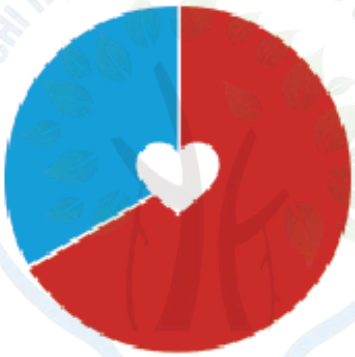

STATIN TRÊN BỆNH NHÂN
ĐÁI THÁO ĐƯỜNG
Những điều cần lưu ý
PGS.TS.BS Hồ Thị Kim Thanh
Được hỗ trợ bởi AstraZeneca cho mục đích giáo dục y khoa


01
STATIN CHO TẤT CẢ
BỆNH NHÂN
ĐÁI THÁO ĐƯỜNG?

2/3 NGUYÊN NHÂN TỬ VONG Ở BN ĐÁI THÁO ĐƯỜNG LIÊN QUAN TỚI BỆNH TIM MẠCH

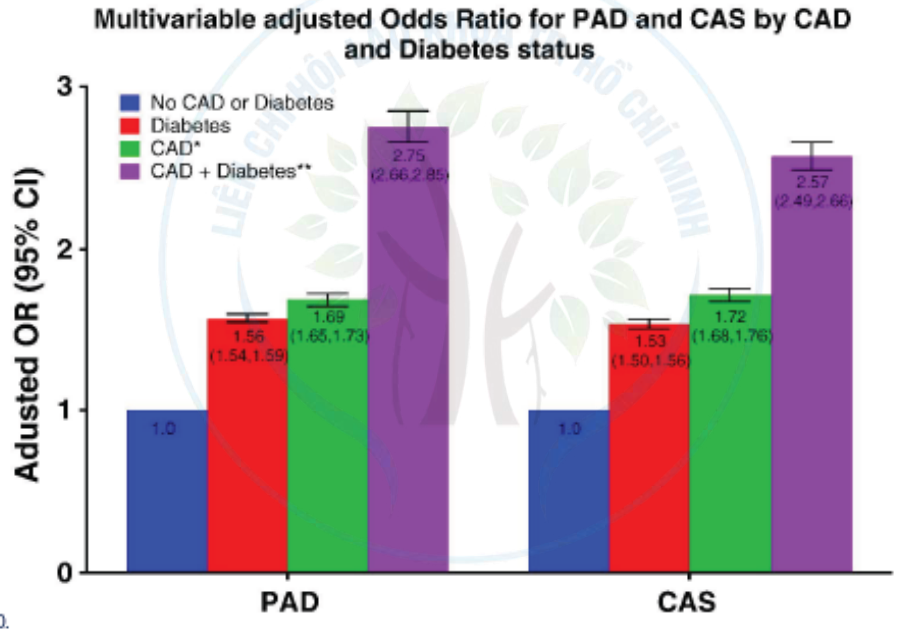
IN PEOPLE WITH DIABETES



2/3 OF DEATHS
ARE ATTRIBUTED TO CVD[1]

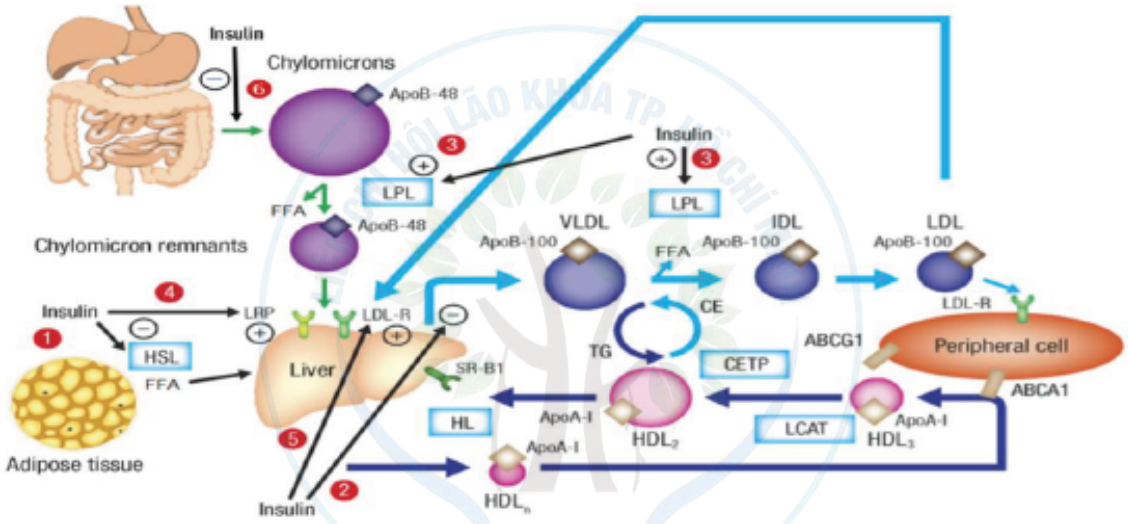
Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus. Atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus–mechanisms, management, and clinical considerations. *Circulation*. 2016;133:2459-2502

ĐTĐ ĐƯỢC XEM NHƯ YTNC TIM MẠCH ĐỘC LẬP TƯƠNG ĐƯƠNG VỚI BỆNH MẠCH VÀNH



AmHeart J 2017;184:114-20.

INSULIN ẢNH HƯỞNG LÊN CHUYỂN HÓA LIPOPROTEIN

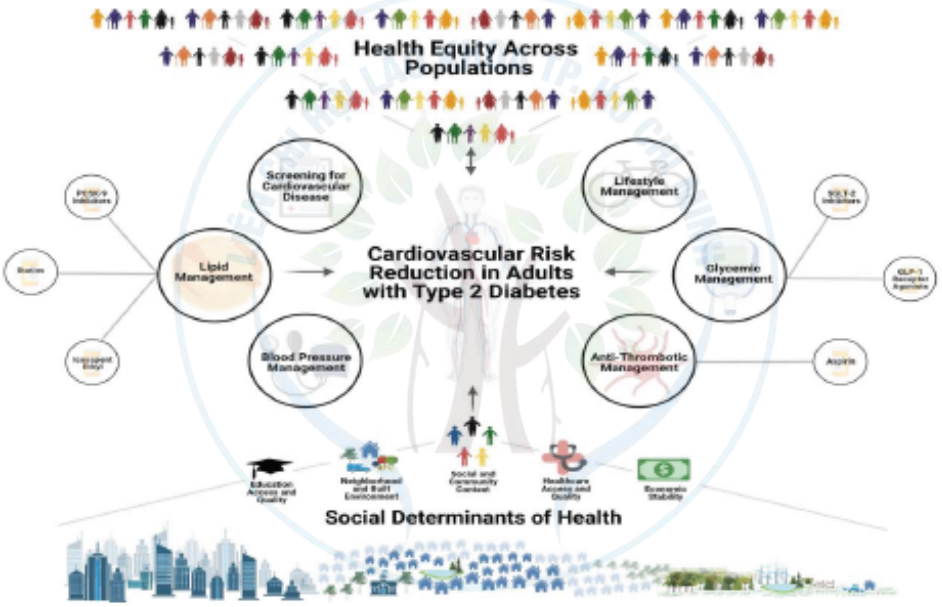


(1) Insulin ức chế hormon nhạy cảm lipase- HSL ở mô mỡ. (2) Insulin ức chế tổng hợp VLDL ở gan. (3) Insulin tăng hoạt tính LPL. (4) Insulin tăng biểu hiện LRP. (5) Insulin tăng biểu hiện LDL-R. (6). Insulin ức chế tổng hợp chylomicrons

Chú thích ABCA1, ATP-binding cassette A1 transporter; ABCG1, ATP-binding cassette G1 transporter; Apo, apolipoprotein; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; HDLn, nascent HDL; HL, hepatic lipase; HSL, hormone-sensitive lipase; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyl transferase; LDL, low-density lipoprotein; LDL-R, LDL receptor; LRP, LDL receptor-related protein; LPL, lipoprotein lipase; SR-B1, scavenger receptor B1; TG, triglyceride; VLDL, very low density lipoprotein.

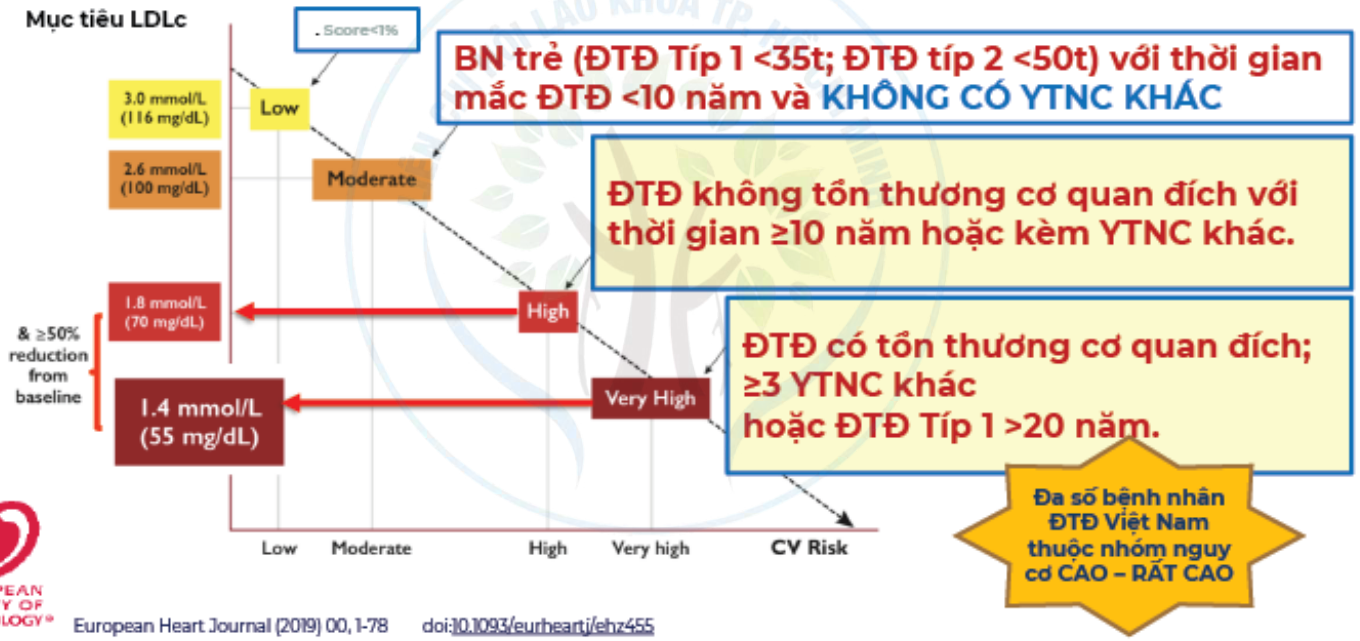
Vergès, B. (2020). Dyslipidemia in Type 1 Diabetes: A Masked Danger. Trends in Endocrinology & Metabolism. doi:10.1016/j.tem.2020.01.015

KIỂM SOÁT LIPID MÁU ĐÓNG VAI TRÒ TRUNG TÂM TRONG PHÒNG NGỪA CÁC BỆNH LÝ TIM MẠCH



Circulation. 2022;145:e722–e759

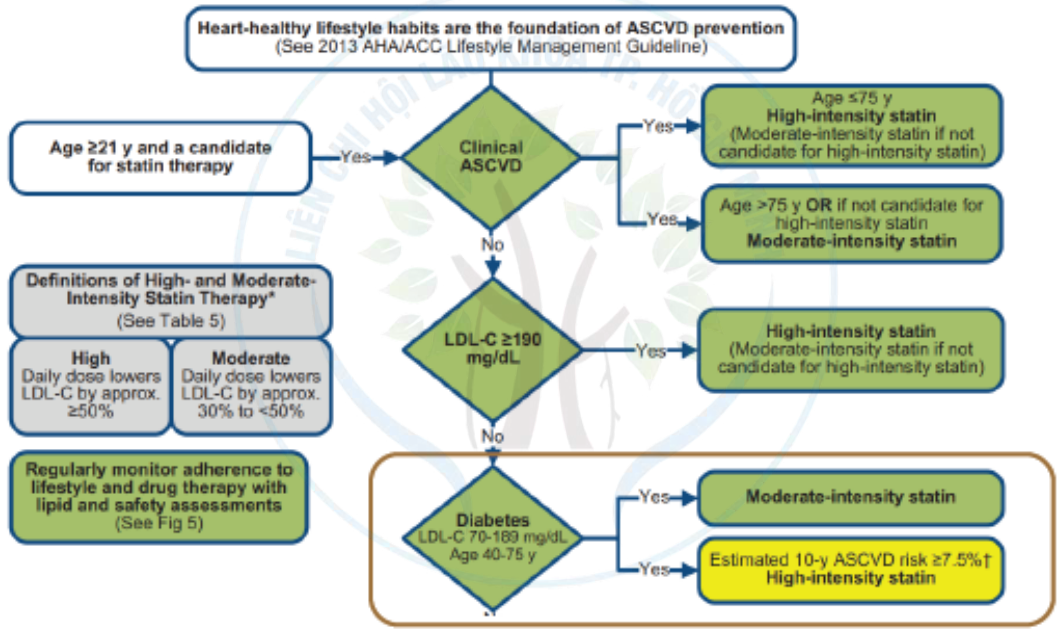
MỤC TIÊU LDL-C TRÊN TỪNG ĐỐI TƯỢNG BN ĐTĐ KHÁC NHAU PHỤ THUỘC VÀO YTNC KÈM THEO



EUROPEAN SOCIETY OF CARDIOLOGY

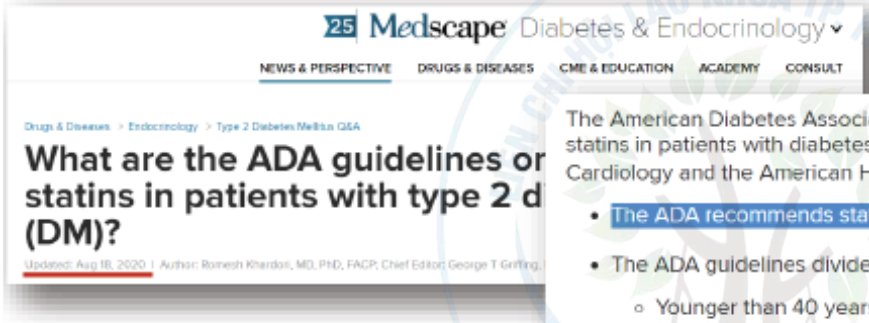
European Heart Journal (2019) 00, 1-78 doi:10.1093/eurheartj/ehz455

ACC/AHA 2013 ĐA SỐ CAC BN ĐTĐ 40-75 TUỔI CÓ CHỈ ĐỊNH DÙNG STATIN



Stone et al 2013 ACC/AHA Blood Cholesterol Guideline

ADA 2020: STATIN NÊN ĐƯỢC DÙNG CHO HẦU HẾT BỆNH NHÂN ĐÁI THÁO ĐƯỜNG



The American Diabetes Association (ADA) provided recommendations on the use of statins in patients with diabetes to align with those of the American College of Cardiology and the American Heart Association.[332]

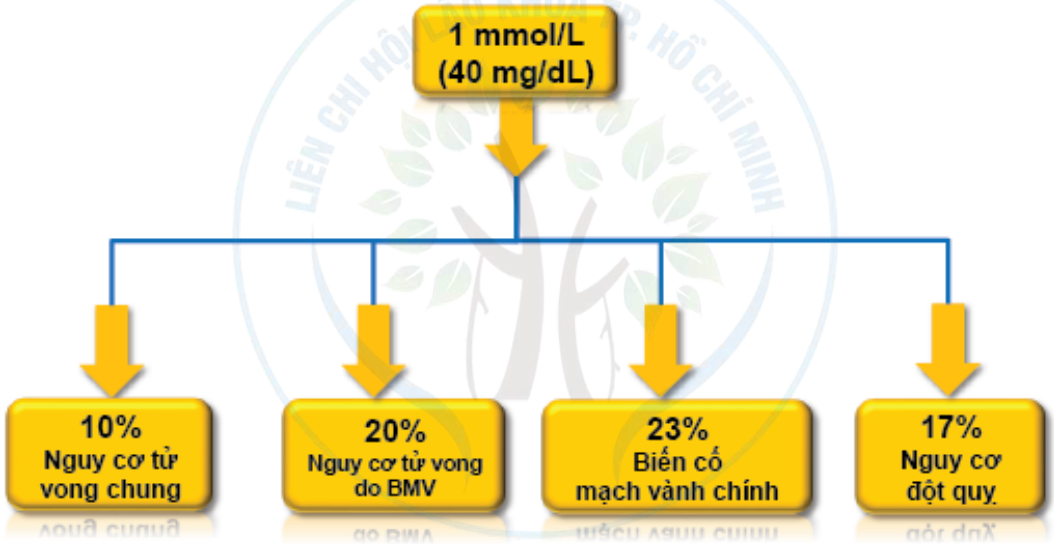
- The ADA recommends statin use for nearly everyone with diabetes.
- The ADA guidelines divide diabetes patients by 3 age groups:
  - Younger than 40 years: No statins for those with no cardiovascular disease (CVD) risk factors other than diabetes; moderate intensity or high-intensity statin doses for those with additional CVD risk factors (baseline LDL cholesterol 100 or greater, high blood pressure, smoking, and overweight/obesity); and high-intensity statin doses for those with overt CVD (including previous cardiovascular events or acute coronary syndrome).
  - Age 40-75 years: Moderate-intensity statins for those with no additional risk factors, and high-intensity statins for those with either CVD risk factors or overt CVD.
  - Older than 75 years: Moderate-intensity statins for those with CVD risk factors; and high-intensity statins for those with overt CVD.

American Diabetes Association.

02
STATIN HẠ LDL-C CÀNG THẤP CÓ CÀNG TỐT?

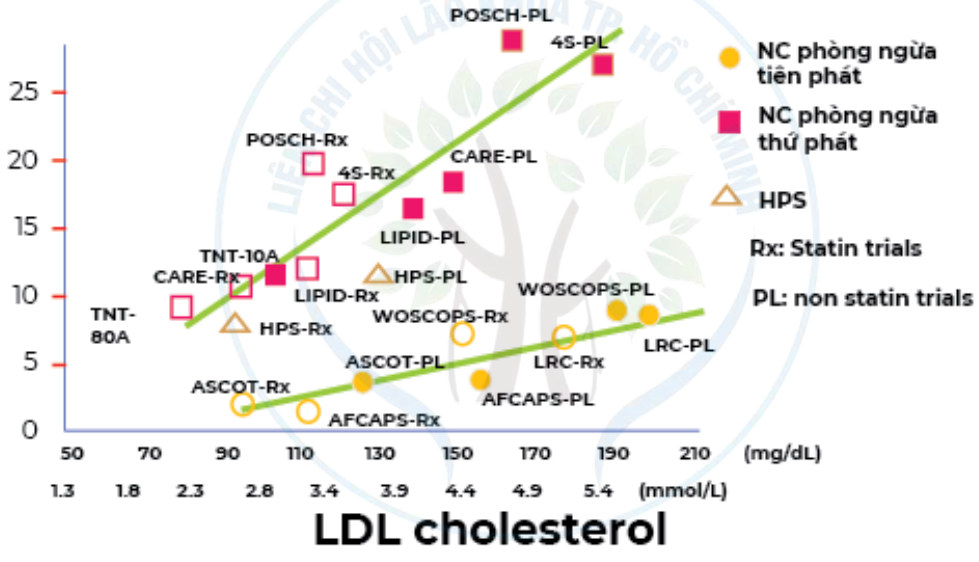
GIẢM LDL-C GIÚP GIẢM BIẾN CỐ TIM MẠCH

Meta-analysis CTT (Cholesterol Treatment Trialists) từ 26 thử nghiệm lâm sang ngẫu nhiên trên 170,000 bệnh nhân đã chứng minh được mối liên hệ giữa việc giảm LDL-C một cách hiệu quả và an toàn bằng statin với giảm kết cục lâm sàng



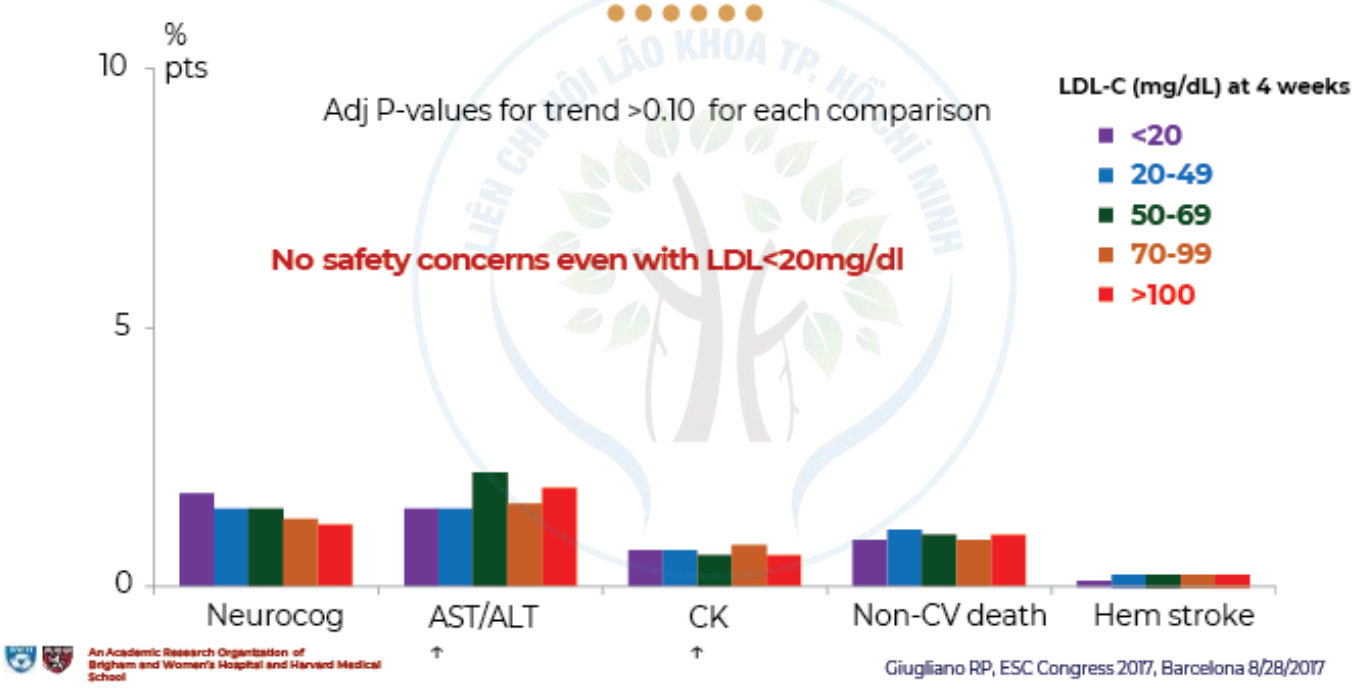
Baigent C et al. Lancet 2005;366:1267–78 Lancet 2010;376:1670–81

LDLC CÀNG THẤP
NGUY CƠ BIẾN CỐ TIM MẠCH CÀNG GIẢM



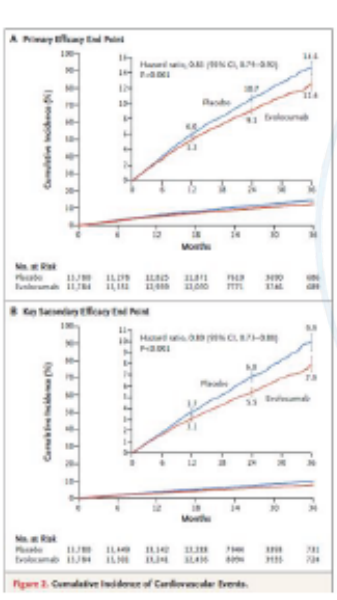
Rosenson RS. Exp Opin Emerg Drugs 2004; 9(2):269-279, LaRosa JC et al. N Engl J Med 2005; 352: 1425-1435

KHÔNG CÓ SỰ KHÁC BIỆT VỀ BIẾN CỐ NGOẠI Ý Ở CÁC MỨC HẠ LDL-C KHÁC NHAU



KHÔNG CÓ QUAN NGẠI VỀ TÍNH AN TOÀN VỚI NỒNG ĐỘ LDL-C RẤT THẤP

Nghiên cứu FOURIER: RCT theo dõi trên 25.982 bệnh nhân được dùng kháng thể đơn dòng evolocumab (PCSK9) thời gian trung vị 2.2 năm



LDL-cholesterol concentration at 4 weeks	<0·5 mmol/L (n=2660)	0·5 to <1·3 mmol/L (n=8003)	1·3 to <1·8 mmol/L (n=3444)	1·8 to <2·6 mmol/L (n=7471)	≥2·6 mmol/L (n=4355)	P trend
Serious adverse events	614 (23%)	1947 (24%)	848 (24%)	1684 (23%)	1022 (23%)	0·19
Adjusted OR (95% CI)	0·97 (0·86–1·10)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·93 (0·84–1·02)	1 (ref)	0·10
Adverse events* leading to discontinuation of study drug	93 (4%)	296 (4%)	126 (4%)	238 (3%)	149 (3%)	0·11
Adjusted OR (95% CI)	1·08 (0·82–1·43)	1·07 (0·86–1·33)	1·07 (0·83–1·39)	0·91 (0·73–1·14)	1 (ref)	0·33
AST or ALT elevation (>3 times ULN)	41 (2%)	120 (1%)	76 (2%)	119 (2%)	83 (2%)	0·09
Adjusted OR (95% CI)	0·66 (0·44–1·01)	0·87 (0·64–1·17)	1·25 (0·90–1·74)	0·91 (0·68–1·24)	1 (ref)	0·64
Creatine kinase elevation (>5 times ULN)	18 (1%)	55 (1%)	19 (1%)	58 (1%)	26 (1%)	0·99
Adjusted OR (95% CI)	1·02 (0·53–1·96)	1·07 (0·65–1·77)	0·88 (0·47–1·65)	1·23 (0·75–2·02)	1 (ref)	0·72
Neurocognitive events	49 (2%)	122 (2%)	51 (1%)	100 (1%)	52 (1%)	0·003
Adjusted OR (95% CI)	1·28 (0·84–1·96)	1·19 (0·79–1·55)	1·10 (0·73–1·65)	0·97 (0·68–1·39)	1 (ref)	0·15
New onset diabetes mellitus†	135/1655 (8%)	389/4863 (8%)	162/1886 (9%)	399/4603 (8%)	220/2728 (8%)	0·63
Adjusted OR (95% CI)	1·06 (0·83–1·35)	1·00 (0·83–1·20)	1·03 (0·83–1·30)	0·95 (0·78–1·14)	1 (ref)	0·48
Cataract-related adverse events	55 (2%)	124 (2%)	61 (2%)	134 (2%)	55 (1%)	0·15
Adjusted OR (95% CI)	1·54 (1·03–2·31)	1·14 (0·82–1·59)	1·34 (0·91–1·98)	1·35 (0·96–1·89)	1 (ref)	0·43
New or progressive malignancy	64 (2%)	205 (3%)	87 (3%)	166 (2%)	99 (2%)	0·32
Adjusted OR (95% CI)	0·90 (0·64–1·27)	1·03 (0·78–1·33)	1·04 (0·77–1·42)	0·88 (0·67–1·15)	1 (ref)	0·72
Haemorrhagic stroke	3 (<1%)	19 (<1%)	7 (<1%)	17 (<1%)	7 (<1%)	0·99
Adjusted HR (95% CI)	0·71 (0·37–2·93)	1·55 (0·62–3·85)	1·39 (0·47–4·14)	1·37 (0·62–3·08)	1 (ref)	0·91
Non-cardiovascular death	25 (1%)	86 (1%)	34 (1%)	66 (1%)	45 (1%)	0·67
Adjusted HR (95% CI)	0·89 (0·53–1·50)	1·06 (0·73–1·55)	1·03 (0·66–1·64)	0·89 (0·60–1·33)	1 (ref)	0·73

Data are n (%) or n/N (%), unless otherwise specified. OR=odds ratio. ref=reference. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ULN=upper limit of normal. HR=hazard ratio. *Excludes 17 patients with injection-site reactions. †Denominator excludes patients who were diagnosed with diabetes mellitus before the week-4 visit.

Table 3: Safety events by achieved LDL-cholesterol concentration at 4 weeks after randomisation

…Không có quan ngại về tính an toàn với nồng độ LDL-C rất thấp trong thời gian trung vị 2,2 năm…

03 STATIN VÀ TÁC DỤNG PHỤ TRÊN CƠ?

TƯƠNG TÁC VỚI THUỐC CHUYỂN HÓA QUA CYP3A4 LÀM TĂNG NGUY CƠ TÁC DỤNG PHỤ

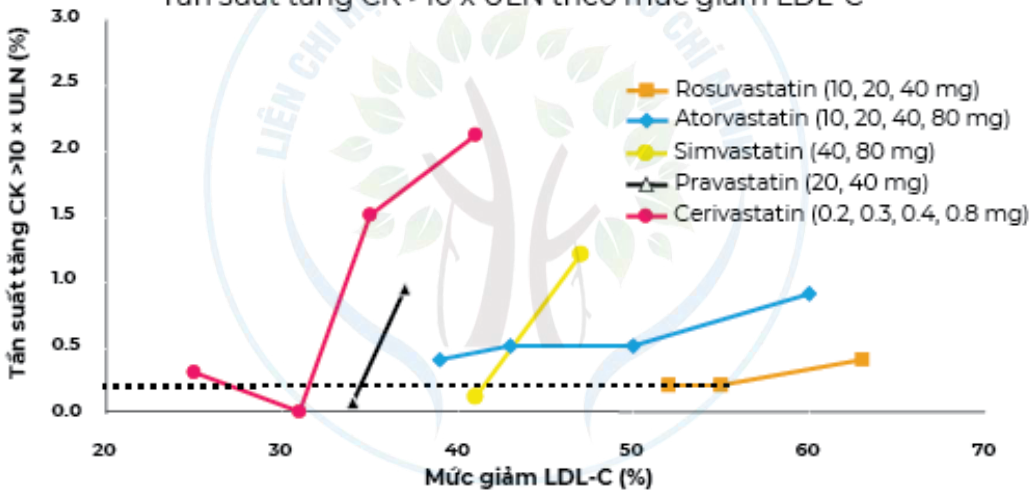
	Cơ chất CYP (statins)	Chất cảm ứng	Chất ức chế
CYP3A4	Atorvastatin, lovastatin, simvastatin	Phenytoin, phenobarbital, barbiturates, rifampin, dexamethasone, cyclophosphamide, carbamazepine, troglitazone, omeprazole	Ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine A, tacrolimus, minbefradil, diltiazem, verapamil, protease inhibitors, midazolam,
CYP2C9	Fluvastatin, rosuvastatin (2C19-minor)	Ketoconazole, fluconazole, sulfaphenazole	Ketoconazole, fluconazole, sulfaphenazole

Rosuvastatin chuyển hóa qua CYP 2C9 hạn chế những tương tác với các thuốc chuyển hóa qua CYP 3A4

Am J Cardiol 2001, 87 (Suppl): 28B-32B
Eur Heart J 1999; 1 (Suppl T): T7-T12

Vui lòng tham khảo Thông tin kê toa các thuốc được phê duyệt tại Việt Nam khi sử dụng

HIỆU QUẢ GIẢM LDL-C VÀ TÍNH AN TOÀN GIỮA CÁC STATIN TRÊN CƠ



1. Brewer H Am J Cardiol 2003;92(Suppl):23K–29K
2. Davidson M Exp Opin Drug Saf 2004;3 (6):547-557

Vui lòng tham khảo Thông tin kê toa các thuốc được phê duyệt tại Việt Nam khi sử dụng

04

STATIN VÀ CHỨC NĂNG GAN?

FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
Lovastatin Dose Limitations
References

Facts about statins

- A class of prescription drugs used together with diet and exercise to reduce blood levels of low-density lipoprotein (LDL) cholesterol ("bad cholesterol")
- Marketed as single-ingredient products, including Lipitor (atorvastatin), Lescol (fluvastatin), Mevacor (lovastatin), Altoprev (lovastatin extended-release), Livalo (pitavastatin), Pravachol (pravastatin), Crestor (rosuvastatin), and Zocor (simvastatin)
- Also marketed as combination products, including Advicor [illegible]statin/niacin [illegible]e)

Không cần đánh giá chức năng gan thường quy ở bệnh nhân dùng Statin

Safe

[2-2 [illegible]s for the class [illegible] more information for the safe and effective use of statins and are based on FDA's comprehensive review of the statin class of drugs (see Data Summary below). The changes include the following:

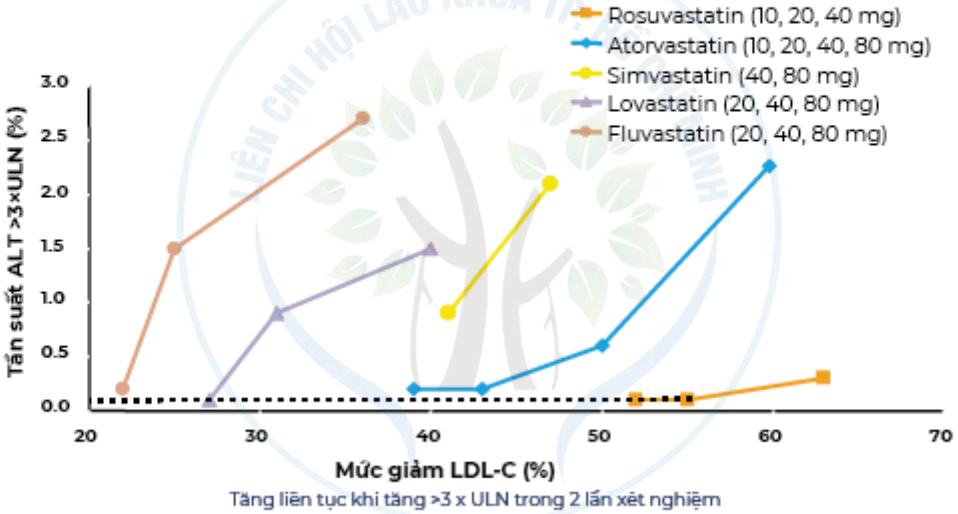
Monitoring Liver Enzymes

Labels have been revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter. FDA has concluded that serious liver injury with statins is rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury.

Infographic About Cholesterol and Statins (/drugs/drug-safety-and-availability/cholesterol-and-statins-infographic)

HIỆU QUẢ GIẢM LDL-C VÀ TÍNH AN TOÀN GIỮA CÁC STATIN TRÊN GAN

Tần suất tăng ALT >3 × ULN theo mức hạ LDL-C[1,2]



Tăng liên tục khi tăng >3 x ULN trong 2 lần xét nghiệm

Brewer H. Am J Cardiol 2003; 92(Suppl): 23K–29K
Davidson M. Exp Opin Drug Saf 2004; 3: 547–557

Vui lòng tham khảo Thông tin kê toa các thuốc được phê duyệt tại Việt Nam khi sử dụng

05

STATIN VÀ CHỨC NĂNG THẬN?

TỈ LỆ MỚI MẮC CKD VÀ SUY GIẢM eGFR GHI NHẬN THẤP HƠN Ở NHÓM SỬ DỤNG STATIN

Table 2 Association of Statin Use with Risk of CKD Progression and Changes in eGFR

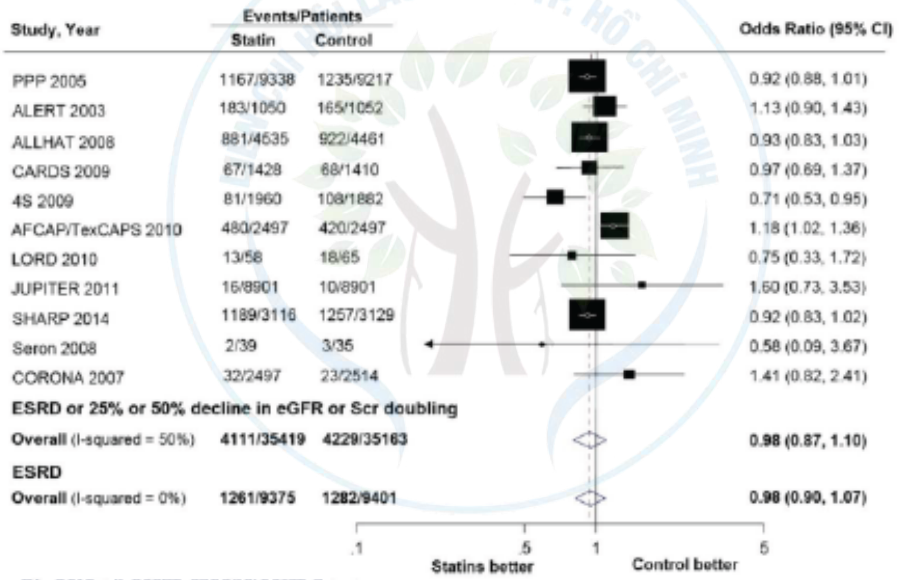
	Unmatched Cohort			Matched Cohort		
	Statin Users	Nonusers	p	Statin Users	Nonusers	p
New-onset CKD HR (95% CI)	0.73 (0.59 to 0.91)	1 (reference)	<0.01	0.75 (0.59 to 0.97)	1 (reference)	0.02
Changes in eGFR, mL/min/1.73 m^2						
1 year	−4.63 (−5.58 to −3.67)	−5.50 (−6.15 to −4.84)	0.18	−4.35 (−5.26 to −3.45)	−5.15 (−6.21 to −4.10)	0.22
2 years	−6.27 (−7.20 to −5.34)	−6.97 (−7.60 to −6.34)	0.27	−6.10 (−7.04 to −5.16)	−7.10 (−8.16 to −6.03)	0.11
3 years	−7.11 (−8.10 to −6.11)	−8.54 (−9.16 to −7.92)	0.02	−7.00 (−7.93 to −5.99)	−8.30 (−9.33 to −7.27)	0.04

Notes: HR (95% CI) was estimated by Poisson generalized linear models adjusted for age, sex, smoking, ACEIs/ARBs, CCBs, beta-blockers, diuretics, history of hypertension, antidiabetic drugs, history of diabetes mellitus, SBP, DBP, HbA1c, FPG, TC, LDL, HDL, TG, WHR, BMI, AST, ALT, BUN, TBIL, UA and baseline eGFR in the unmatched cohort analyses. Changes in eGFR were estimated by linear mixed-effects models.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval.

Zhao M, Ren L, Zhou Z, Wang T, Li J. The Association Between Statin Use and Risk of Chronic Kidney Disease in Community-Dwelling Older People in Shanghai, China. Clin Epidemiol. 2022 Jun 25;14:779-788. doi: 10.2147/CLEP.S360395. PMID: 35782995; PMCID: PMC9242432.

KHÔNG CÓ SỰ KHÁC BIỆT NGUY CƠ XUẤT HIỆN SUY THẬN KHI DÙNG STATIN SO VỚI PLACEBO

Phân tích gộp 57 nghiên cứu, 143,888 bệnh nhân



Su X, et al. Am J Kidney Dis, 2016. pii: S0272-6386(16)00132-3

HIỆU QUẢ & TÍNH AN TOÀN CỦA ROSUVASTATIN TRÊN BỆNH NHÂN CKD

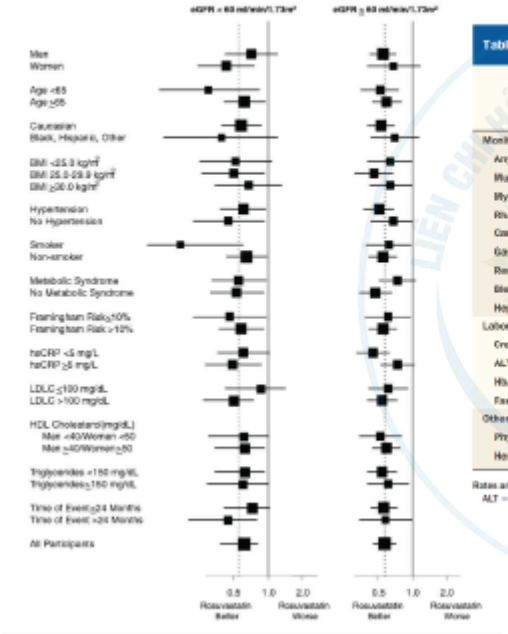


Table 4 Occurrence of Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events of Interest During Follow-Up

	eGFR <60 mL/min/1.73 m²			eGFR ≥60 mL/min/1.73 m²		
	Randomized Rosuvastatin	Randomized Placebo	p Value	Randomized Rosuvastatin	Randomized Placebo	p Value
Monitored adverse events, n (rate)						
Any serious adverse event	315 (9.16)	320 (9.40)	0.73	1,035 (7.36)	1,056 (7.36)	0.75
Muscular weakness, stiffness, or pain	292 (8.75)	303 (9.24)	0.52	1,129 (8.32)	1,072 (7.78)	0.15
Myopathy	2 (0.05)	4 (0.11)	0.39	8 (0.05)	5 (0.03)	0.40
Rhabdomyolysis	1 (0.03)*	0 (0.0)	—	0 (0.0)	0 (0.0)	—
Cancer	79 (2.10)	76 (2.05)	0.87	219 (1.44)	238 (1.56)	0.41
Gastrointestinal disorders	387 (12.1)	403 (12.8)	0.48	1,365 (10.2)	1,308 (9.64)	0.14
Renal disorders	146 (4.02)	141 (3.90)	0.79	388 (2.59)	339 (2.25)	0.05
Bleeding	76 (2.04)	61 (1.64)	0.21	182 (1.20)	214 (1.41)	0.11
Hepatic disorders	33 (0.88)	35 (0.93)	0.76	183 (1.20)	151 (0.98)	0.07
Laboratory values†						
Creatinine, >100% increase from baseline, n (%)	3 (0.08)	0 (0.0)	—	13 (0.08)	10 (0.06)	0.53
ALT >3 × ULN on consecutive visits, n (%)	2 (0.05)	4 (0.1)	0.41	21 (0.14)	13 (0.08)	0.17
HbA1c (% at 24 months)	5.9 (5.6–6.2)	5.8 (5.6–6.1)	0.001	5.9 (5.7–6.1)	5.8 (5.6–6.1)	0.01
Fasting glucose (mg/dl at 24 months)	97 (90–107)	96 (90–106)	0.29	98 (91–106)	98 (90–107)	0.23
Other events, n (rate)						
Physician reported diabetes	54 (1.44)	52 (1.40)	0.91	216 (1.42)	164 (1.07)	0.01
Hemorrhagic stroke	2 (0.06)	3 (0.08)	0.64	4 (0.03)	6 (0.04)	0.53

Rates are per 100 person-years. All blood values were done fasting. *Occurred after trial completion. †HbA1c (%), and fasting glucose (mg/dl) are reported as median (IQR) values at 24 months.
ALT = alanine transferase; ULN = upper limit of normal; other abbreviations as in Table 1.

Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol. 2010 Mar 23;55(12):1266-1273. doi: 10.1016/j.jacc.2010.01.020. Epub 2010 Mar 4. PMID: 20206456.

KHUYẾN CÁO CỦA HỘI THẬN THẾ GIỚI

KDIGO

Bệnh nhân CKD (G3a-G5):
Khuyến cáo điều trị với statin hoặc statin + ezetimibe
(khuyến cáo mức độ IA)
Rosuvastatin 10 mg được chứng minh an toàn trên bệnh nhân CKD G3a-G5
(Nghiên cứu Aurora)

Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

- G1-G2: eGFR ≥ 60 ml/phút/1.73 m2
- G3a-G5: eGFR < 60 ml/phút/1.73 m2

KDIGO clinical practice guideline for Lipid Management in Chronic Kidney Disease. Kidney International Supplements (2013) 3, 262; doi:10.1038/kisup.2013.30.

HIỆU QUẢ & TÍNH AN TOÀN TRÊN BỆNH NHÂN CHÂU Á

The American Journal of Cardiology
Volume 99, Issue 3, 1 February 2007, Pages 410-414
ELSEVIER

Review
Safety a... Statins in Asian...

Statin Safety in Asian Populations

Most side effects of statins are dose related, so concerns about elevated risks are appropriate in patients who may have increased sensitivity to statins. However, evidence to date shows no increased rates of adverse ...tins.6, ...

Rosuvastatin không tăng thêm tác động bất lợi trên dân số châu Á

exposure to rosuvastatin observed in Asian subjects ($p < 0.0001$) did not appear to be the result of body weight or environmental factors. The mechanisms for this effect are not fully explained; SLCO1B1 (the gene for OATP1B1) genotypes did not account for the observed pharmacokinetic differences between Asian and Caucasian subjects. The investigators raised the possibility that other genetic influences or environmental factors could account for the increased plasma exposure. There was no increase in any safety or tolerability issue in the Asian subjects.

KẾT LUẬN

Rối loạn lipid máu ở bệnh nhân đái tháo đường: **thường gặp, tăng nguy cơ CVD.**

Điều trị giảm lipid máu đóng vai trò trung tâm trong phòng ngừa các bệnh lý tim mạch. **Giảm LDL-C càng thấp càng tốt.**

Statin cho đến hiện tại vẫn giữ vai trò quan trọng trong phòng ngừa tiên phát và thứ phát CVD ở bệnh nhân đái tháo đường.

Tư vấn cho bệnh nhân hiểu rõ về lợi ích và nguy cơ của thuốc. **Hiệu quả và tính an toàn của Rosuvastatin đã được chứng minh trên bệnh nhân người châu Á.**