

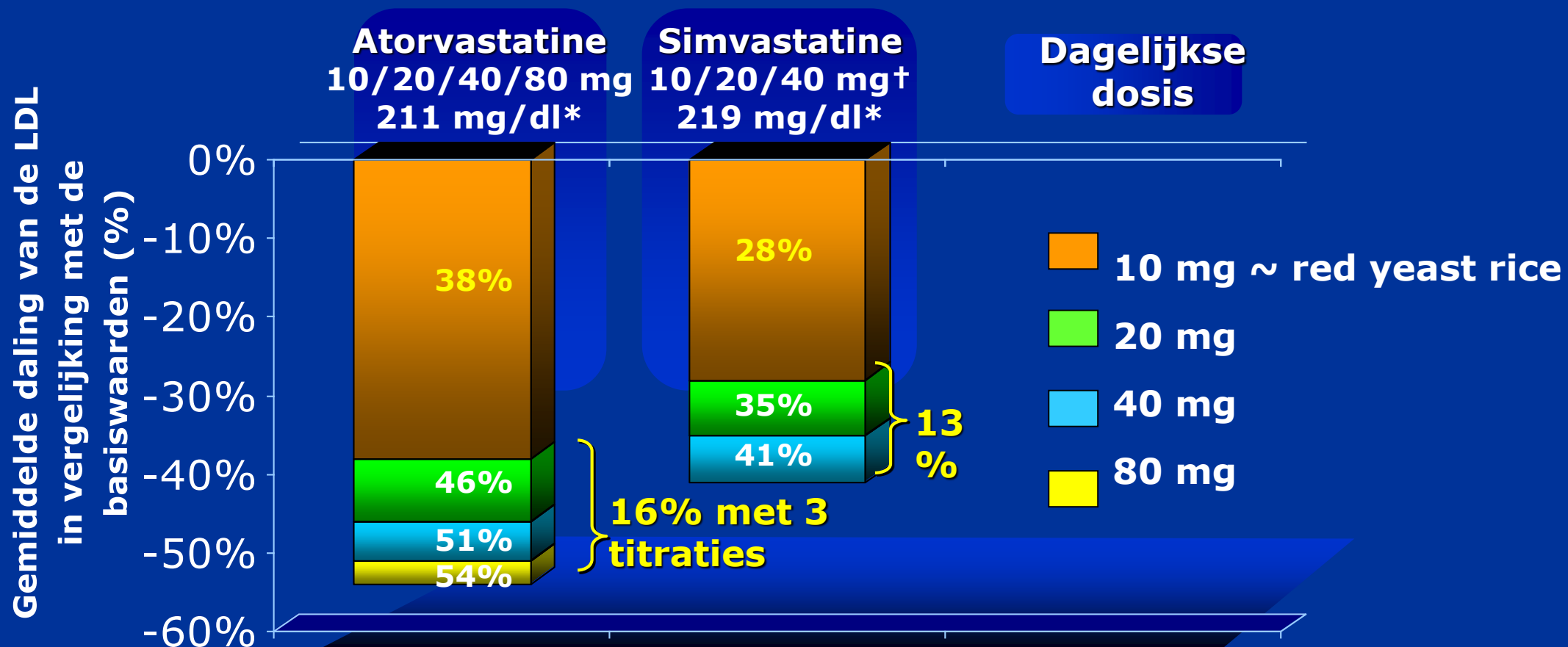
Presentation of a position paper on red yeast rice

Luc Missault¹, MD, DSc & Michel Hermans², MD, PhD,
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¹Belgische Cardiologische Liga en AZ Sint Jan Brugge,
²UCLouvain; ³ULBrussels



De laagste dosis van het statine geeft de grootste relatieve of procentuele LDL-daling

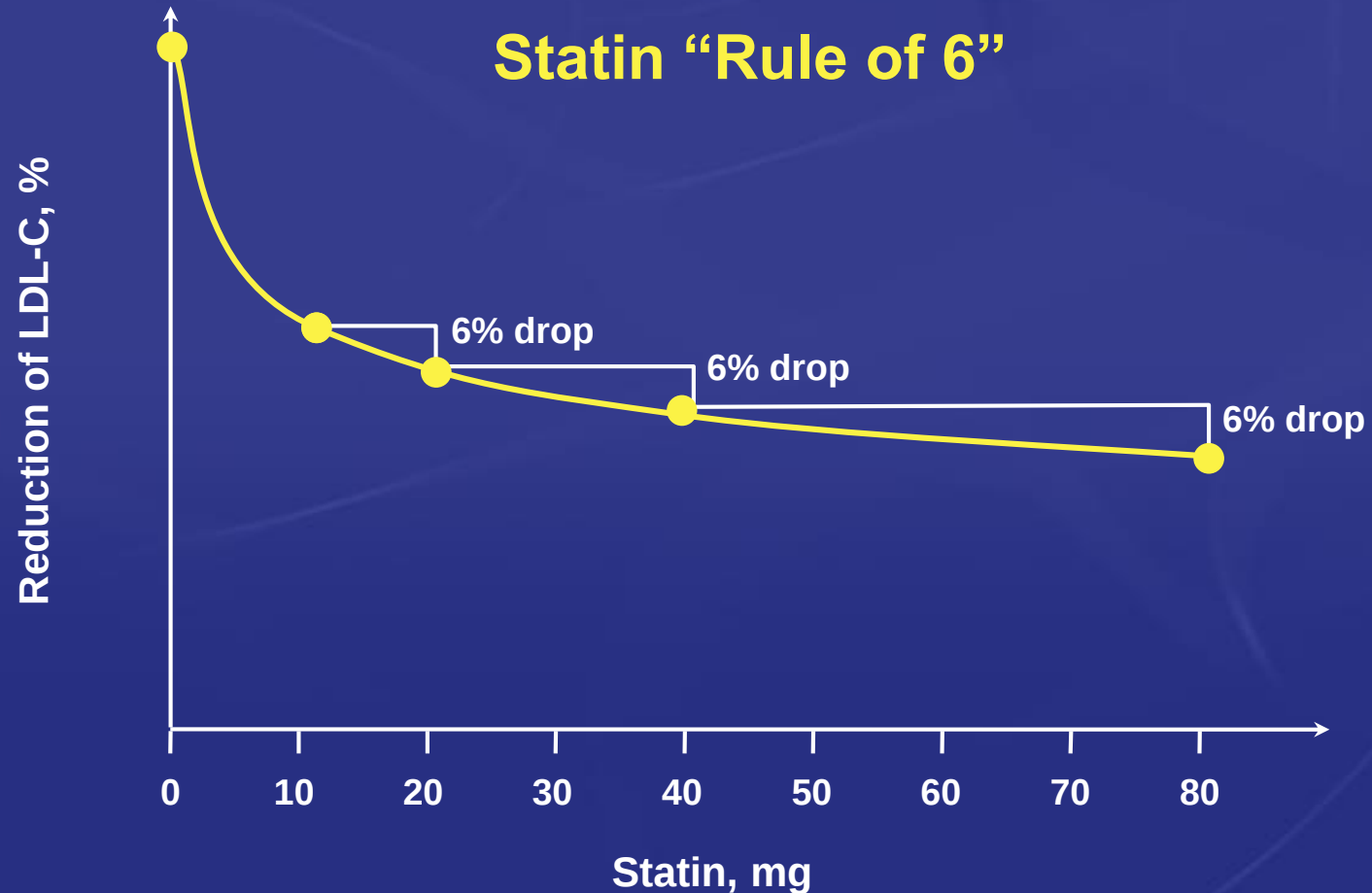


* Gemiddelde LDL basiswaarde

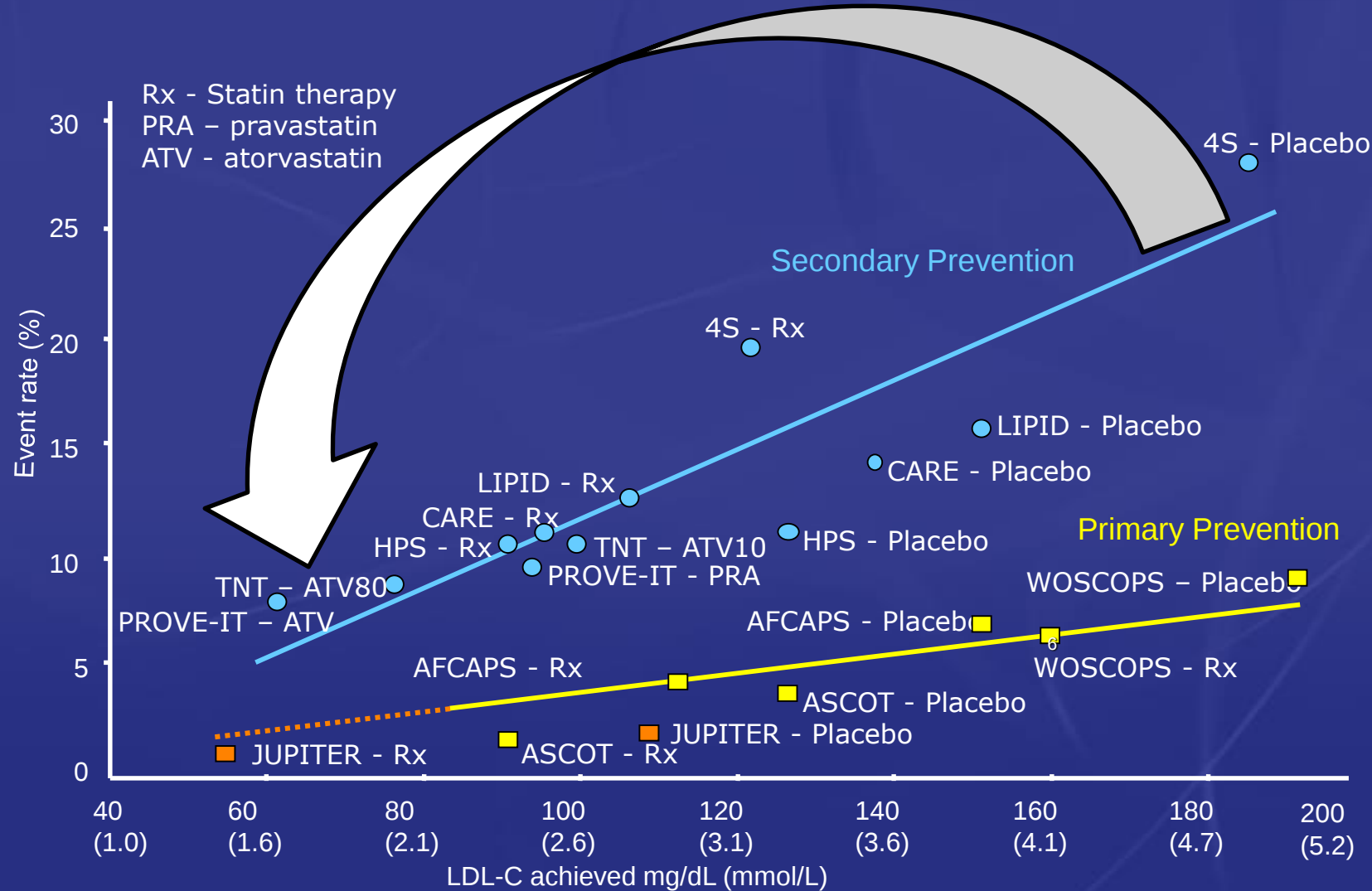
† maximale dosis van simvastatine 40 mg

Modified from Jones P et al. *Am J Cardiol* 1998;81:582-587

Doubling a Statin Dose Yields Only a 6% Incremental Drop in LDL-C



Door de behandeling bereikte LDL-C is sterk gecorreleerd met CV events...



Adapted from Rosensen RS. Exp Opin Emerg Drugs 2004;9(2):269-279

LaRosa JC et al. N Engl J Med 2005;352:1425-1435

High Dose / High Intensity Statin Treatment

- ◆ Advisable for many patients
 - In patients with ACS to be initiated in hospital
 - Very high risk groups, 2nd prevention a.o.: LDL-C target <70 mg/dl
 - Very elevated baseline LDL-C
- ◆ But not necessary in every patient
 - Lesser risk category, eg moderate risk: LDL-C target <115mg/dl
 - Smaller distance-to-LDL-C-target value
- ◆ Some patients do not tolerate high dose high / intensity statin (side effects)

FDA warning on simvastatin 80 mg

FDA NEWS RELEASE

For Immediate Release: March 19, 2010

Media Inquiries: Elaine Gansz Bobo, 301-796-7567; elaine.bobo@fda.hhs.gov

Consumer Inquiries: 888-INFO-FDA

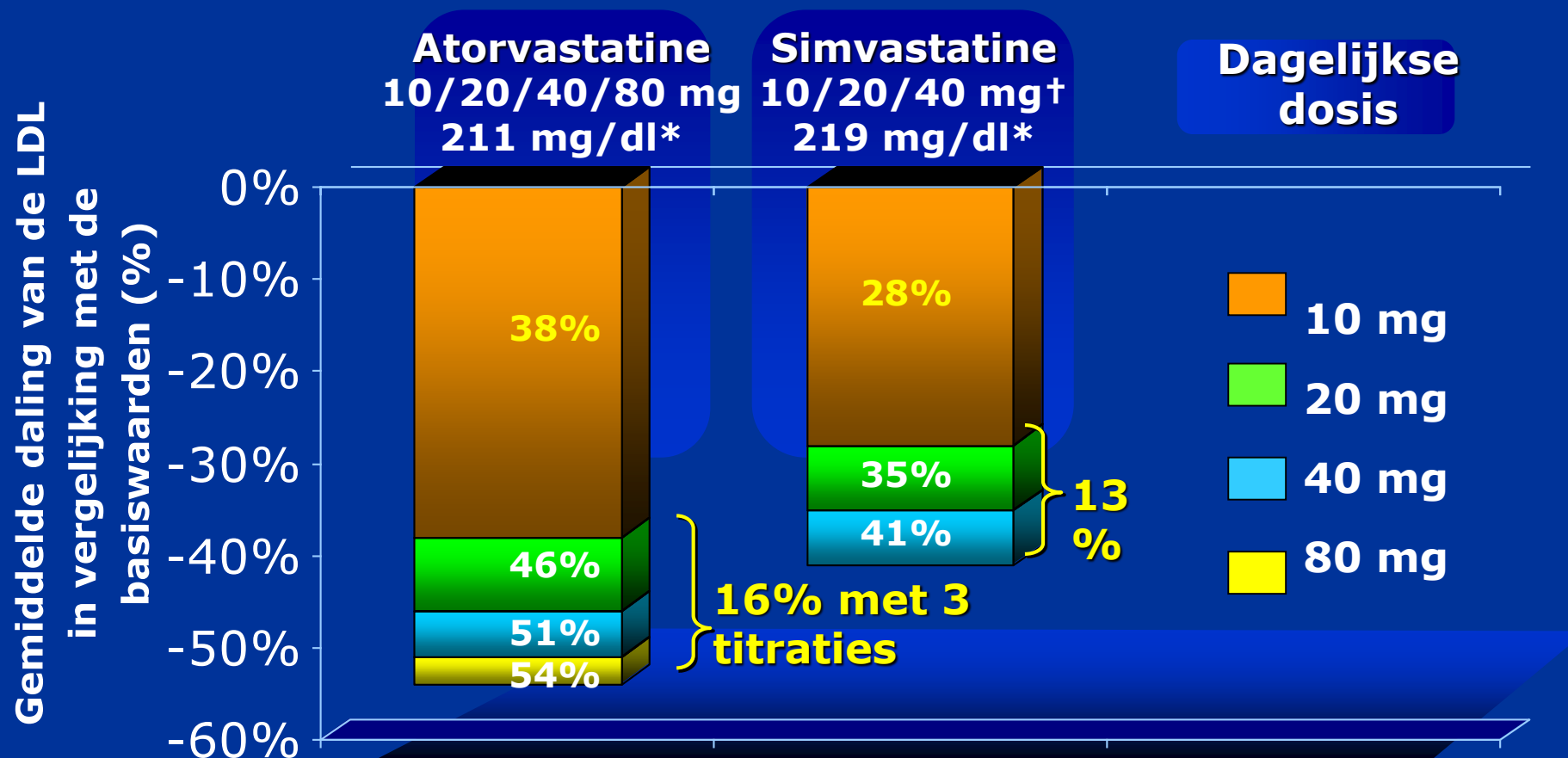
FDA Warns about Increased Risk of Muscle Injury with Zocor

Highest approved dose of cholesterol-lowering medication could cause harm to muscles

The U.S. Food and Drug Administration today warned patients and healthcare providers about the potential for increased risk of muscle injury from the cholesterol-lowering medication Zocor (simvastatin) 80 mg. Although muscle injury (called myopathy) is a known side effect with all statins, today's warning highlights the greater risk of developing muscle injury, including rhabdomyolysis, for patients when they are prescribed and use higher doses of this drug.

Rhabdomyolysis is the most serious form of myopathy and can lead to severe kidney damage, kidney failure, and sometimes death.

De laagste dosis van het statine geeft de grootste relatieve of procentuele LDL-daling



Anderzijds ... vooral de hogere dosissen kunnen leiden tot spiermoeheid, myalgie, myopathie, rhabdomyolyse...

* Gemiddelde LDL basiswaarde

† maximale dosis van simvastatine 40 mg

Modified from Jones P et al. *Am J Cardiol* 1998;81:582-587

Statin Associated Muscle Symptoms (SAMS)

- Wanneer de patient niet zeker weet dat hij/zij een statine neemt (gerandomiseerde dubbelblinde klinische studies): **slechts 1-5%**
- Cave: in veel studies: eerst inlooperperiode om tolerantie na te gaan met selectie van tolererende patienten als gevolg (minder drop-outs)
- Wanneer de patient weet dat hij/zij een statine neemt: **tot 20%!** rapporteert spierklachten in observationele (niet-geblindeerde) studies.
- 'A lot of patients are **unable or unwilling** to take prescription statins due to real or presumed side effects or by personal conviction'
- Er bestaat helaas geen biomarker of bloedtest om aan te tonen of uit te sluiten dat iemand SAMS heeft.

**“Ideal world
vs
Real world”**

5

DANGERS OF STATIN DRUGS

YOUR DOCTOR ISN'T TELLING YOU ABOUT



THE TRUTH ABOUT STATINS

"Dr. Roberts presents the other side of the statin story."
—Dr. Paul D. Thompson, Director of Cardiology at Hartford Hospital



Risks and Alternatives to Cholesterol-Lowering Drugs

Barbara H. Roberts, M.D.

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Movement Disorders

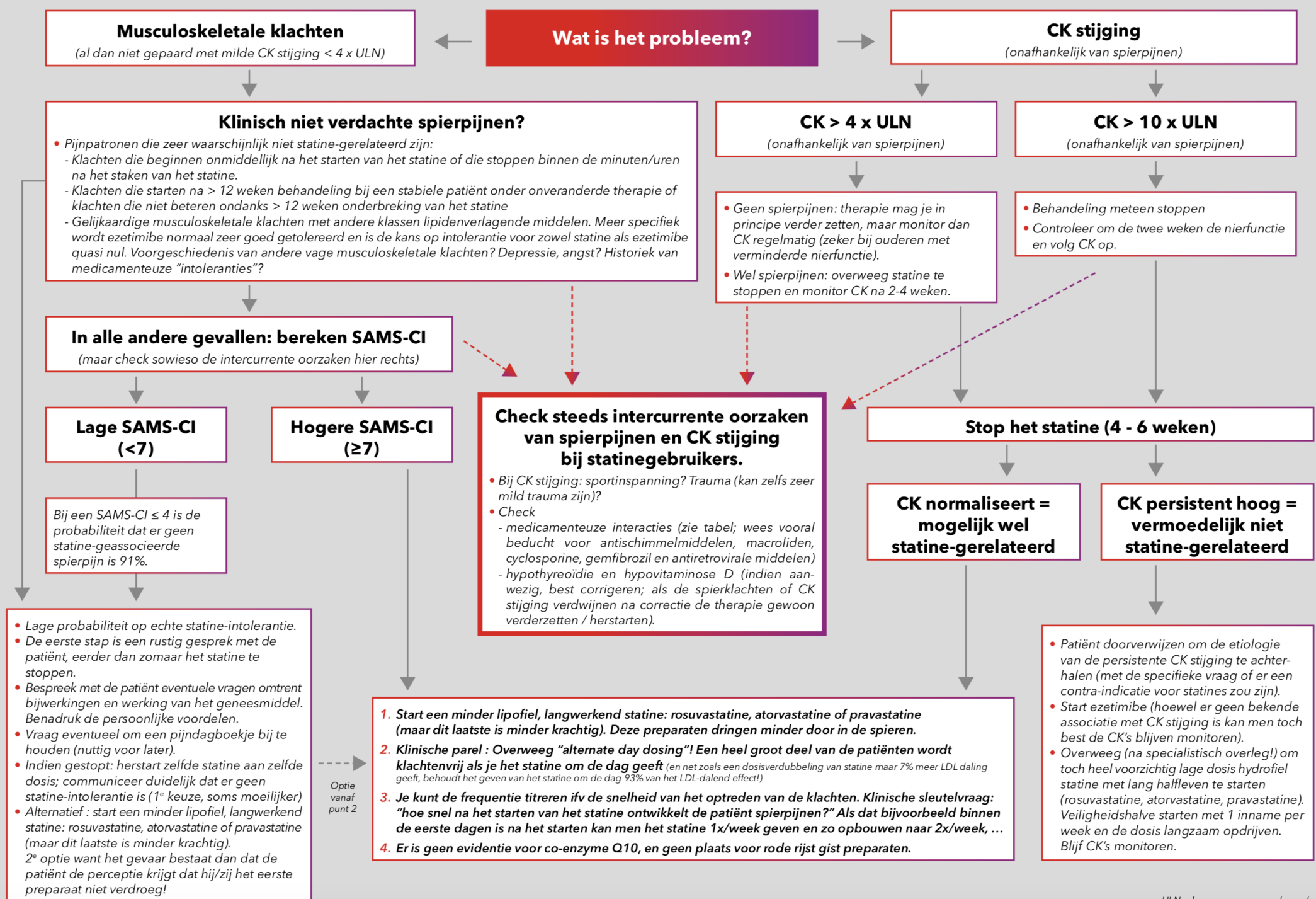
Official Journal of the International
Parkinson and Movement Disorder Society



BRIEF REPORTS

Statins May Facilitate Parkinson's Disease: Insight Gained From a Large, National Claims Database

Guodong Liu, PhD,¹ Nicholas W. Sterling, PhD,²
Lan Kong, PhD,¹ Mechelle M. Lewis, PhD,^{2,3}
Richard B. Mailman, PhD,^{2,3} Honglei Chen, MD, PhD,⁴
Douglas Leslie, PhD,¹ and Xuemei Huang, MD, PhD^{2,3*}



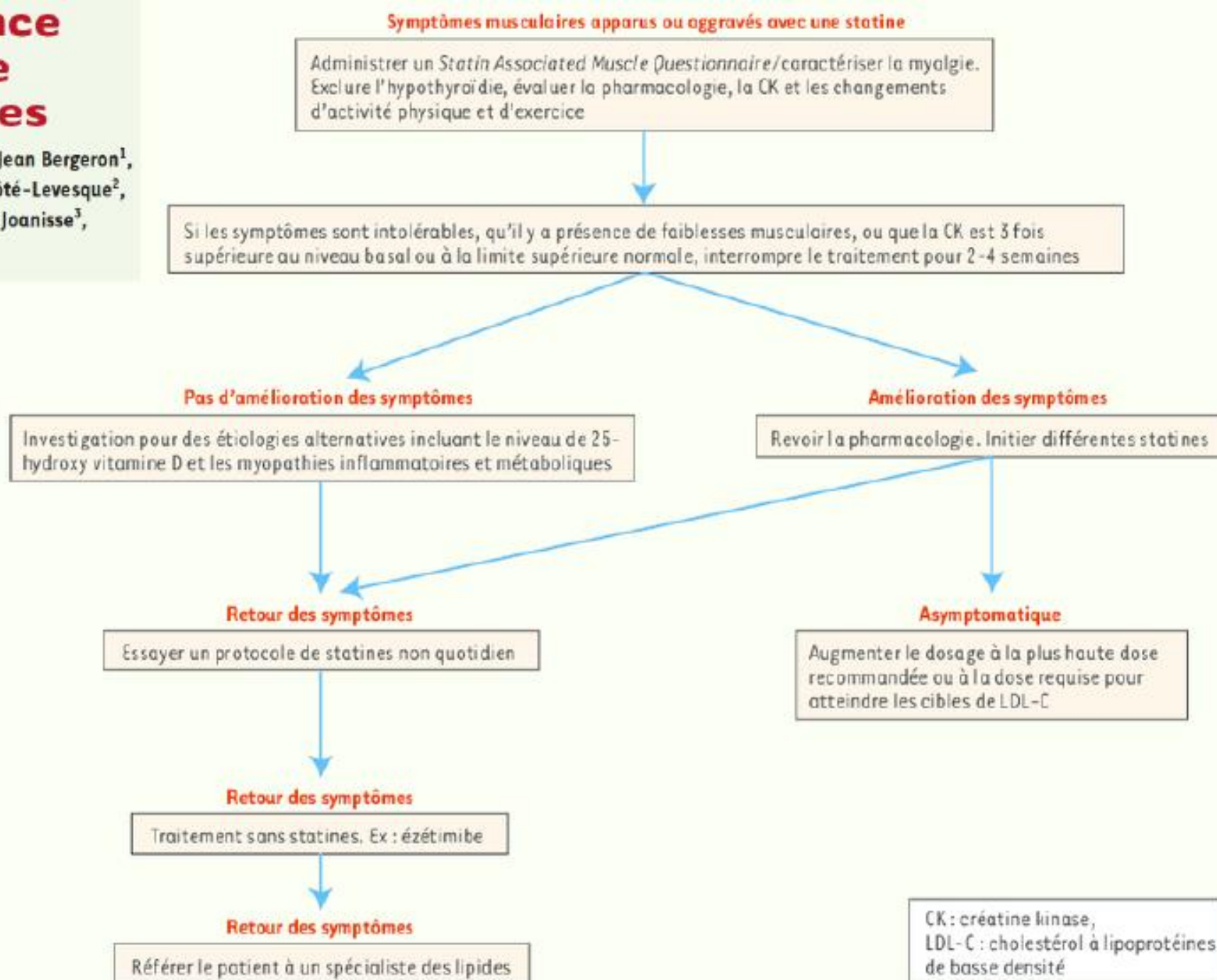
Statin intolerance – suggestions to “solve”

- Retry...
- “Restore confidence”...
 - Lower the dose...
- Highest tolerated dose...
- Alternate day administration...
 - Single weekly dose...

! No validation in clinical trials (morbi/mortality) !

L'intolérance musculaire aux statines

Antoine Boulanger-Piette¹, Jean Bergeron¹,
Joël Desgreniers², Michèle Côté-Levesque²,
Dominic Brassard², Denis R. Joannisse³,
Jérôme Frenette¹



Conseils
empiriques

....



Red Yeast Rice



= the product of the yeast *Monascus Purpureus* grown on (normal) rice

1) Contains several compounds:

- plant sterols, substances known to inhibit absorption
 - monacolins, substances known to inhibit cholesterol synthesis
- (Of note: = cfr. combination therapy...)

2) One of these, "monacolin K," is a potent inhibitor of HMG-CoA reductase, and is also known as mevinolin or lovastatin (Mevacor®, produced by Merck)

Nutriceuticals / Red Yeast Rice / “Monacolines”

- Natuurlijk produkt bevat slechts heel weinig monacolin K
- “Extracten” (≠ “topping of spiking”)
- In België (Cholesfytol®, ...)
- Hoeveelheid monacolines in rode gist rijst tabletten is heel exact bepaald itt tot natuurlijke rode gist rijst (cfr. plantenstanolen/sterolen)

Lipid-Lowering Efficacy of Red Yeast Rice in a Population Intolerant to Statins

American Journal of Cardiology 2010;105:664-666.

Carmelo V. Venero, MD^a, Jose V. Venero, MD^b, Dale C. Wortham, MD^a, and Paul D. Thompson, MD^{c,d,*}

Table 1

Lipid levels before and after red yeast rice use (n = 25)

Variable	Before Treatment (mg/dl)	After Treatment (mg/dl)	Change (%)	p Value
Total cholesterol	250 ± 39	214 ± 48	-15 ± 10	<0.001
Low-density lipoprotein cholesterol	164 ± 35	129 ± 38	-21 ± 14	<0.001
High-density lipoprotein cholesterol	59 ± 21	58 ± 20	-0.5 ± 12	0.48
Triglycerides	146 ± 68	134 ± 59	-6 ± 21	0.06

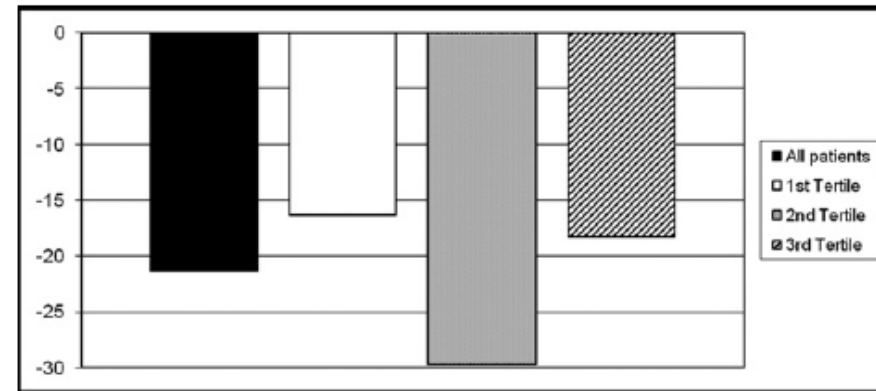


Figure 1. Percentage of LDL cholesterol reduction according to pre-treatment LDL cholesterol tertile: first tertile (n = 8, LDL cholesterol 74 to 147 mg/dl, mean 123); second tertile (n = 8, LDL cholesterol 155 to 181 mg/dl, mean 168); and third tertile (n = 9, LDL cholesterol 185 to 223 mg/dl, mean 198).

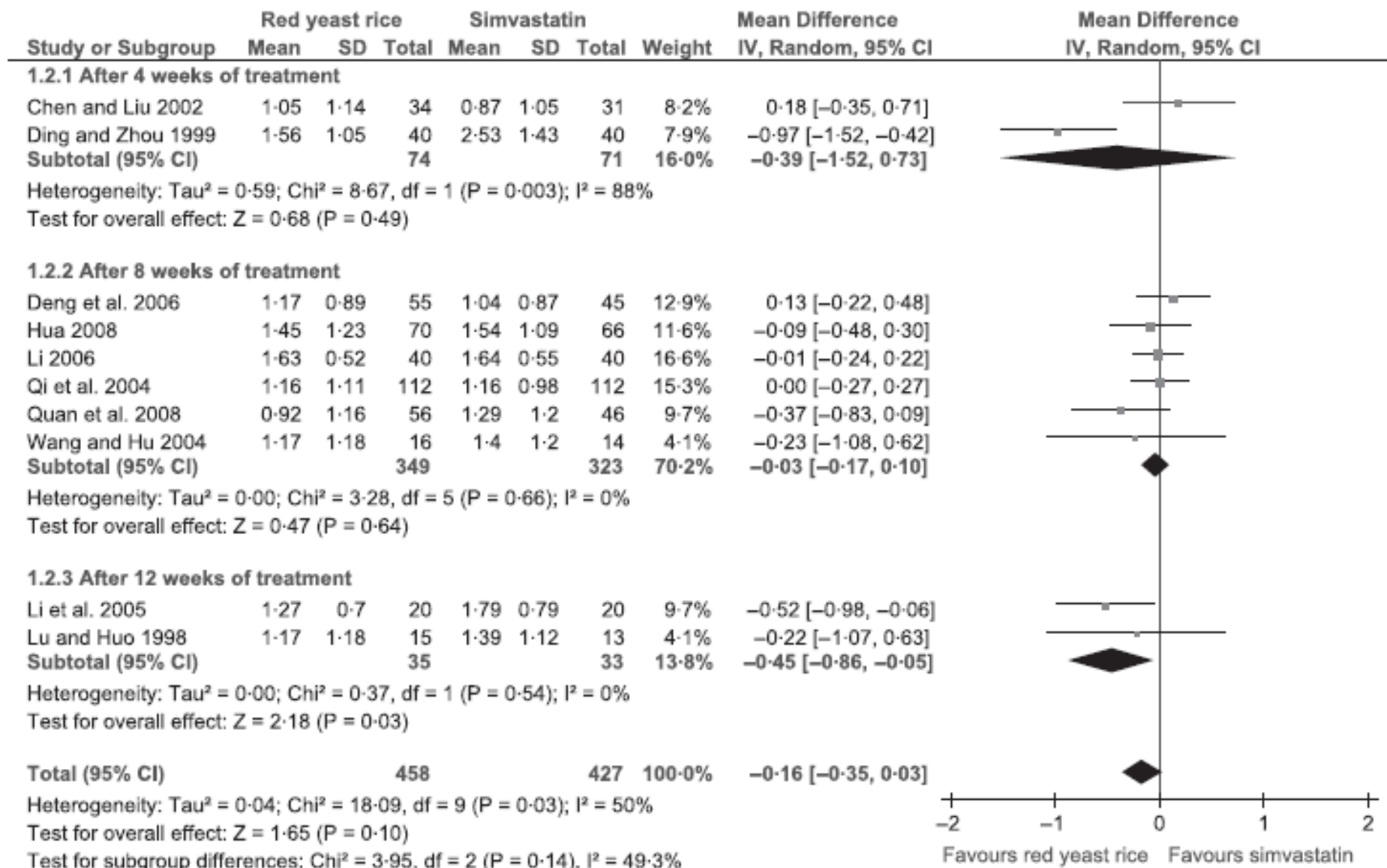
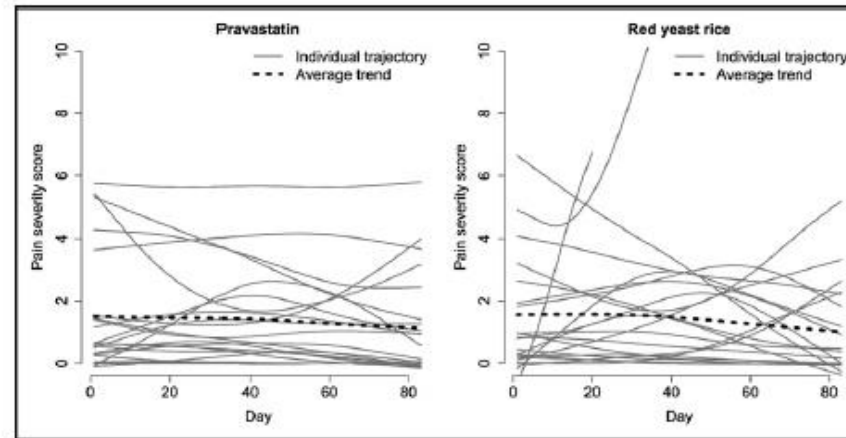


Fig. 5. Forest plot of comparisons of xuezhikang versus simvastatin (outcome: LDL-C).

X: 1,2 -3,6 g versus S: 10-20 mg

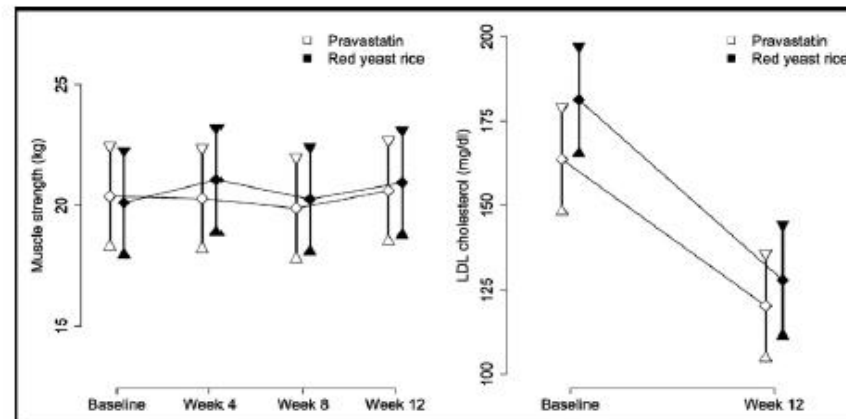
Tolerability of Red Yeast Rice (2,400 mg Twice Daily) Versus Pravastatin (20 mg Twice Daily) in Patients With Previous Statin Intolerance (Am J Cardiol 2010;105:198–204)

Steven C. Halbert, MD^{a,e}, Benjamin French, PhD^{a,b}, Ram Y. Gordon, MD^f, John T. Farrar, MD^a, Kathryn Schmitz, PhD^a, Patti B. Morris, RD^f, Paul D. Thompson, MD^g, Daniel J. Rader, MD^{c,d}, and David J. Becker, MD^{f,*}



No differences!

Figure 2. Individual maximum pain severity scores (*solid lines*) and average trend (*dashed line*) during study period for each treatment group. Individual trajectories and average trend plots were obtained using scatterplot smoother.

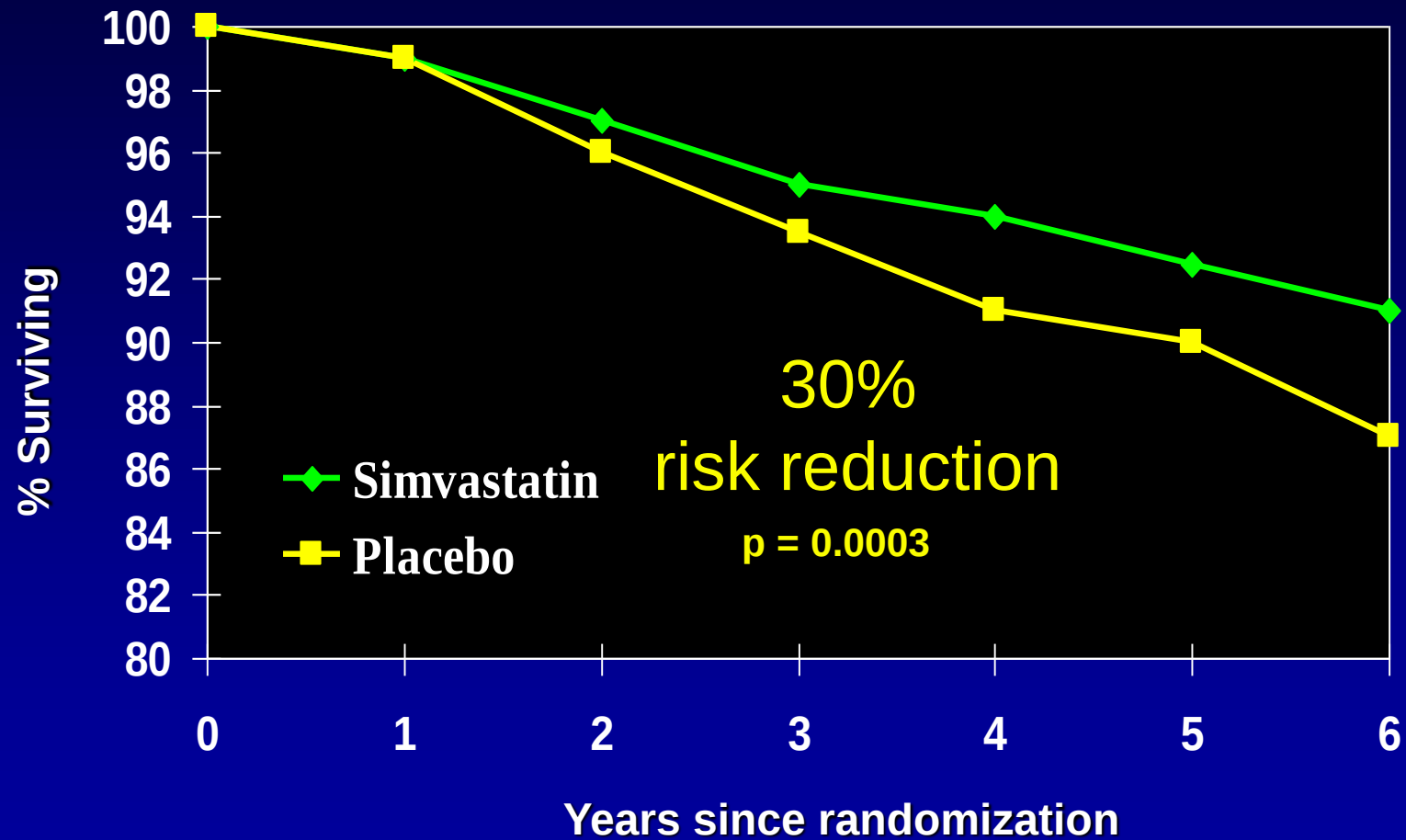


No differences!

Figure 3. Point estimates and 95% CIs for mean muscle strength and mean LDL cholesterol for pravastatin group (*white*) and red yeast rice group (*black*).

4S

Primary Endpoint: Overall Survival



Effect of Xuezhikang, an Extract From Red Yeast Chinese Rice, on Coronary Events in a Chinese Population With Previous Myocardial Infarction

American Journal of Cardiology 2008;101:1689-1693

Zongliang Lu, MD, PhD^a, Wenrong Kou, MD^a, Baomin Du, MD^b, Yangfeng Wu, MD^c,
Shuiping Zhao, MD, PhD^d, Osvaldo A. Brusco, MD^e, John M. Morgan, MD^f, and
David M. Capuzzi, MD, PhD^{f,*} on behalf of the Chinese Coronary Secondary
Prevention Study Group

The study medication consisted of 300-mg capsules of XZK, each containing the combination of lovastatin, also termed monoclolin K (2.5 to 3.2 mg/capsule); a small quantity of lovastatin hydroxyl acid; as well as ergosterol and some other components.

Total cholesterol	5.38 ± 0.83 (208 $\pm$ 25)	5.35 ± 0.67 (207 $\pm$ 26)
LDL cholesterol	3.34 ± 0.78 (129 $\pm$ 29)	3.34 ± 0.65 (129 $\pm$ 28)
HDL cholesterol	1.19 ± 0.36 (46 $\pm$ 15)	1.19 ± 0.39 (46 $\pm$ 15)
Triglycerides	1.85 ± 0.83 (164 $\pm$ 74)	1.85 ± 0.86 (164 $\pm$ 77)

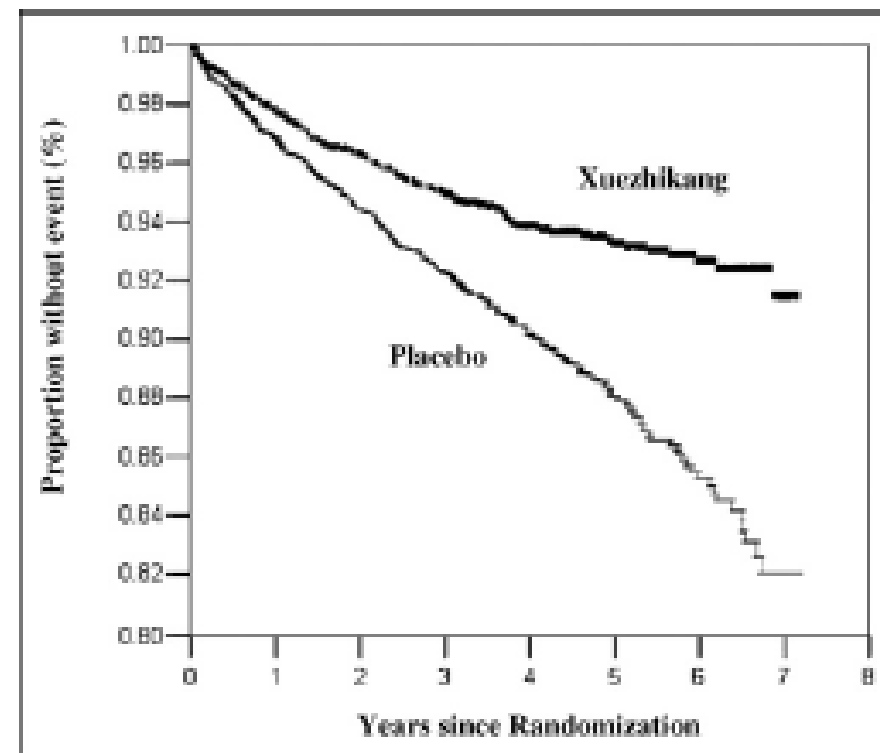


Figure 1. Kaplan-Meier curves for the proportion of patients without primary events in the XZK and placebo groups.

ORIGINAL ARTICLE

Impact of Xuezhikang on coronary events in hypertensive patients with previous myocardial infarction from the China Coronary Secondary Prevention Study (CCSPS)

JIAN-JUN LI, ZONG-LIANG LU, WEN-RONG KOU, ZUO CHEN, YANG-FENG WU, XUE-HAI YU, YU-CHENG ZHAO; ON BEHALF OF THE CHINESE CORONARY SECONDARY PREVENTION STUDY (CCSPS) GROUP

Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, P. R. China

Table II. Changes of lipid profiles (mg/dL) and blood pressure (mmHg) after Xuezhikang therapy.

Lipid profile (mg/dL) and blood pressure (mmHg)		Placebo (n = 1341)	Xuezhikang (n = 1363)	P-value
Total cholesterol	Base-line	208.1 ± 25.8	207.6 ± 26.1	0.59
	After therapy	203.1 ± 37.2 ^a	185.0 ± 34.1 ^a	<0.001
Triglyceride	Base-line	166.0 ± 75.7	164.8 ± 76.1	0.68
	After therapy	156.8 ± 82.9 ^b	146.0 ± 76.6 ^a	0.00
High-density lipoprotein cholesterol	Base-line	45.9 ± 14.4	45.9 ± 14.5	0.89
	After therapy	47.0 ± 12.8	48.0 ± 13.0 ^a	0.06
Low-density lipoprotein cholesterol	Base-line	129.4 ± 28.9	129.2 ± 28.2	0.89
	After therapy	125.1 ± 35.9 ^b	107.4 ± 32.2 ^a	<0.001

Totaal n=2704
Placebo n=1341
Xuezhikang 0,6 g bid n=1363
4.5 yrs follow-up

CHD

-43%

p=0.02

Coronary death

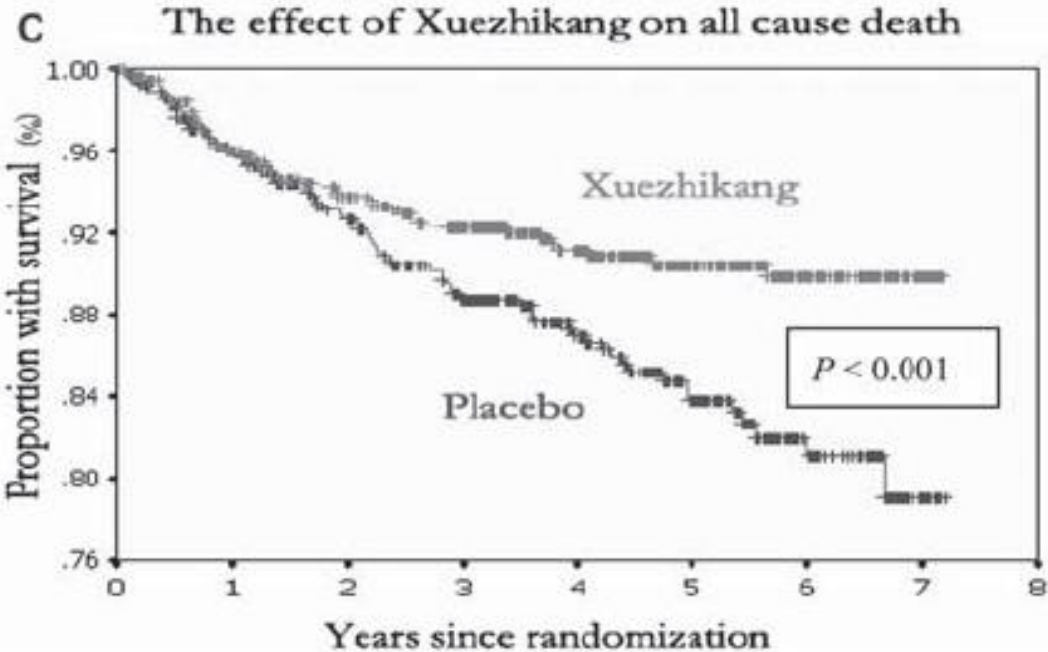
-30%

p<0.01

All death

-35.8%

p=0.001



Effect of xuezhikang on cardiovascular events and mortality in elderly patients with a history of myocardial infarction: a subgroup analysis of elderly subjects from the China Coronary Secondary Prevention Study

J Am Geriatr Soc 2007;55:1015-22.

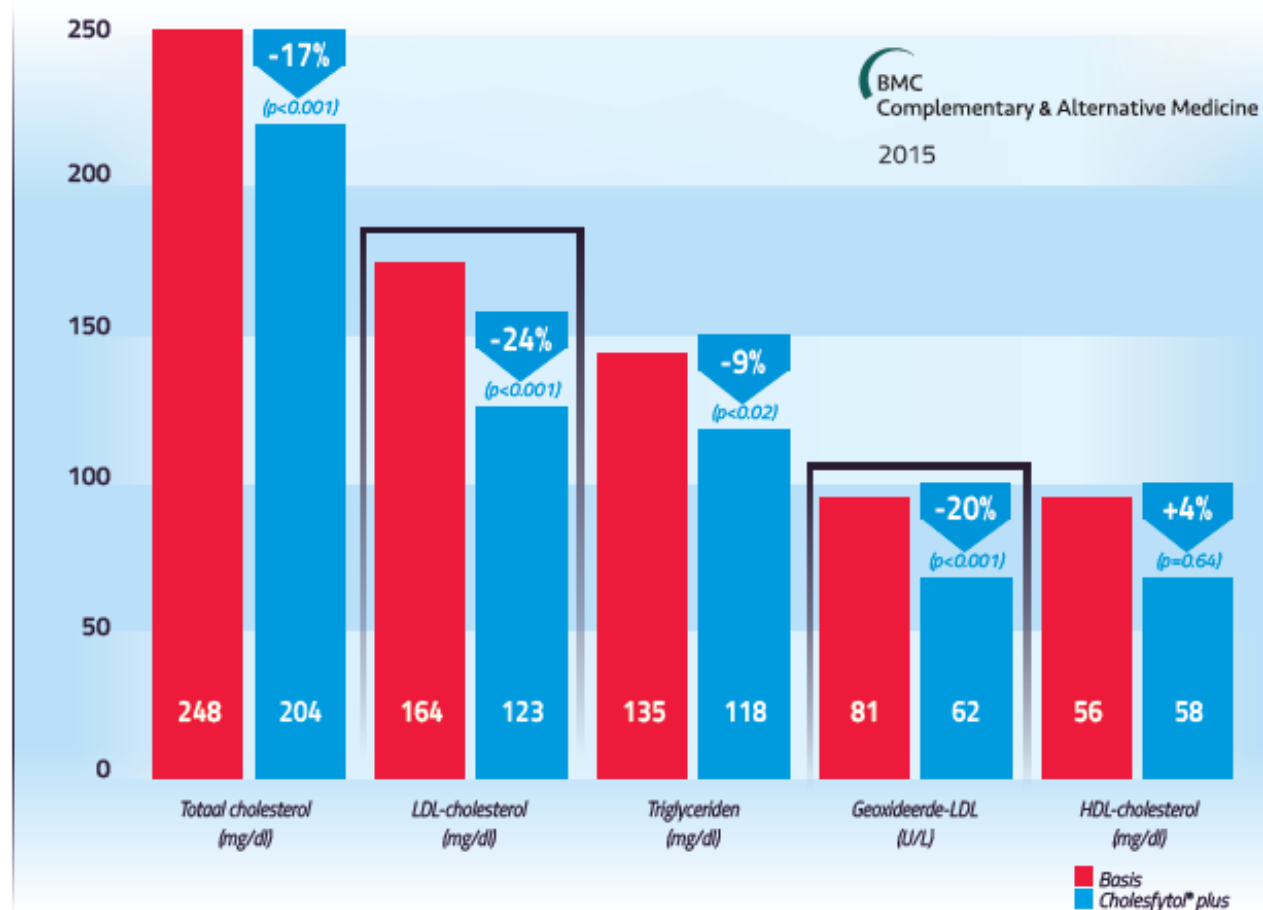
1,445 patients, aged 65 to 75, were chosen from 4,780 patients with a history of myocardial infarction.

Xuezhikang therapy reduced the incidence of coronary events 36.9% ($P=.001$), death from coronary heart disease 31.0% ($P=.04$), all-cause mortality 31.9% ($P=.01$), stroke 44.1% ($P=.04$), the need for a percutaneous coronary intervention or coronary artery bypass graft 48.6% ($P=.07$), and malignancies 51.4% ($P=.03$).

NNT for 4 years to prevent one coronary event, one coronary death, and one mortality due to all causes was estimated to be 18, 33, and 23, respectively.

Studie Cholesfytol plus universiteit Antwerpen

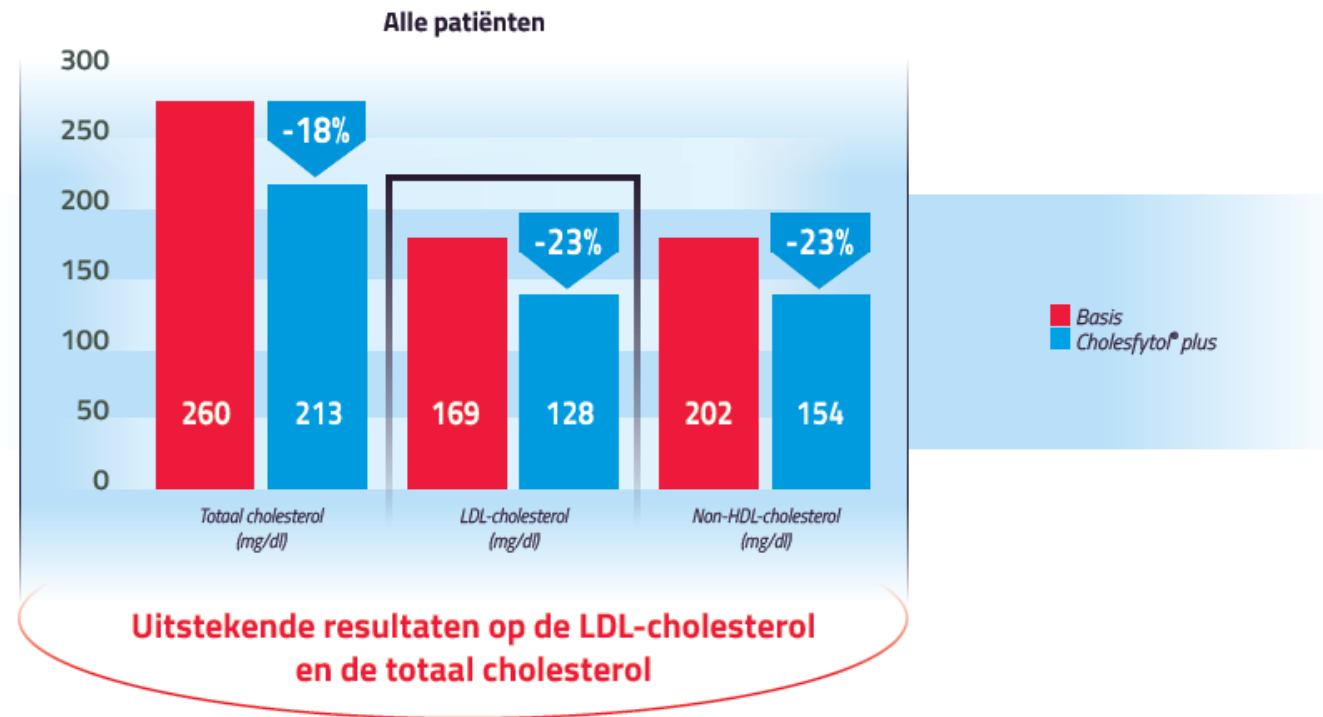
Dubbelblinde gerandomiseerde studie tegen placebo op 50 patiënten die beantwoorden aan de criteria van het metabool syndroom. 8 weken behandeling, 1 tablet 's avonds



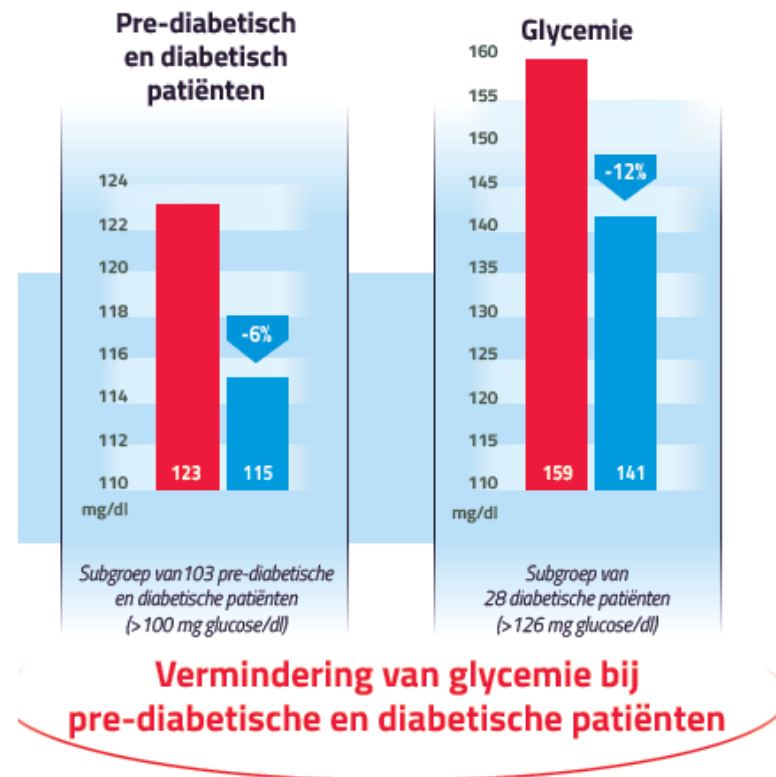
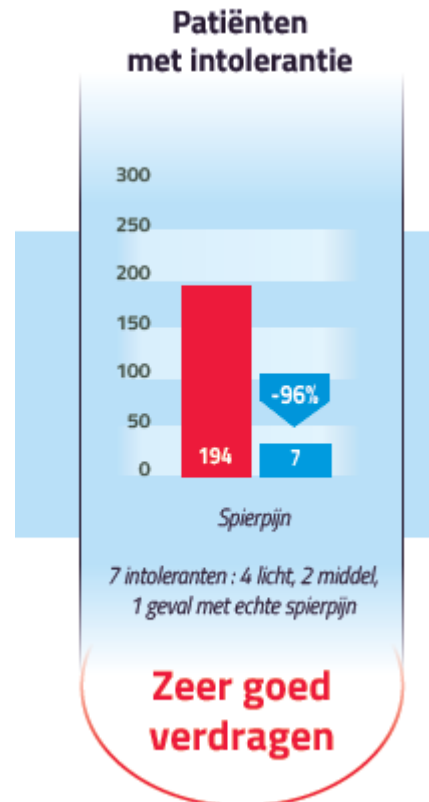
- > Efficiëntie van de behandeling op het cholesterolgehalte
- > Efficiëntie op de oxidatie van LDL
- > Geen neveneffecten
- > Systolische bloeddruk : -10,4 mmHg ($p < 0.001$)
- > Diastolische bloeddruk : -7,6 mmHg ($p < 0.05$)

Studie Cholesfytol

Observationele studie op 624 patiënten gedurende 2 maanden, 1 tablet 's avonds



Studie Cholesfytol



ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation[†]

Pag. 1787: § 6.4

Dietary supplements and functional foods active on plasma lipid values

“Innovative nutritional strategies to improve dyslipidaemias have been developed; they are based

- either on changing some ‘risky’ dietary components

or

- on encouraging the consumption of specifically targeted ‘healthy’ functional foods and/or dietary supplements; these so-called ‘nutriceuticals’ can be used either as alternatives or in addition to lipid-lowering drugs.”

Dietary supplements and functional foods active on plasma lipid values

Phytosterols

Soy protein

Dietary fibre

PUFA (fish oil, α -Linolenic acid)

Red Yeast Rice



European Heart Journal (2011) 32, 1769–1818
doi:10.1093/eurheartj/ehr158

ESC/EAS GUIDELINES

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Red Yeast Rice "RYR"

Different commercial preparations of RYR have different concentrations of monacolins, the bioactive ingredients, and lower TC and LDL-C, but the long-term safety of the regular consumption of these products is not fully documented.

In one RCT from China in patients with CAD, a partially purified extract of RYR reduced recurrent events by 45%.



European Heart Journal (2011) 32, 1769–1818
doi:10.1093/eurheartj/ehr158

ESC/EAS GUIDELINES

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Table 9 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence	References
Lifestyle interventions to reduce TC and LDL-C levels			
Reduce dietary saturated fat	+++	A	63
Reduce dietary trans fat	+++	A	64
Increase dietary fibre	++	A	65
Reduce dietary cholesterol	++	B	66
Utilize functional foods enriched with phytosterols	+++	A	67
Reduce excessive body weight	+	B	68
Utilize soy protein products	+	B	69
Increase habitual physical activity	+	A	70
Utilize red yeast rice supplements	+	B	71,72
Utilize phytosterol supplements	±	B	73

Rode gist rijst als 'nutraceutical/nutriceutical'

- Als nutraceutical vermeld in Europese guidelines
- Non prescription statin = vrij verkoopbaar in zogenaamde gezondheidswinkels
- Gevaar bijwerkingen... (SAMS)
 - US-FDA, Frankrijk ANSMPS, België HGR:
 - ✓ Special warnings on instructions for use labels
 - ✓ Registratie als geneesmiddel vereist voor bepaalde dosissen cfr reguliere statines
 - ✓ Vrije verkoop verbieden en dus registratie verplichten? (moeilijker acces...)
- Indien te veel regulering wordt evenwel acces moeilijker en blijft er niets meer over om patienten die geen regulier statine 'kunnen of willen' nemen te behandelen
- RGR kan ook met ezetimibe worden gecombineerd zodat grotere LDL-C dalingen kunnen bereikt worden ('RYR in addition to lipid lowering drugs')

Statine of monacoline?

- Is de term monacoline 'misleiding'?
- Labeling als monacoline laat toe om het product als 'natuurlijk statine' voor te stellen
- Het gebruik van de term 'monacoline' is een voordeel: patient associeert het product niet met klassiek farmacologische statine dat hij niet kan of wil nemen

Citrinine

- Fermentatie van rijst levert niet alleen monacoline maar ook citrinine
- Citrinine is ubiquitair aanwezig in allerlei voedingsproducten zoals granen, appels, kaas, specerijen en olijven
- Citrinine wordt beschouwd als een 'mycotoxine', omdat het in hoge dosis onder meer potentieel nefrotoxisch kan worden
- Controle is nodig op gecommercialiseerde RGR producten zodat deze geen citrinine bevatten
- Alle Belgische rode gist rijst producten zijn volkomen citrininevrij

Conclusion

- CV prevention and LDL-C lowering should be performed according to scientific evidence by well informed physicians
- Statins are beneficial
- Individual approach to patients according to risk category, treatment target and distance-to-LDL-C target, comorbidity, tolerance, age and expected lifespan
- Amongst different statin treatment options RYR may play a helpful role in accomplishing our goals as physicians