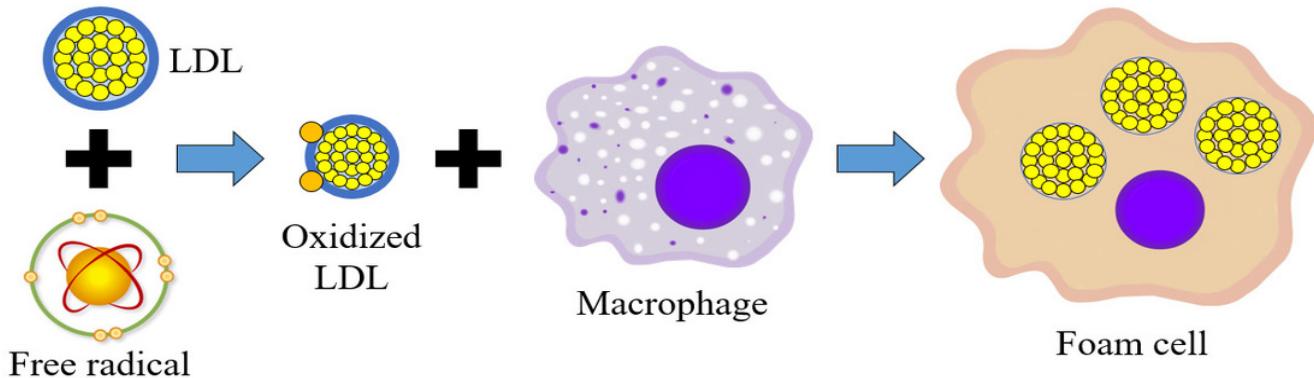
Nedostatak vitamina B6, B9 i B12  
dovodi do zadržavanja viših koncentracija  
homocisteina u krvi

Povišene vrednosti homocisteina su  
samostalni faktor rizika za razvoj KVB



# OKSIDATIVNI STRES

- Slobodni radikali i lipidna peroksidacija, prema brojnim studijama koje su do danas objavljene, predstavljaju glavni okidač za nastanak bolesti krvnih sudova tako što dovode do procesa ateroskleroze i **promena na endotelu krvnih sudova**.
- Lipidna peroksidacija LDL-čestica predstavlja jedan od glavnih procesa koji doprinose nastajanju arterogenog procesa.



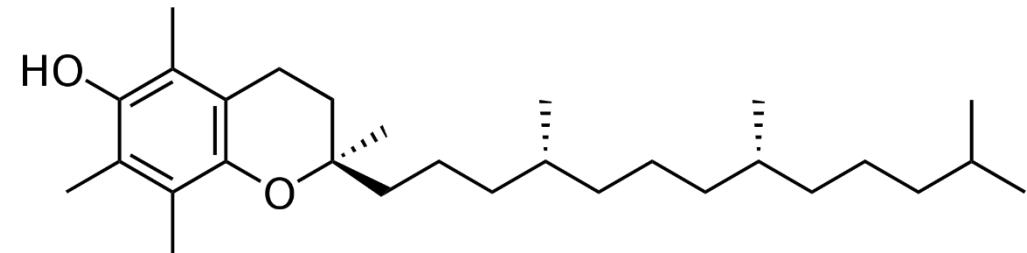
## ANTIOKSIDATIVNA ZAŠTITA

Antioksidansi su biološki aktivne materije koje uklanjaju višak slobodnih radikala i na taj način sprečavaju razvoj oksidativnog stresa



# VITAMIN E

- Snažan antioksidans
- Doprinosi zaštiti ćelija od oksidativnog stresa i pomaže očuvanje zida ćeljske membrane
- Sprečava oksigenaciju LDL čestica



# POLIFENOLI

- Najzastupljeniji epigalo-katehin galat iz ekstrakta zelenog čaja
- Imaju jako antioksidativno dejstvo
- EGCG 25x jači od borovnice
- U studijama su pokazali i hipolipemijski efekat na LDL i ukupni holesterol

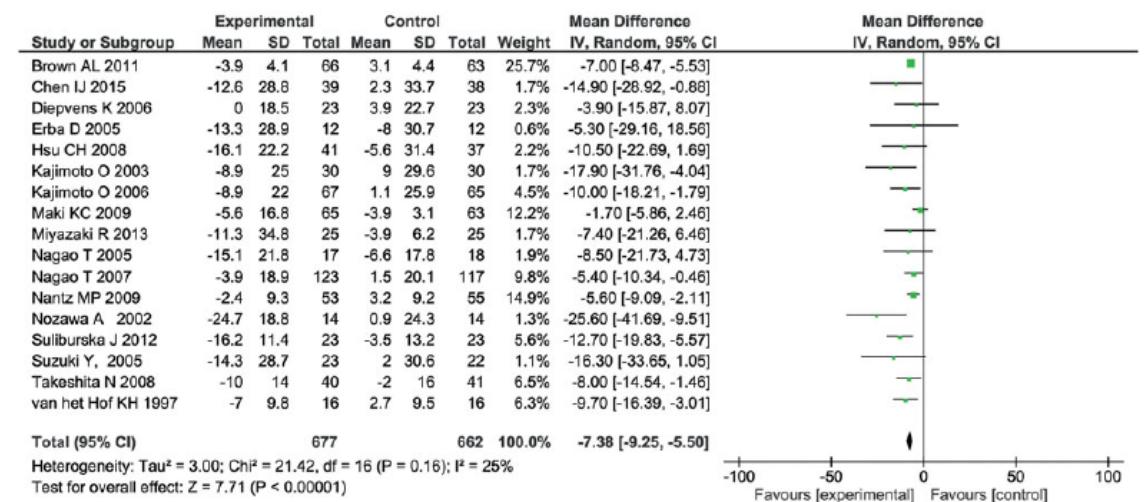


Figure 2. Meta-analysis of the effect of EGCG on LDL cholesterol compared with control arms. Sizes of data markers indicate the weight of each study in the analysis. WMD: weighted mean difference (the result was obtained from a random-effects model).

# ARTERINORM

REGULACIJA LIPIDNOG STATUSA

Monakolin K

Polikozanoli

Niacin

↓ HOMOCISTEIN

Folna kiselina

Vitamin B6

Vitamin B12

ANTIOKSIDATIVNI EFEKAT

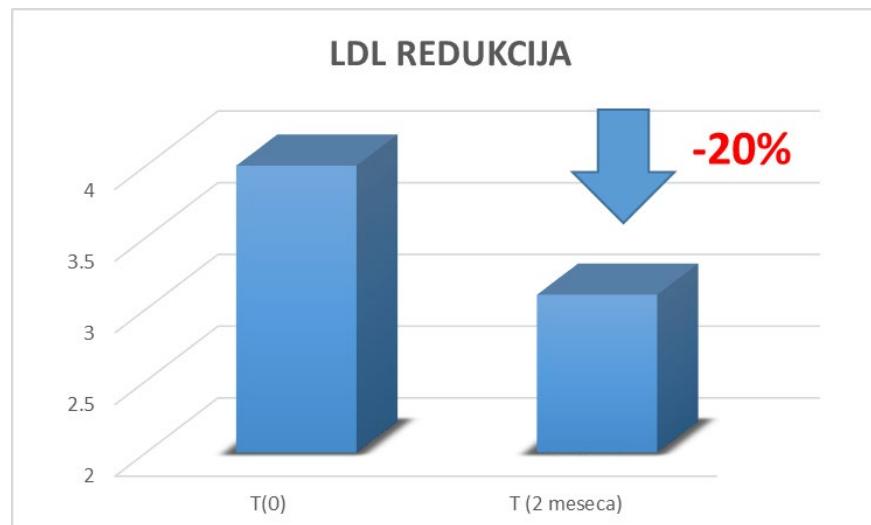
Polifenoli

Vitamin E

# ARTERINORM klinički dokazana

## BRZA EFIKASNOST

- Nakon 2 meseca redukcija LDL holesterola za 20%
- Efekat jednak kao sa 20mg pravastatina



Antihyperlipidaemic effect of a *Monascus purpureus* brand dietary supplement on a large sample of subjects at low risk for cardiovascular disease: A pilot study

Arrigo F.G. Cicero<sup>a,\*</sup>, Marco Brancaleoni<sup>b</sup>, Luca Laghi<sup>a</sup>, Franco Donati<sup>c</sup>, Marco Mino<sup>c</sup>

<sup>a</sup> Department of Internal Medicine and Applied Biotechnology, Atherosclerosis and Metabolic Diseases Study Centre "G. Descovich", University of Bologna, S. Orsola-Malpighi University Hospital Via Massarenti, 9-40138 Bologna, Italy

<sup>b</sup> Italian Association for the Study of Phytotherapy and Phytopharmacology (AISF), Italy

<sup>c</sup> Difass Research and Development, Italy

Available online 9 September 2005

### Summary

**Objectives:** We planned to carry out a pilot study to evaluate the efficacy and safety as an antihypercholesterolemic agent of a brand dietary supplement made of *Monascus purpureus* titrated extract, octacosanols and niacin on 111 Caucasian patients with low cardiovascular disease risk (<20% by Framingham algorithms), comparing them with the antihypercholesterolemic effect of a low dosage of Pravastatin on 20 subjects with similar risk profile.

**Results:** In our study, the tested dietary supplement determined a significant decrease of Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), and Triglycerides (TG) in moderately hypercholesterolemic subjects without clinically relevant change in liver and muscular toxicity markers. The reduction of LDL-C reached the 20%, and it is similar to that obtained with a well-known effective statin like Pravastatin.

**Conclusions:** Further long-term and double blind evaluation have to be carried out before to infer the observed results, however it appears that the studied dietary supplements could be a safe and efficacious antihypercholesterolemic agent for patients at low risk for cardiovascular diseases.

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# ARTERINORM klinički dokazana

## DUGOROČNA PRIMENA PRUŽA DODATNE BENEFITE

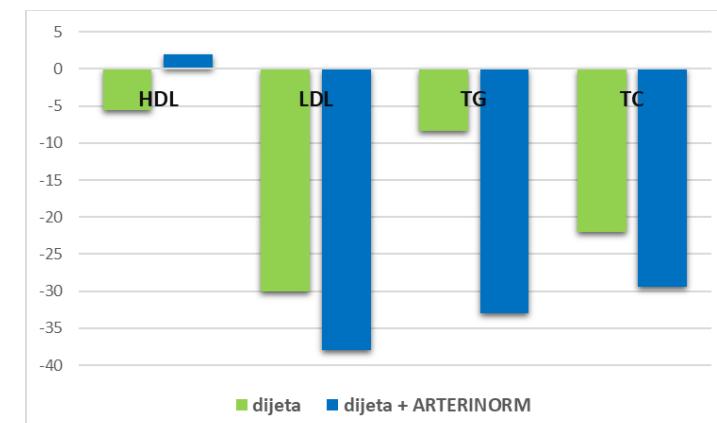
- Brža redukcija TC, LDL i TG
- Dugoročna primena najznačajnija za sniženje TG i povećanje HDL
- Bez pojave neželjenih efekata

Lipid/lipoproteins	Mean change (%) in group A 4 months (T1)	Mean change (%) in group B 4 months (T1)	P value	Mean change (%) in group A 8 months (T2)	Mean change (%) in group B 8 months (T2)	P value
TC	-7.6	-21.3	NS	-22	-29.4	NS
TG	-1.4	-6	NS	-8.4	-33	<0.001
HDLC	-2	-2	NS	-5.5	2	NS
LDLC	-10.3	-29	NS	-30	-38	NS
Non-HDLC	-9.13	-26	NS	-27	-37	NS

HDLC high density lipoprotein-cholesterol, LDLC low-density lipoprotein-cholesterol, TC Total cholesterol, non-HDLC non high density lipoprotein-cholesterol, TG triglycerides, NS not significant

Comparison between groups (Diet vs. Diet + Dif 1Stat)

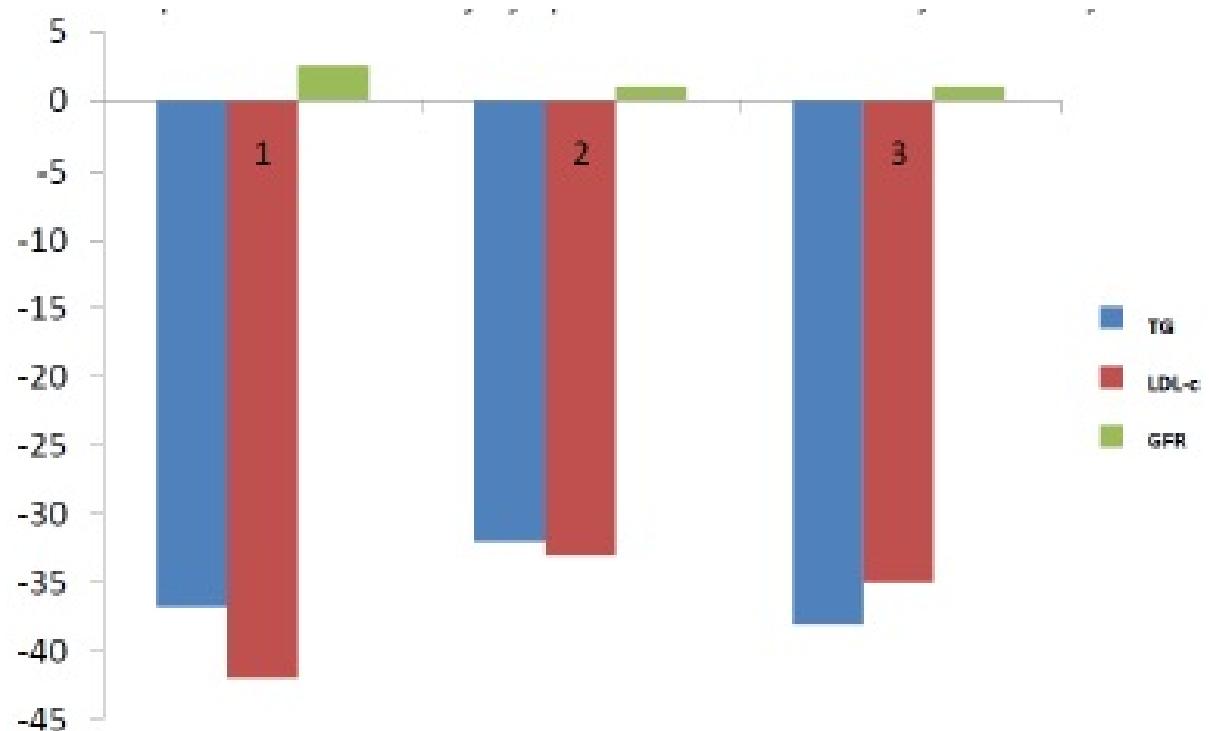
Differences are calculated as follows Diet (group A) versus Diet plus Dif 1Stat (group B): T1 versus T1; T2 versus T2



# ARTERINORM klinički dokazana

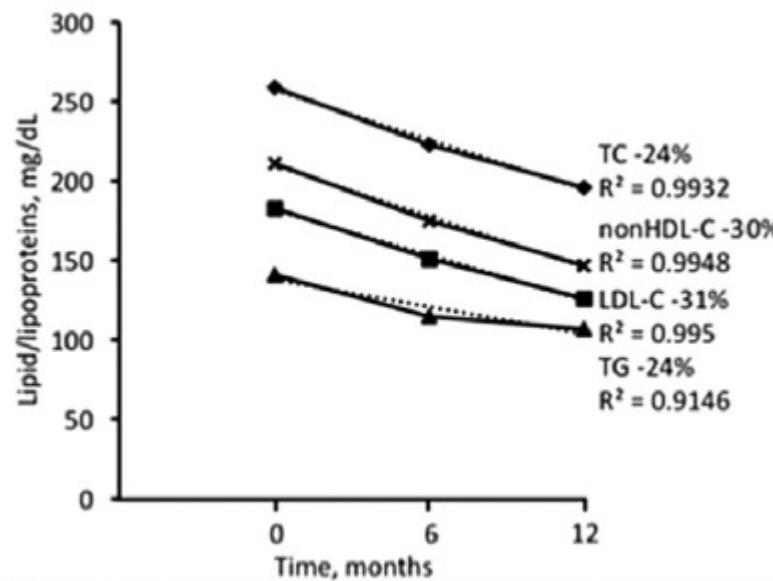
## BEZBEDNOST

- Bez neželjenih efekata u praćenju **2 godine 1104 bolesnika** sa HBB



# ARTERINORM klinički dokazana

## EFIKASNOST I BEZBEDNOST KOD PACIJENATA KOJI NETOLERIŠU STATINE ILI EZETIMIB



Mean changes in plasma ALT, AST,  $\gamma$ -glutamyl transferase, CK and glomerular filtration rate after 6 (T1) and 12 (T2) months treatment with diet plus MP.

Safety parameter (means)	Sampling time point					p
	Male (T0)	Male (T1)	%Δ	Male (T2)	%Δ	
<b>Males</b>						
ALT $\pm$ SD, UL	20 $\pm$ 8	19 $\pm$ 6	-5	18 $\pm$ 8	-10	ns
AST $\pm$ SD, UL	25 $\pm$ 6	24 $\pm$ 9	-4	21 $\pm$ 4	-16	ns
$\gamma$ -GT $\pm$ SD, UL	17 $\pm$ 4	14 $\pm$ 5	-17	16 $\pm$ 3	-5.8	ns
CK $\pm$ SD, UL	195 $\pm$ 15	186 $\pm$ 21	-4.6	193 $\pm$ 32	-1.02	ns
GFR $\pm$ SD, mL/min/m <sup>2</sup>	97.9 $\pm$ 0.06	97.8 $\pm$ 0.02	-0.1	97.2 $\pm$ 0.06	-0.7	ns
Cramp and myalgia	No	No	NA	No	NA	NA
<b>Females</b>						
ALT $\pm$ SD, UL	19 $\pm$ 6	16 $\pm$ 3	-15.7	17 $\pm$ 5	-10	ns
AST $\pm$ SD, UL	15 $\pm$ 4	14 $\pm$ 2	-6.7	13 $\pm$ 3	-13	ns
$\gamma$ -GT $\pm$ SD, UL	16 $\pm$ 7	15 $\pm$ 2	-6.25	17 $\pm$ 4	6.25	ns
CK $\pm$ SD, UL	188 $\pm$ 18	175 $\pm$ 13	-7	168 $\pm$ 18	-10	ns
GFR $\pm$ SD, mL/min/m <sup>2</sup>	98.2 $\pm$ 0.09	98.2 $\pm$ 0.08	0.2	98.4 $\pm$ 0.01	0.2	ns
Cramp and myalgia	No	No	NA	No	NA	NA

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GFR, glomerular filtration rate;  $\gamma$ -glutamyl transferase ( $\gamma$ -GT); MP, Monascus purpureus; NA, not applicable; ns, not significant; p, result of unpaired T-test versus baseline; T, sampling time point (0 = baseline, 1 = 6 months, 2 = 12 months); %Δ, percent change in lab parameter compared to baseline.

# UPOTREBA



**Jednom dnevno,  
najbolje pred spavanje,  
popiti jednu kapsulu.**



Nakon perioda  
upotrebe od 3  
meseca ovog  
proizvoda  
poželjno je  
proveriti nivo  
holesterola u krvi.



Bez glutena,  
mleka, lakoze i  
GMO.



Proizvod ne treba  
da uzimaju osobe  
preosetljive na  
neki od sastojaka  
proizvoda.



Proizvod nije  
namenjen deci,  
trudnicama i  
dojiljama.



Osobe na terapiji  
dislipidemija, pre  
upotrebe ovog  
proizvoda treba  
da se konsultuju  
sa svojim lekarom  
ili farmaceutom.

# PREPORUČEN KOD PACIJENATA:

Sa povišenim LDL holesterolom, trigliceridima ili ukupnim holesterolom

Sa niskim HDL holesterolom u umerenom KV riziku

Koji odbijaju ili netolerišu statinsku terapiju

Kao dodatak statinskoj terapiji



✓ PRIRODNA I BEZBEDNA STRATEGIJA ZA  
EFIKASNU KONTROLU LIPIDNOG  
STATUSA I PREVENCIJU  
KARDIOVASKULARNIH BOLESTI

✓ KLINIČKI DOKAZANA ORIGINALNA  
FORMULA

✓ TROSTRUKO DEJSTVO NA PREVENCIJU  
NASTANKA I RAZVOJA ATEROSKLOROZE

30 kapsula