CẬP NHẬT VỀ PHỐI HỢP THUỐC TRONG ĐIỀU TRỊ RỐI LOẠN LIPID MÁU

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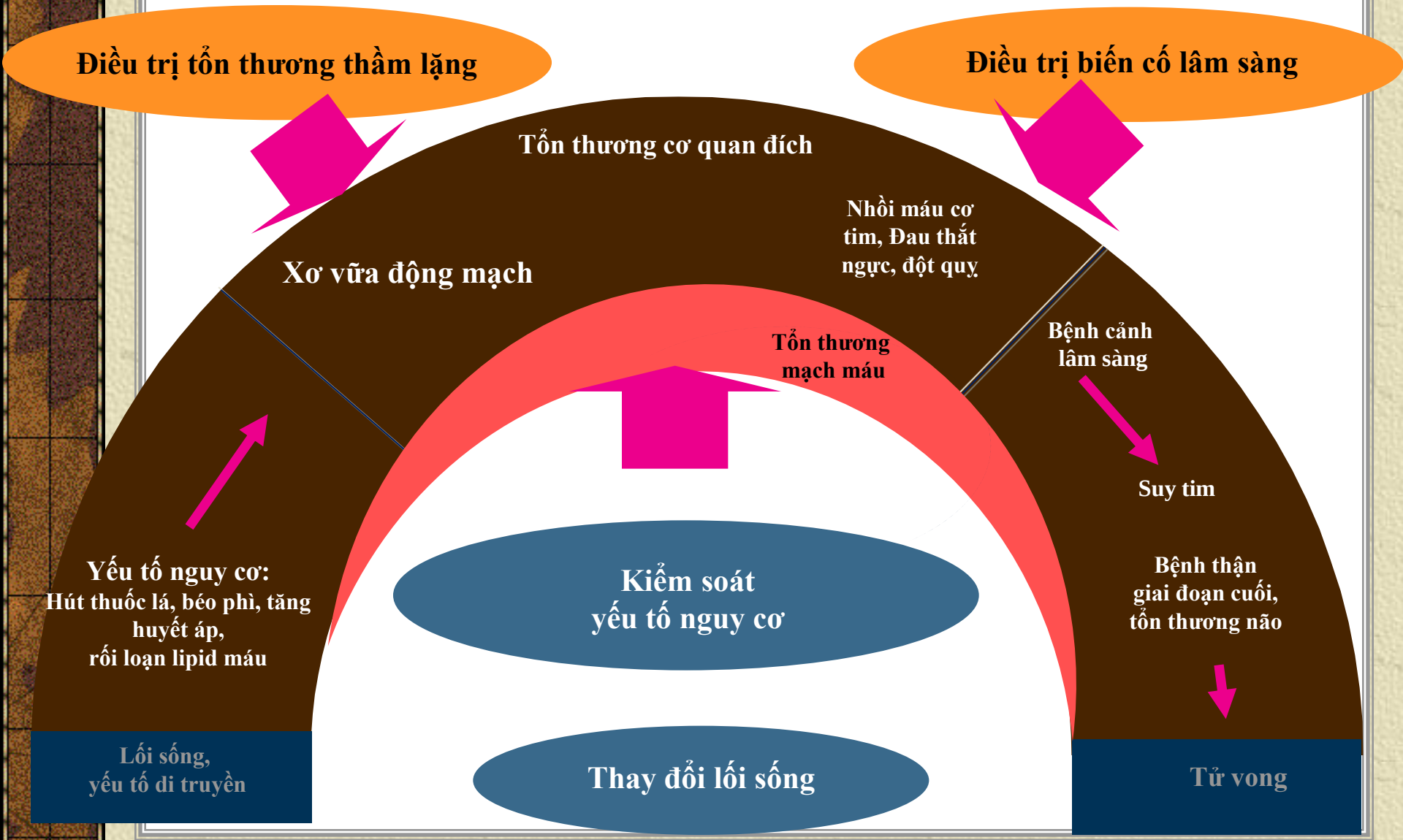
Bệnh viện Tim Tâm Đức
Viện Tim Tp. HCM

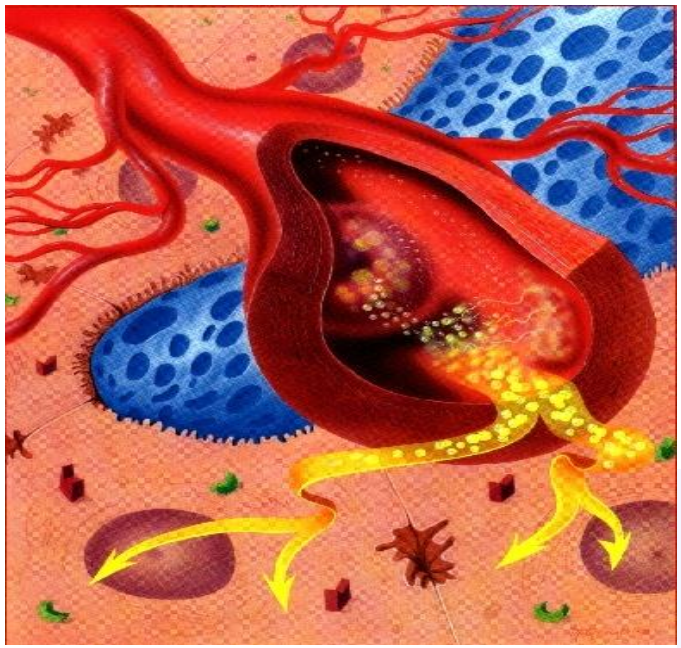
Tiến trình bệnh lý tim mạch



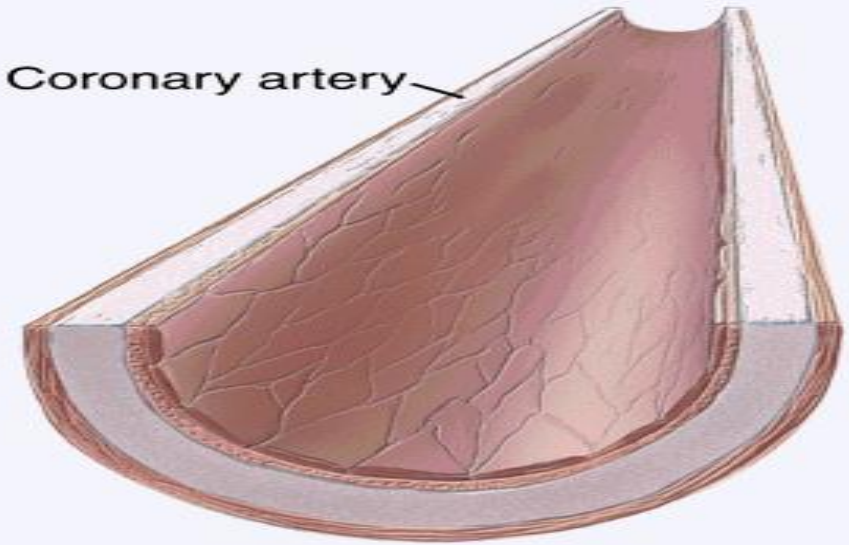
Tiếp cận lý tưởng để phòng ngừa bệnh tim mạch

- Điều trị các YTNC tim mạch
  - Rối loạn lipid máu : giảm LDL-C, tăng HDL-C
  - THA
  - ĐTĐ
- Điều trị làm chậm tiến triển XVĐM (điều trị tổn thương im lặng)
- Điều trị các biến cố làm nặng: giảm và ổn định mảng xơ vữa

Rối loạn lipid máu



- **Tăng LDL-C**
- **HDL-C thấp**
- **Tăng Triglycerid**



Tác động của LDL-C

- Tăng 1% LDL-C sẽ tăng >2% bệnh động mạch vành trong 6 năm

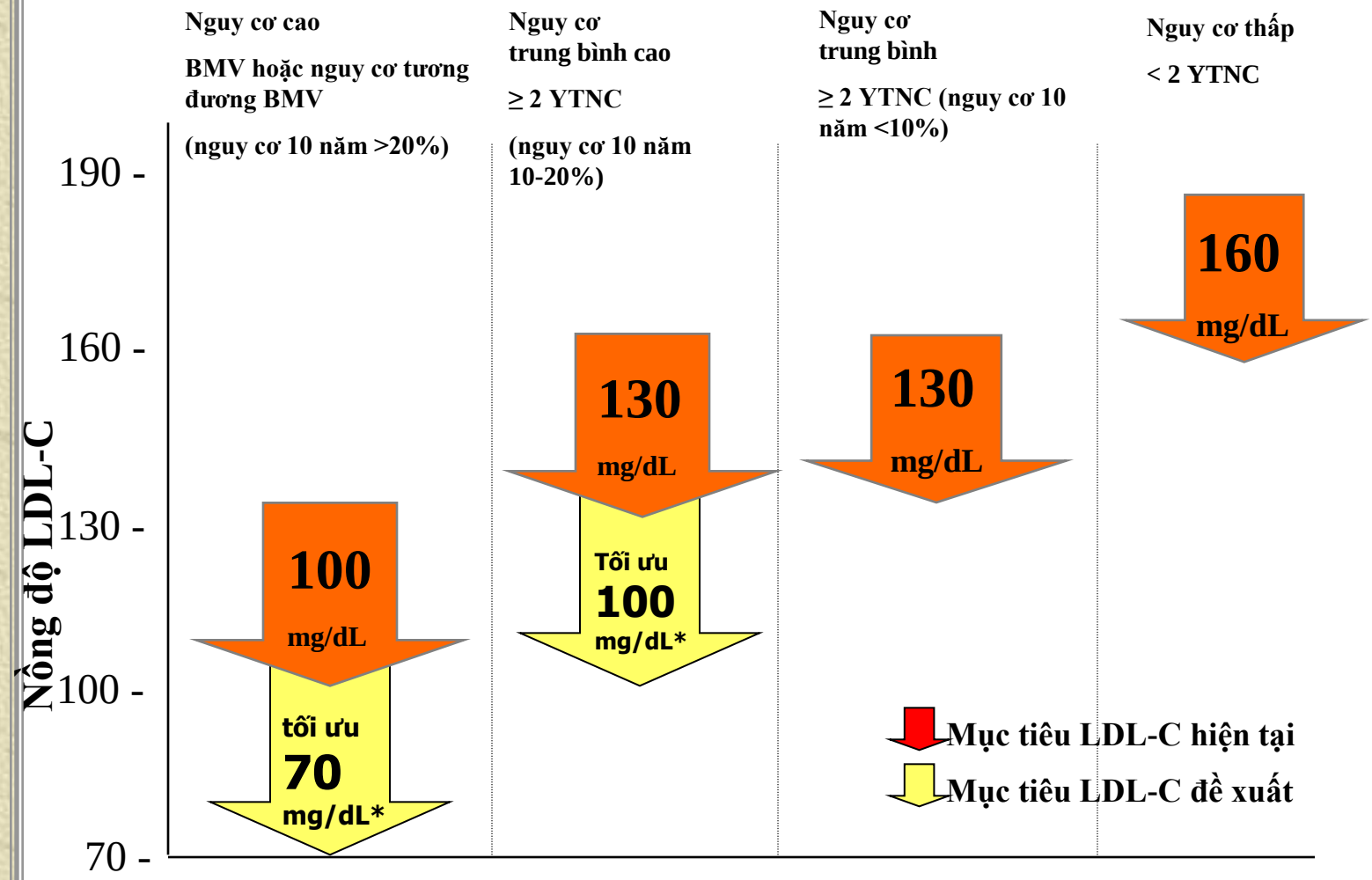
- Giảm 10 mg/dL LDL-C sẽ làm giảm 5.4% nguy cơ tim mạch trong 5 năm

LDL-C = low-density lipoprotein cholesterol; CAD = coronary artery disease.

Wilson PW. *Am J Cardiol.* 1990;66:7A-10A.

Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet.* 2005;366:1267-1278.

NCEP ATP III: LDL-C mục tiêu



*Liệu pháp ưu tiên

70 mg/dL =1.8 mmol/L; 100 mg/dL = 2.6 mmol/L; 130 mg/dL = 3.4 mmol/L; 160 mg/dL = 4.1 mmol/L

TL: Grundy SM et al. Circulation 2004;110:227-239.

Các nghiên cứu chứng minh hiệu quả statin trong phòng ngừa tiên phát bệnh tim mạch

- WOSCOPS, AFCAPS/ TexCAPS
- ASCOT- LLA; ALLHAT
- CARDS; PROSPER
- JUPITER

Các nghiên cứu về statins giúp phòng ngừa thứ cấp/ b/n bệnh động mạch vành mạn

- Nghiên cứu 4S (1994); LIPID (1998)
- CARE (1996); TNT (2005); IDEAL (2005)

Nguyên nhân của rối loạn lipid máu thứ cấp: tăng cholesterol máu

SELECTED CAUSES OF SECONDARY HYPERLIPIDEMIA	
Related to hypercholesterolemia	
Hypothyroidism	Dysglobulinemia
Nephrotis syndrome	Cushing's syndrome
Chronic liver disease (mainly primary Billary cirrhosis)	Hyperparathyroldism
Acute intermittent porphyria	

TL: Mosca L, Waters D. In Cardiology, ed. by MH Crawfodt, J P Dimarco, WJ Paulus Mosby Elsevier 2010, 3rd ed, p 89-108

ESC/EAS 2011: khẳng định ý nghĩa nền tảng của việc giảm LDL-C qua CTT

1 mmol/L (40 mg/dL)

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration** **Lancet 2010; 376: 1670–81**

- **10%** All-cause mortality
- **20%** CAD death
- **24%** Major coronary events
- **15%** Stroke

TL: Reiner K Z et al. ESC/EAS Guideline for the management of dyslipiclemia. Eur. Heart. J 2011; 32: 1769-1818

Hướng dẫn điều trị RLLM ESC/EAS 2011

Table 8 Recommendations for treatment targets for LDL-C

Recommendations	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Current available evidence suggests that the clinical benefit is largely independent of the type of statin but depends on the extent of LDL-C lowering; therefore, the type of statin used should reflect the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient.[15,100] More details on this are provided in Addendum II to these guidelines.

The following scheme is proposed:

- Evaluate the total CV risk of the subject
- Involve the patient with decisions on CV risk management
- Identify the LDL-C target for that risk level
- Calculate the percentage reduction of LDL-C required to achieve that goal
- Choose a statin that, on average, can provide this reduction
- Since the response to statin treatment is variable, up-titration to reach target is mandatory
- If the statin cannot reach the goal, consider drug combinations.

Table 14 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

TL: Reiner K Z et al. ESC/EAS Guideline for the management of dyslipiclemia. Eur. Heart. J 2011; 32: 1769-1818

ESC/EAS 2011: Giá trị của HDL-C

Table 5 Recommendations for lipid analyses for screening for CVD risk

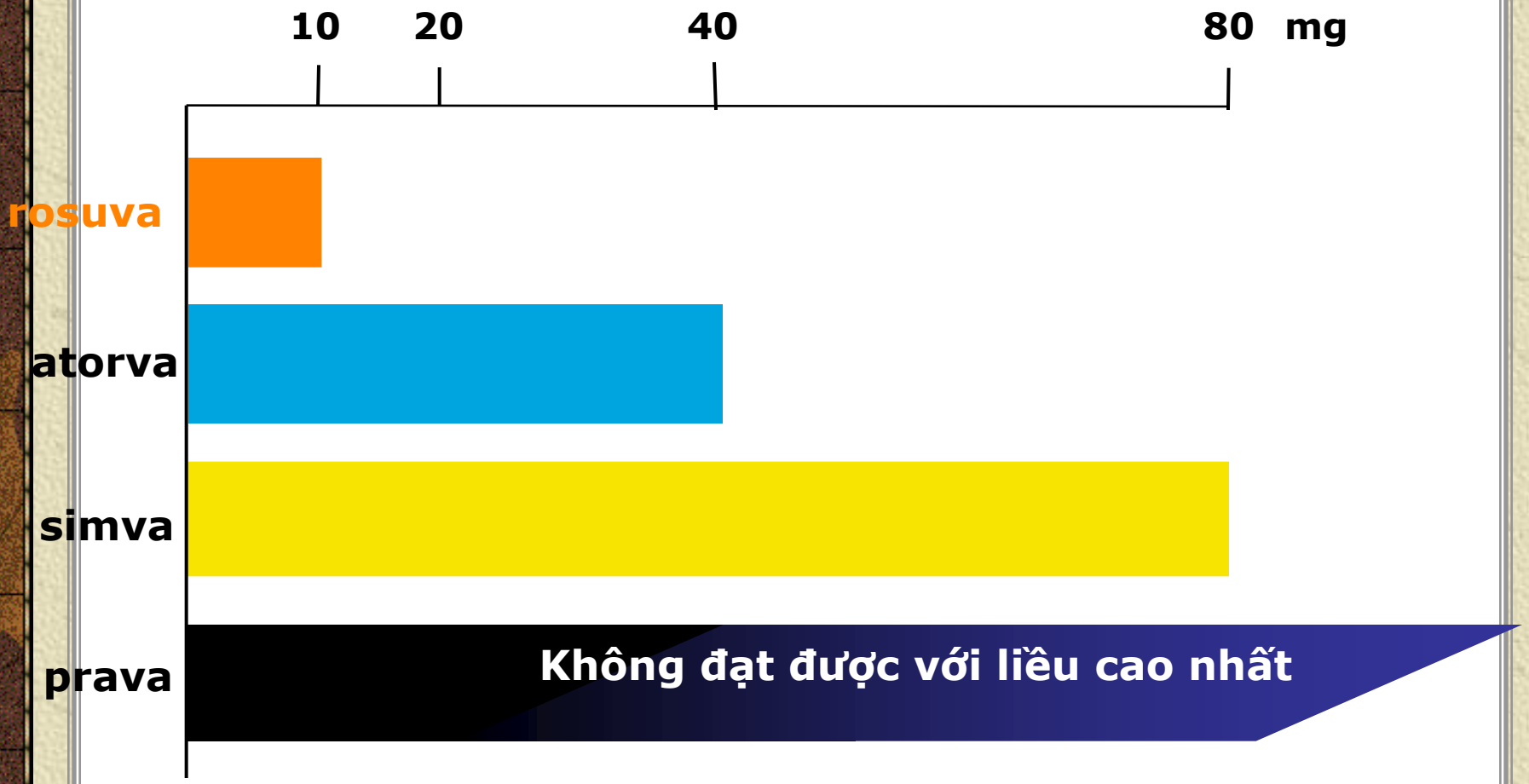
Recommendations	Class[a]	Level[b]
TC is recommended to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening and risk estimation.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
HDL-C is a strong risk factor and is recommended to be used for risk estimation.	I	C
Non-HDL-C should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
Apo B should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
The ratio apo B/apo A1 combines the risk information of apo B and apo A1 and may be recommended as an alternative analysis for risk screening.	IIb	C
The ratio non-HDL-C/HDL-C may be recommended as an alternative analysis for risk screening.	IIb	C

High-density lipoprotein and cardiovascular disease risk

Low levels of HDL-C constitute a strong, independent, and inverse predictor of the risk of premature development of atherosclerosis and CVD.[11] Moreover, the decrease in CV risk relative to HDL-C levels is especially dramatic over the range of HDL-C from ~0.65 to 1.17 mmol/L (25–45 mg/dL).[148] Elevation of ≥7.5% in HDL-C, together with a reduction in LDL-C to a target of <2.0 mmol/L (less than ~80 mg/dL), represented the minimum requirement for plaque regression in a meta-analysis of four intervention trials, which involved use of intravascular ultrasound to evaluate changes in coronary atheroma volume.[149]

TL: Reiner K Z et al. ESC/EAS Guideline for the management of dyslipiclemia. Eur. Heart. J 2011; 32: 1769-1818

Liều statin cần để giảm 30-45% LDL-C



Jones P.H. et al. Am J Cardiol 2003;92:152–160

Tiếp cận hiện tại và tương lai: giảm nguy cơ mạch máu lớn và vi mạch còn tồn tại

LDL-C

TARGET

The Lower

The Better

- Liệu pháp statin

- Liệu pháp phối hợp

➢ MACROVASCULAR DISEASE

Major reduction in CV morbi-mortality BUT

Up 65-90% of CV Events Not Prevented

Mục tiêu toàn diện có tối ưu?

LDL-C

HDL-C

TG

An toàn của các statin: cách sử dụng rất quan trọng trong điều trị

Dược động học lâm sàng các statins

	Rosuva	Atorva	Simva	Lova	Prava	Fluva
T 1/2, h	20.8	15–30	2–3	2.9	1.3–2.8	0.5–2.3
Urinary excretion, %	10	<2	13	10	20	6
CYP-3A4 metabolism	No	Yes	Yes	Yes	No	No
CYP metabolism	2CY9	3A4	3A4	3A4	sulfation	2CY9

Adapted from Blum (31).

Atorva = atorvastatin; CYP = cytochrome P450; CYP-3A4 = cytochrome p450-3A4; Fluva = fluvastatin; Lova = lovastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin; T 1/2 = half life.

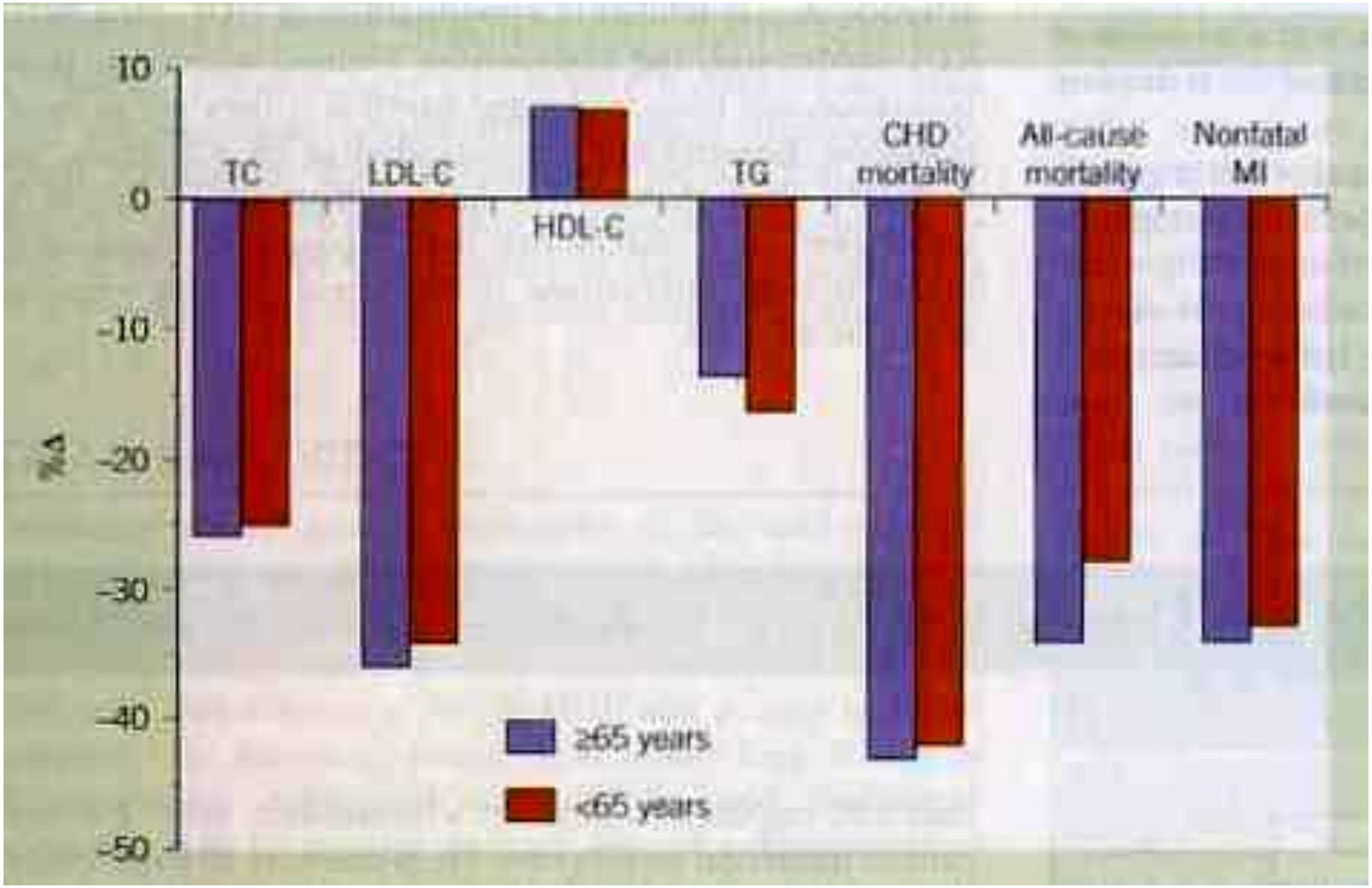
* Atorvastatin: đào thải thận < 2%, không cần chỉnh liều GFR < 30 ml/mn/1,73 m

TL: Harper CR et al. J Am Coll Cardiol 2008; 51: 2375-2384

Điều trị tăng cholesterol máu ở người cao tuổi

- Lợi ích: cao hơn người trẻ, do tần suất bệnh tim mạch cao
- Chú ý:
  - Chuyển hóa của statins
  - Tương tác thuốc

Giảm biến cố động mạch vành/ người cao tuổi tăng cholesterol máu điều trị bằng statin: n/c 4S



TL: Miettiners TA et al. Circulation 1997; 96: 4211-4218

Chronic Kidney Disease and the Study of Heart and Renal Protection (SHARP)

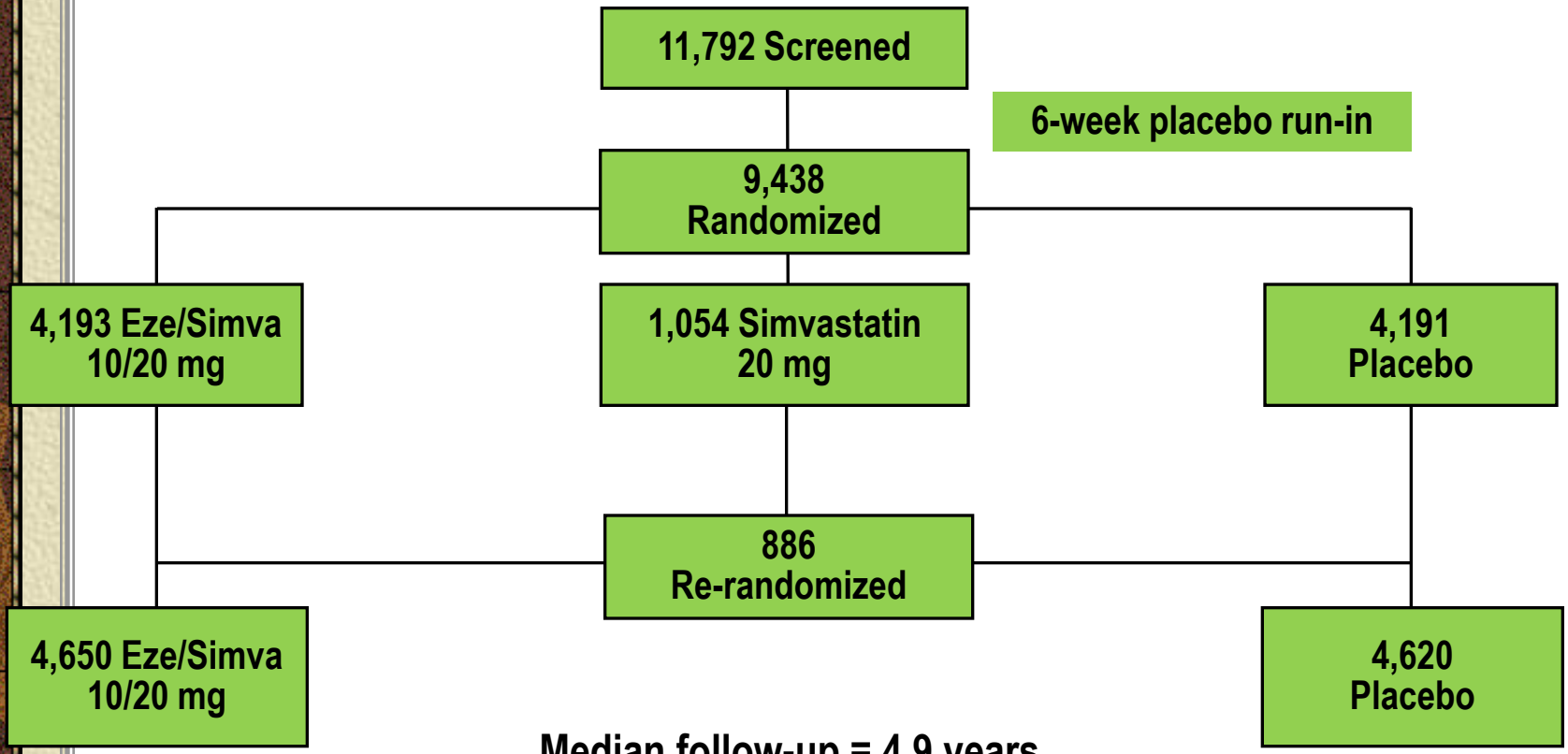
Dyslipidemia in Patients With CKD

- CKD is associated with elevated triglyceride levels, low HDL-C levels, and increased small dense LDL particles[1]

CKD = chronic kidney disease.

1. Tsimihodimos V et al. *Am J Nephrol.* 2008;28:958–973.
2. Kaysen GA et al. *J Ren Nutr.* 2009;19:357–364.

SHARP: Study Design[1]



Median follow-up = 4.9 years

The 1-year simvastatin arm was included to enable the comparison of Eze/Simva to simvastatin alone with regard to safety and lipids

SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin.

1. Baigent C et al. *Lancet*. 2011;377:2181–2192.

SHARP: Baseline Characteristics in Patients Randomized to Eze/Simva 10/20 mg or Placebo[1]

All patients	**(n=9,270)**
Mean age, y	62
Men, % of pts	63
Mean systolic BP, mm Hg	139
Mean diastolic BP, mm Hg	79
Mean body mass index, kg/m^2	27
Current smoker, % of pts	13
Vascular disease, % of pts	15
Diabetes mellitus, % of pts	23
Nondialysis patients only	**(n=6,247)**
Mean eGFR, mL/min/1.73 m^2	26.6
Albuminuria[a], % of pts	80

[a]Defined as ≥30 mg/g urinary albumin:creatinine ratio.

SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin; BP = blood pressure; eGFR estimated glomerular filtration rate.

1. Baigent C et al. *Lancet*. 2011;377:2181–2192.

SHARP: Effect on LDL Cholesterol by Treatment Group at 1 Year[1-3]

	Eze/Simva (n=391)	Simva (n=108)	Placebo (n=365)
LDL cholesterol, mg/dL[a]	66	79	108

At 1 year, the mean LDL-C was 26% lower in the simvastatin 20 mg arm and 38% lower in the Eze/Simva 10/20-mg arm relative to placebo (approximately 10% of patients sampled at year 1)

[a]Nonfasting blood samples; patients no longer taking study medication were included in all lipid measurements.
SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin.

1. Baigent C et al. Lancet. 2011;377:2181–2192.

2. SHARP Collaborative Group. Am Heart J. 2010;160:785–794.

3. SHARP Clinical Study Report (MK-0653A Prot. No. 044), 2011.

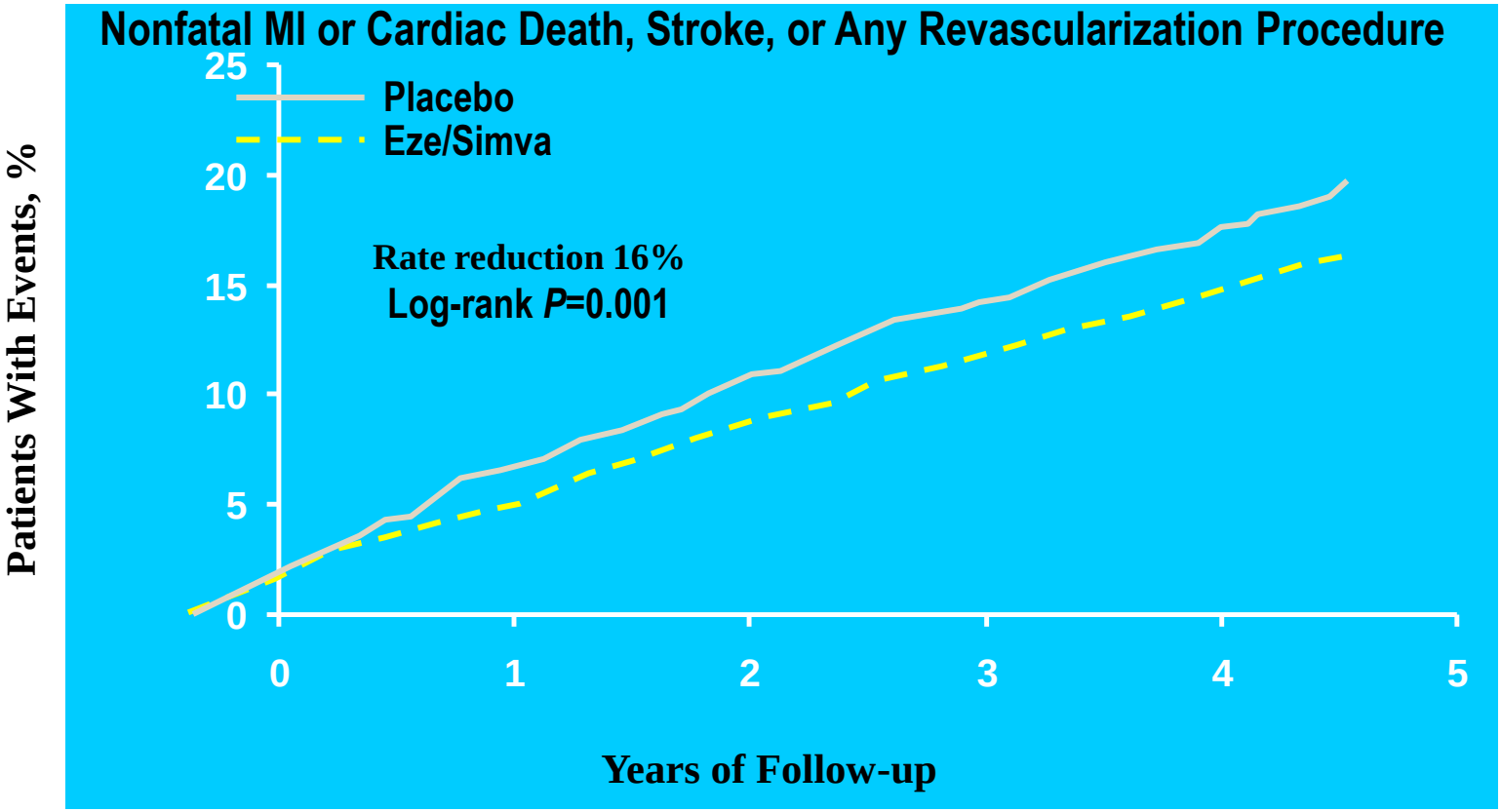
SHARP: Effect on LDL Cholesterol by Treatment Group at 2.5 Years[1-4]

	Eze/Simva 10/20 mg (n=3,473)	Placebo (n=3,452)	Absolute Difference	Percentage Difference	*P* Value
LDL cholesterol, mg/dL[a]	70	103	33	-32%	<0.0001

[a]Nonfasting blood samples; patients no longer taking study medication were included in all lipid measurements.
SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin.

1. Baigent C et al. Lancet. 2011;377:2181–2192.
2. SHARP Collaborative Group. Am Heart J. 2010;160:785–794.
3. Data on file.
4. SHARP Clinical Study Report (MK-0653A Prot. No. 044), 2011.

SHARP: Major Vascular Events in Patients Initially Assigned to Eze/Simva or Placebo (Primary End Point)[1,2]



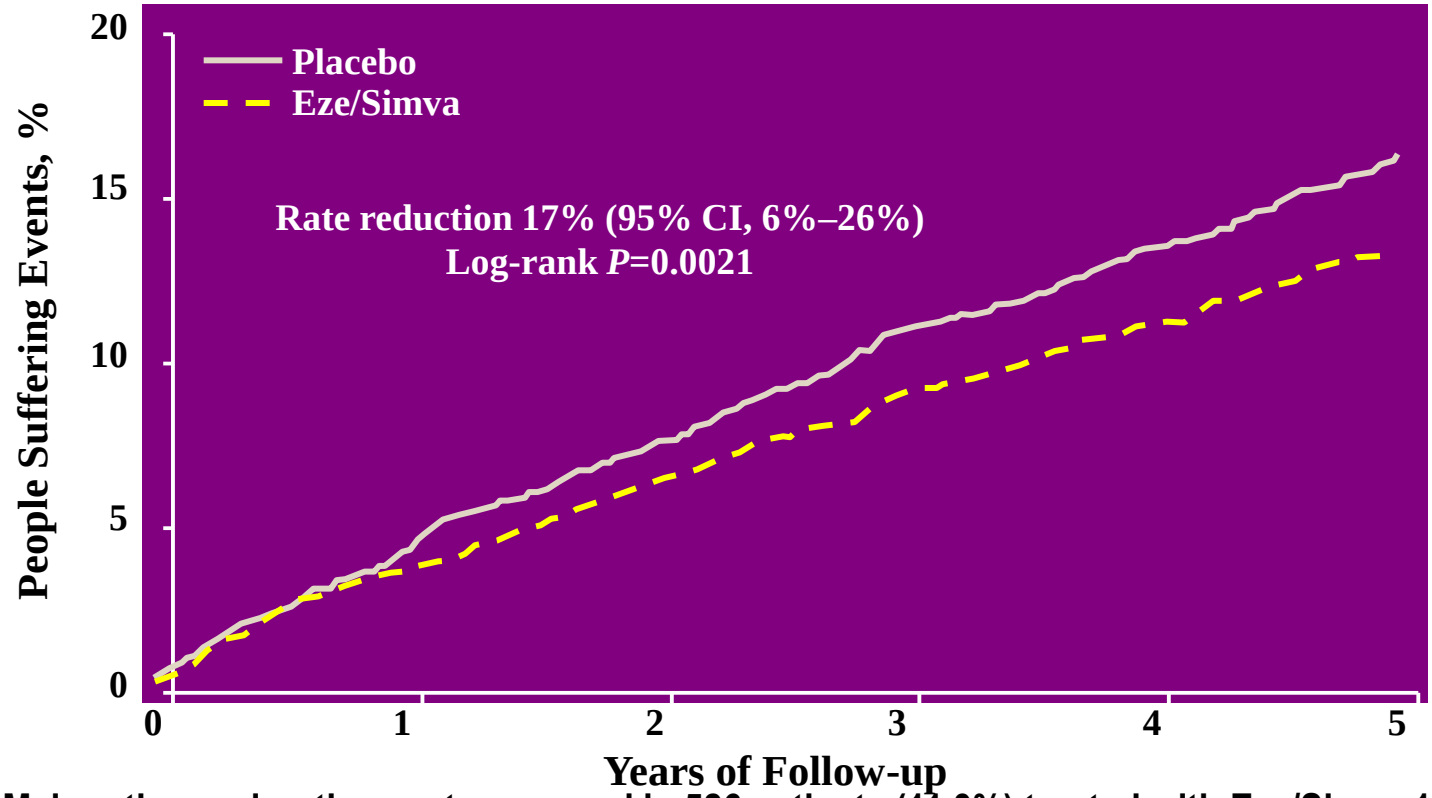
Major vascular events occurred in 639 patients (15.2%) treated with Eze/Simva 10/20 mg vs 749 patients (17.9%) treated with placebo, corresponding to a 16% relative risk reduction

SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin; MI = myocardial infarction.

1. Data on file; **2.** Baigent C et al. *Lancet*. 2011;377:2181–2192.

SHARP: Major Atherosclerotic Events[1]

Coronary Death, Nonfatal MI, Ischemic Stroke, or Arterial Revascularization



Major atherosclerotic events occurred in 526 patients (11.3%) treated with Eze/Simva 10/20 mg vs 619 patients (13.4%) treated with placebo, corresponding to a 17% relative risk reduction

SHARP = Study of Heart and Renal Protection; MI = myocardial infarction; Eze/Simva = ezetimibe/simvastatin; CI = confidence interval.

1. Baigent C et al. *Lancet*. 2011;377:2181–2192.

SHARP: Muscle Safety[1]

	No. of Pts (%)	
	Eze/Simva 10/20 mg (n=4,650)	Placebo (n=4,620)
CK >10 × but ≤40 × ULN	17 (0.4)	16 (0.3)
CK >40 × ULN (ITT)	4 (0.1)	5 (0.1)
Myopathy[a] (ITT)	9 (0.2)	5 (0.1)
Myopathy[a] (on treatment)	8 (0.2)	3 (0.1)
Rhabdomyolysis[b] (ITT)	4 (0.1)	1 (0.0)
Rhabdomyolysis[b] (on treatment)	4 (0.1)	0 (0.0)

[a]Myopathy defined as CK >10 × ULN with muscle symptoms.
[b]Rhabdomyolysis defined as myopathy with CK >40 × ULN.
SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin; CK = creatine kinase; ULN = upper limit of normal; ITT = randomized intention-to-treat comparison.

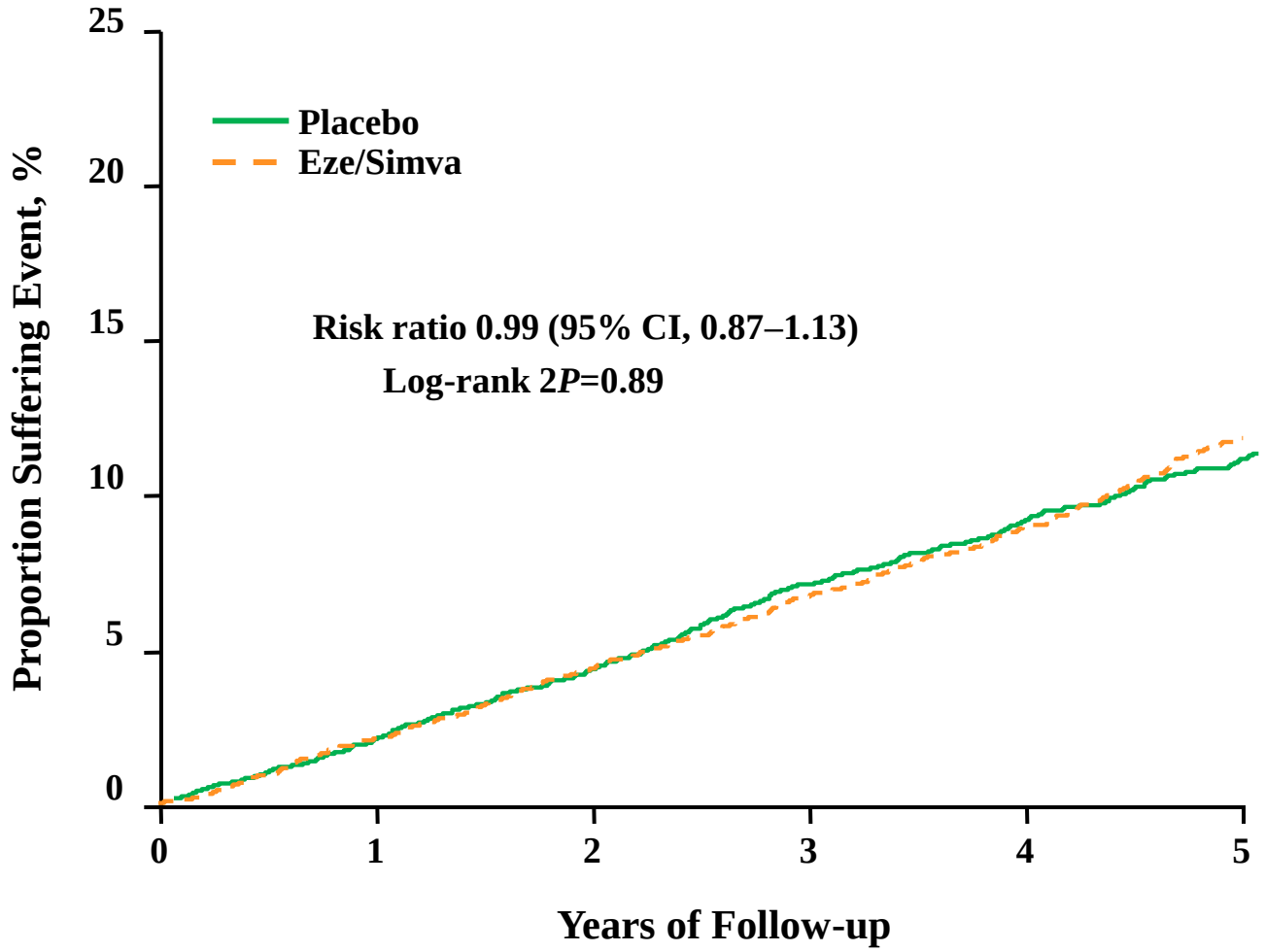
SHARP: Liver Safety

	No. of Pts (%)	
	Eze/Simva 10/20 mg (n=4,650)	Placebo (n=4,620)
Hepatitis[1]		
Infective	12 (0.3)	12 (0.3)
Noninfective	6 (0.1)	4 (0.1)
No cause identified	3 (0.1)	3 (0.1)
Any hepatitis	21 (0.5)	18 (0.4)
ALT/AST consecutive >3 × ULN[1,2]	30 (0.7)	26 (0.6)

SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin; ALT = alanine aminotransferase; AST = aspartate aminotranferase; ULN = upper limit of normal.

1. Baigent C et al. *Lancet*. 2011;377:2181–2192; **2.** MSD. Worldwide Product Circular. WPC –MK0653A-T112011.

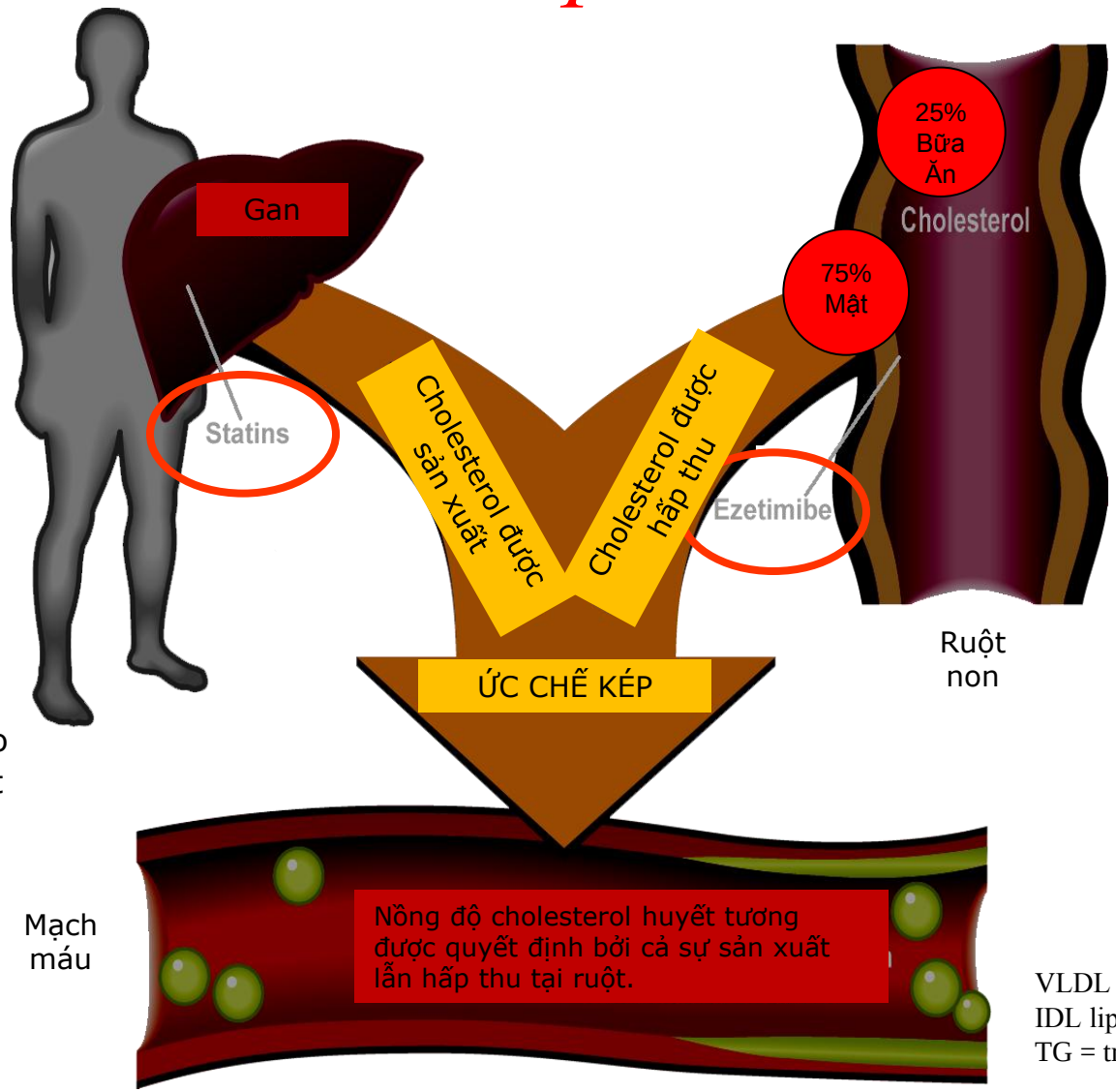
SHARP: Cancer Incidence[1,2]



SHARP = Study of Heart and Renal Protection; Eze/Simva = ezetimibe/simvastatin; CI = confidence interval.

. SHARP presentation slides. SHARP Web site. http://www.sharpinfo.org/slides.htm. Accessed February 15, 2012; **2.**

Cơ chế ức chế kép



Tổng hợp cholesterol nội sinh (VLDL, IDL, LDL)

Khoảng 50% được hấp thu vào trong huyết tương[2]

Mạch máu

Hấp thu cholesterol tại ruột (chylomicron, TG, sterol thực vật)

Cholesterol trong ruột từ mật (~75%) và bữa ăn (~25%)[1]

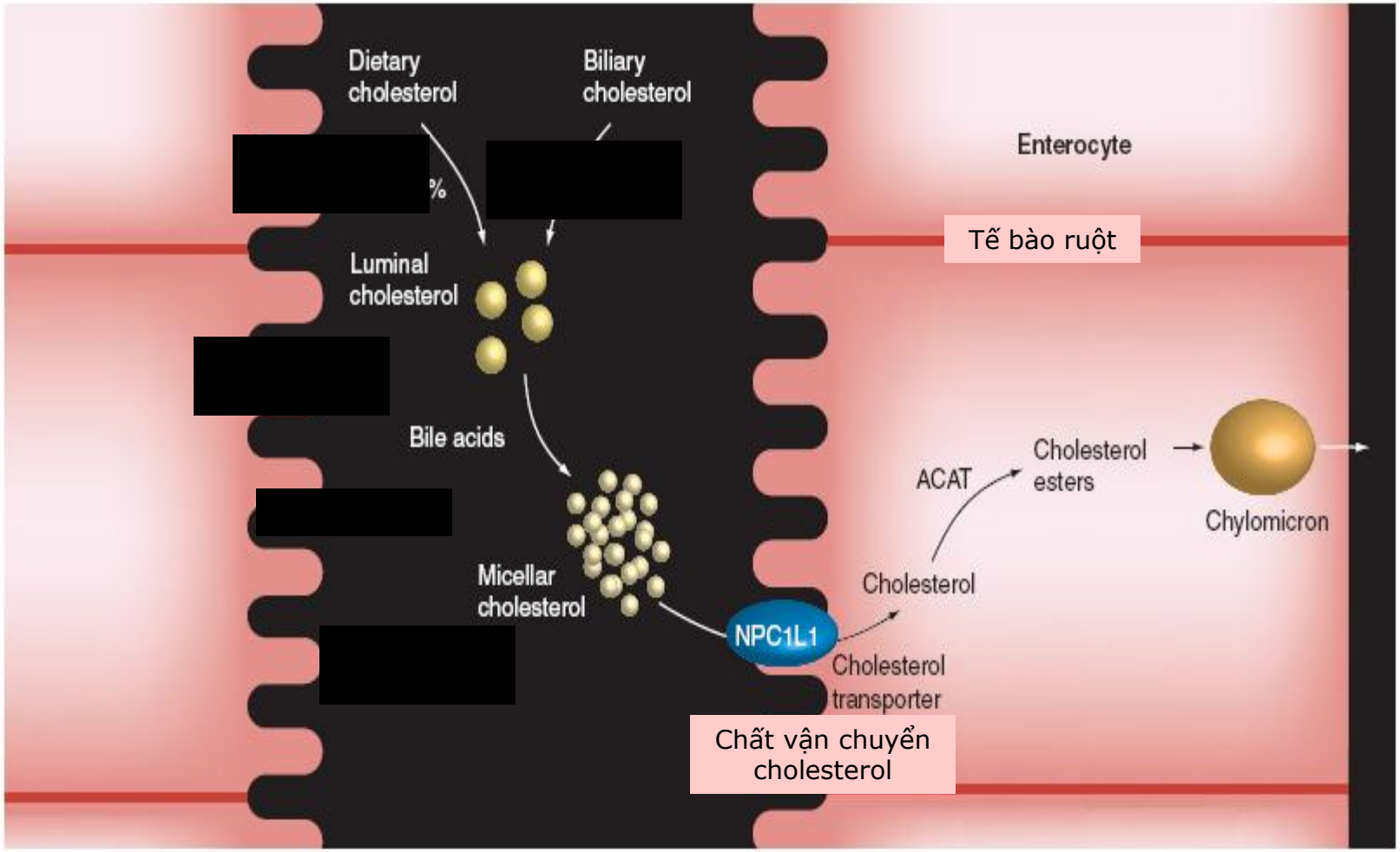
Ruột non

VLDL = lipoprotein tỉ trọng rất thấp.
IDL lipoprotein tỉ trọng trung bình.
TG = triglyceride.

1. Shepherd J. *Eur Heart J Supplements.* 2001:3(suppl E):E2–E5.
2. Homan R et al. *Curr Pharm Design.* 1997;3:29–44.

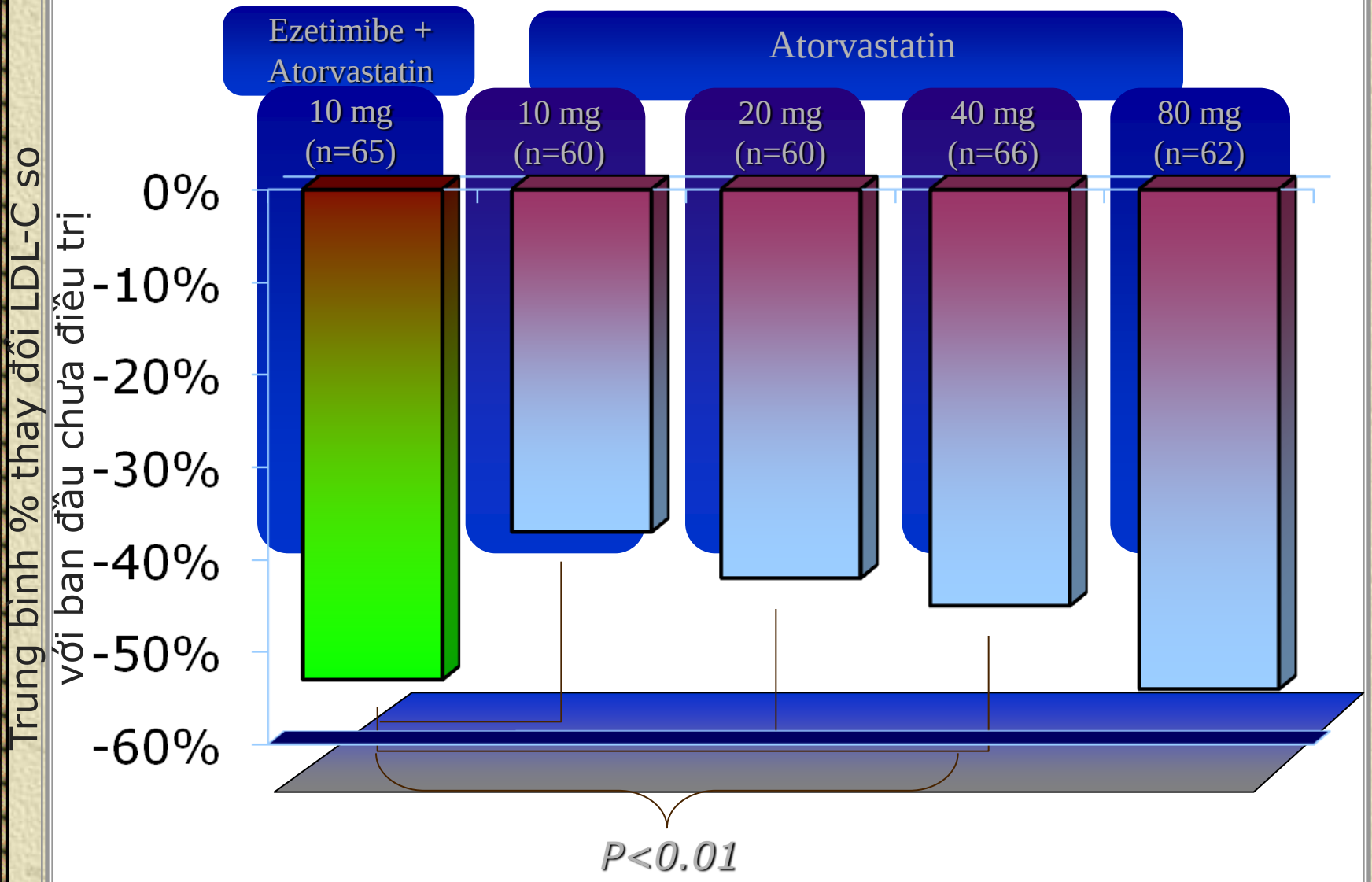
Ezetimibe: Cơ Chế Tác Dụng (1)*

- Ezetimibe **ức chế chọn lọc hấp thu cholesterol,** tác động **tại bờ bàn chải** của ruột non.



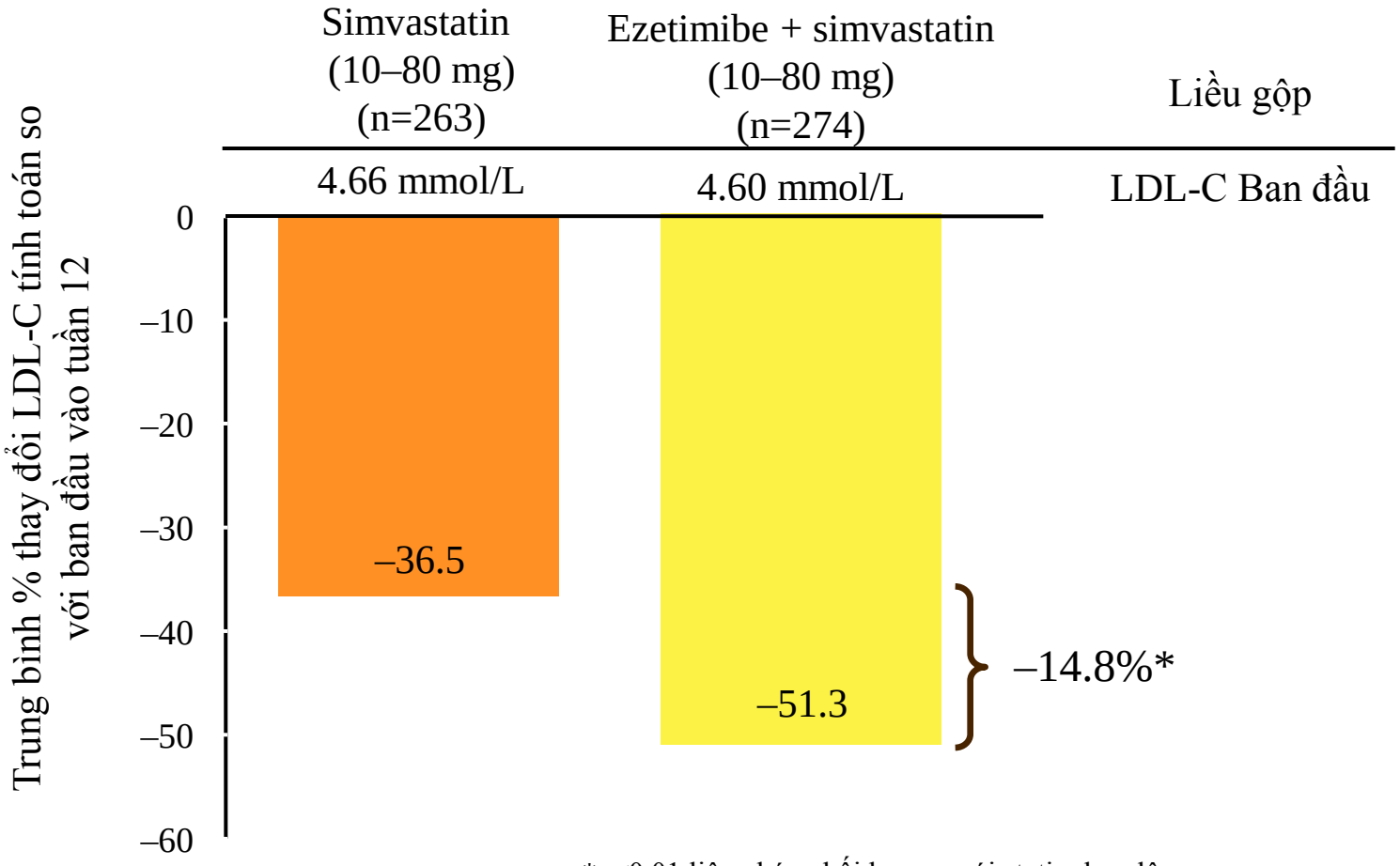
*EZETROL®, MSD

Ezetimibe: hiệu quả "10 + 10 = 80"



Ballantyne CM et al. *Circulation* 2003;107:2409-2415.

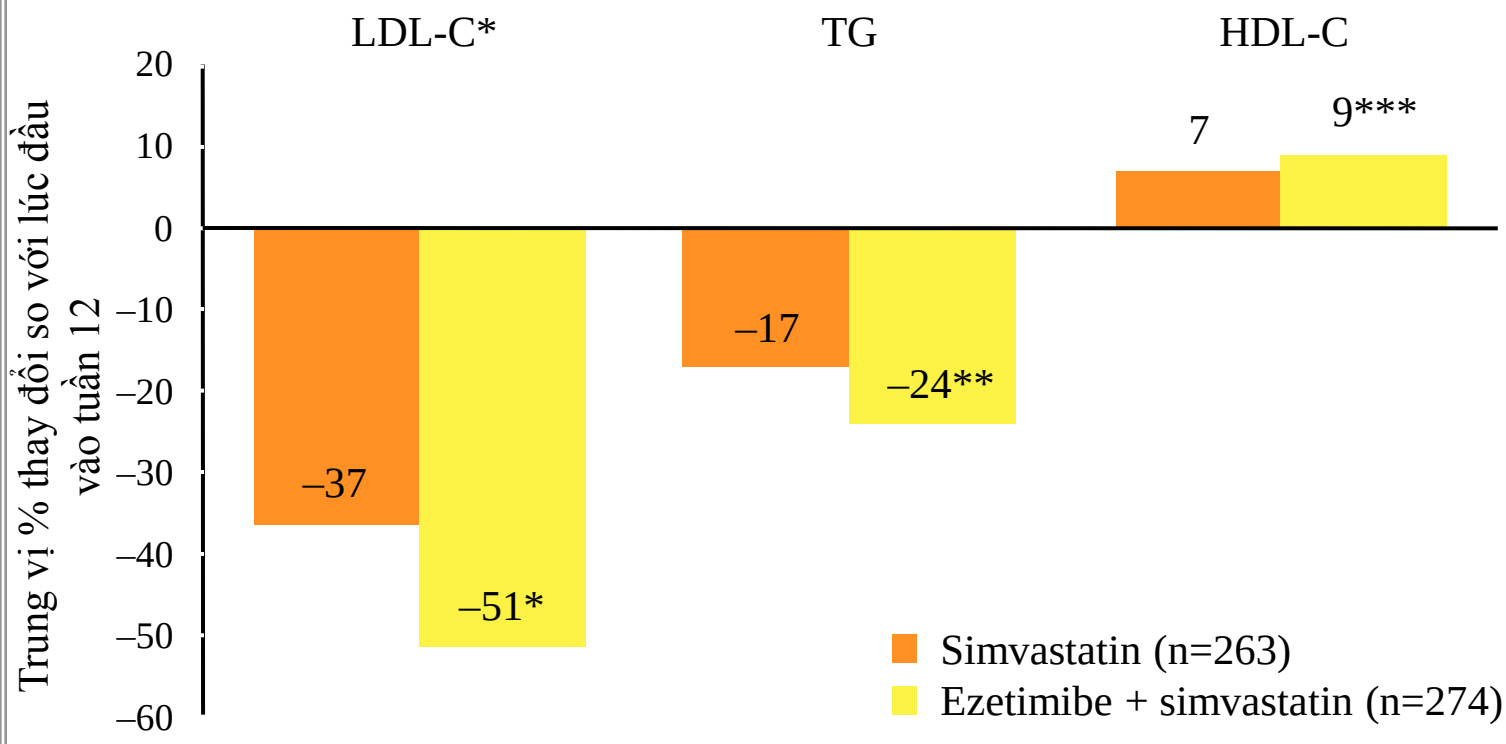
Ezetimibe phối hợp với Simvastatin: Kết quả gộp với LDL-C



*p<0.01 liệu pháp phối hợp so với statin đơn độc

Adapted from Davidson MH et al *J Am Coll Cardiol* 2002;40:2125–2134.

Ezetimibe phối hợp với Simvastatin: Kết quả gộp cho LDL-C, TG, và HDL-C



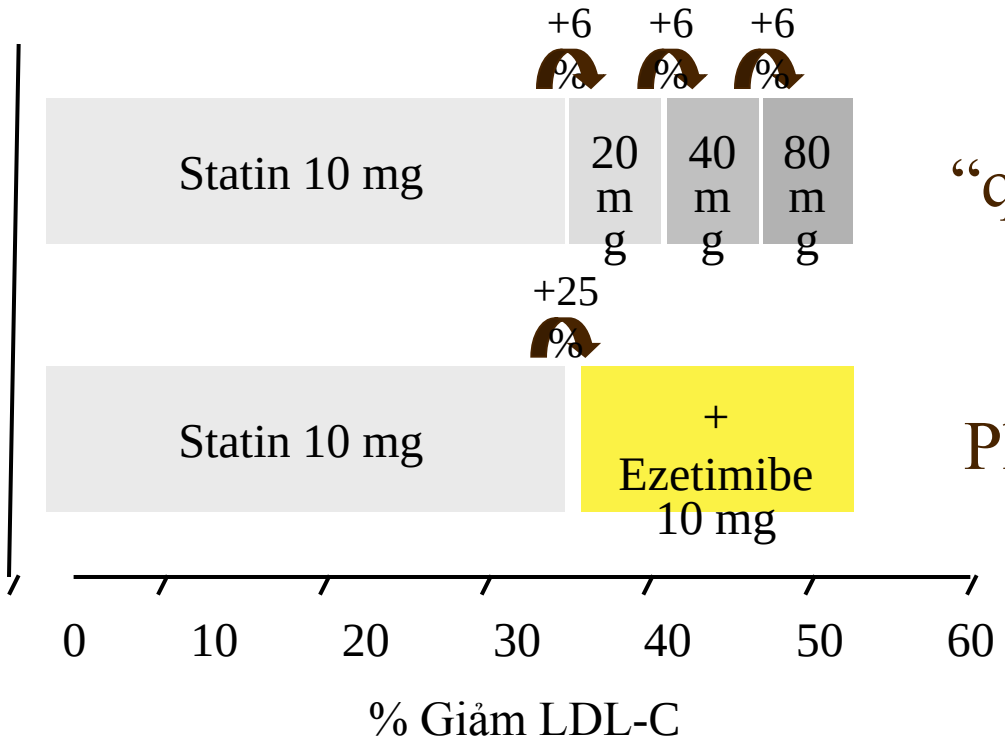
* LDL-C tính toán

** p<0.01 phối hợp so với statin đơn độc

*** p=0.03 phối hợp so với statin đơn độc

Adapted from Davidson MH et al *J Am Coll Cardiol* 2002;40:2125–2134.

Ezetimibe phối hợp với Statin: Kiểm soát hiệu quả LDL-C



"quy tắc số 6"

Phối hợp một bước

- Phối hợp một bước ezetimibe tương đương tăng gấp đôi liều statin 3 lần (10+10 = 80)

Adapted from Stein E *Eur Heart J Suppl* 2001;3(suppl E):E11-E16.

Kết luận

- Điều trị rối loạn lipid máu: giảm LDL-C, tăng HDL-C giảm TG
- Mục tiêu LDL-C: càng thấp càng tốt
- Statins đơn độc: khó đạt mục tiêu LDL-C < 70 mg/dL
- Statin + ezetimibe: hiệu quả cao, an toàn, giảm tử vong tim, đột quỵ và các biến cố khác do XVĐM