ĐIỀU TRỊ RỐI LOẠN LIPID MÁU

I. Sơ lược về lipid máu:

1. Đánh giá nguy cơ:

Có 2 bảng nguy cơ SCORE: dành cho nước nguy cơ tử vong do bệnh tim mạch thấp (<150/100 000 tử vong), và cao (> 350/100 000 tử vong). Việt Nam chắc ở nước nguy cơ cao, dự báo nguy cơ tử vong do CVD trong 10 năm. Nếu ≥ 10% là nguy cơ rất cao. Từ 5 đến < 10% là nhóm nguy cơ cao.

Cần lưu ý có những bệnh nhân không cần phải tính điểm SCORE nhưng nguy cơ đã thuốc nhóm cao đến rất cao rồi như***: Đã biết CVD, đái tháo đường kéo dài, tăng cholesterol máu có tính gia đình, bệnh thận mạn, mảng xơ vừa động mạch cảnh hoặc động mạch đùi, coronary artery calcium score > 100, hay Lp(a) rất cao.***

Bệnh nhân nên tầm soát yếu tố nguy cơ từ 40 tuổi ở nam, 50 tuổi ở nữ. Có thể dùng các CLS xâm lấn, hoặc không xâm lấn.

Table 4 Cardiovascular risk categories

Very-high-risk	People with any of the following: 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 >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
[a]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

Box 5 Risk estimation: key messages

In apparently healthy persons, CVD risk is most frequently the result of multiple, interacting risk factors. This is the basis for total CV risk estimation and management.
Risk factor screening including the lipid profile should be considered in men >40 years old, and in women >50 years of age or post-menopausal.
A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under- and overtreatment.
Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring, and all risk factors require immediate attention. This is true for patients with documented CVD, older individuals with long-standing DM, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium score >100, or extreme Lp(a) elevation.
All risk estimation systems are relatively crude and require attention to qualifying statements.
Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org).
The total risk approach allows flexibility; if optimal control cannot be achieved with one risk factor, trying harder with the other factors can still reduce risk.

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; SCORE = Systematic Coronary Risk Estimation.

Box 4 Factors modifying Systematic Coronary Risk Estimation risks

Social deprivation: the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference, respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years and women: <60 years).
Chronic immune-mediated inflammatory disorder.
Major psychiatric disorders.
Treatment for human immunodeficiency virus infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.
Non-alcoholic fatty liver disease.

CVD = cardiovascular disease.

2. Bilan lipid máu:

Table 6 **Physical and chemical characteristics of human plasma lipoproteins**

	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs (%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80–100	90–95	2–4	2–6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95–1.006	30–80	50–65	8–14	12–16	4–7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006–1.019	25–30	25–40	20–35	16–24	7–11	ApoB-100	ApoC-II, C-III, E
LDL	1.019–1.063	20–25	4–6	34–35	22–26	6–15	ApoB-100	
HDL	1.063–1.210	8–13	7	10–20	55	5	ApoA-I	ApoA-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	35–46	17–24	6–9	Apo(a)	ApoB-100

Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PLs = phospholipids; TGs = triglycerides; VLDL = very low-density lipoprotein.

Có 6 thành phần lipid chính: Chymomicron, VLDL, IDL, LDL, HDL, Lp(a).

Diễn tiến mảng xơ vữa tỉ lệ với thời gian phơi nhiễm với các ApoB và LDL. Tăng triglycerides cũng có liên quan xấu đến ASCVD. Tuy nhiên, những bằng chứng hiện nay cho thấy việc tăng nồng độ HDL-c dường như không giảm nguy cơ ASCVD.

LDL-c có thể ước tính theo ***công thức Friedewald*** như sau:

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/2.2) \text{ in mmol/L}$$

or

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/5) \text{ in mg/dL}$$

Cần lưu ý nếu TG > 400 mg/dL thì không thể sử dụng công thức trên được.

Mẫu máu lấy để thử có thể là lúc đói, hoặc lúc không đói (non-fasting), vì các nghiên cứu cho thấy giá trị tương tự nhau. Cần lưu ý là nếu lúc không đói, trung bình Triglycerid sẽ tăng cao hơn 27 mg/dL so với lúc đói.

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.

II. Các mục tiêu điều trị:

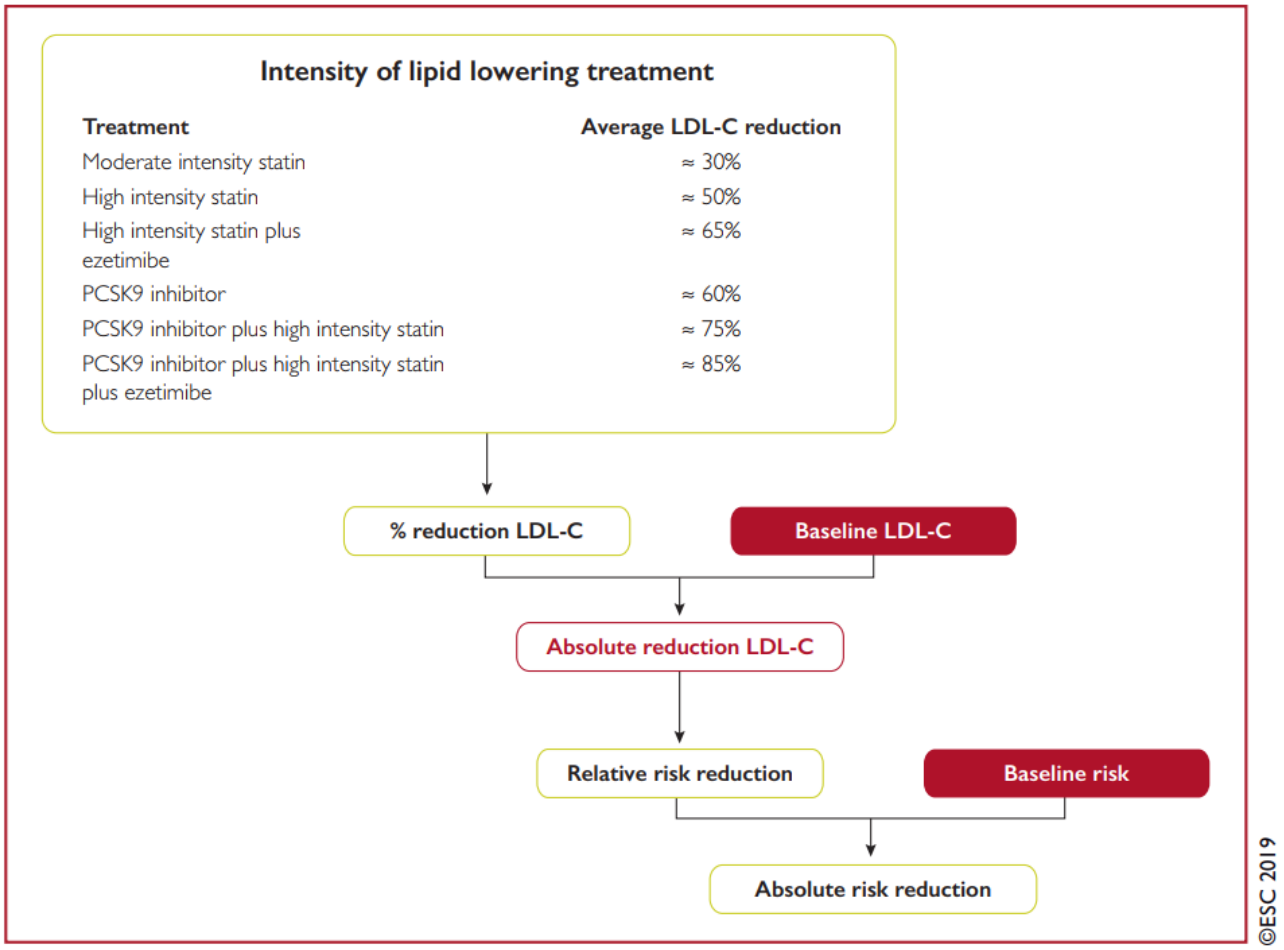
1. Mục tiêu LDL-c:

Mục tiêu chung: Giảm LDL-c càng thấp càng tốt, ***ít nhất giảm ≥ 50% so với ban đầu*** và ở dưới ngưỡng tuyệt đối nào là tùy thuộc vào nhóm nguy cơ:

- Rất cao (< 55 mg/dL),
- Cao (< 70 mg/dL),
- Trung bình (<100 mg/dL)

LDL-c là mục tiêu cần giảm đầu tiên, hiệu quả:

- Cứ **1 mmol/L LDL-c (~40 mg/dL) giảm được 10% tử vong trong vòng 5 năm**; 20% bệnh lí mạch máu lớn, bệnh mạch vành, tử vong do CAD, hay đột quỵ (làm tròn), khi sử dụng statin.



2. Mục tiêu non-HDL và ApoB:

Đây là 2 mục tiêu thứ phát, sau khi đã giảm LDL-c thì giảm tiếp hai chỉ số này. Cụ thể:

(i) **non-HDL-C** < 2.2 mmol/L (<85 mg/dL), <2.6 mmol/L (<100 mg/dL), và <3.4 mmol/L (<130 mg/dL) lần lượt ở bệnh nhân có nguy cơ tim mạch rất cao, cao và trung bình; và

(ii) **ApoB** <65 mg/dL, <80 mg/dL, and <100 mg/dL lần lượt ở bệnh nhân có nguy cơ tim mạch rất cao, cao và trung bình

3. Mục tiêu HDL-c:

Không có mục tiêu cụ thể, ESC 2019 khuyến cao > 30 mg/dL, nhìn chung thì hay lấy mốc > 40 mg/dL.

Recommendations for treatment goals for low-density lipoprotein cholesterol

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.

Table 7 Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.[118]
[b]The term 'baseline' refers to the LDL-C level in a person not taking any lipid-lowering medication, or to the extrapolated baseline value for those who are on current treatment.

III. Các thuốc sử dụng:

Các thuốc thường dùng: Statin, Ức chế hấp thu (exzetimibe), Fibrates.

1. Statins:

Statin liều trung bình – cao là liều được trông đợi giảm được 25-50% LDL-c so với ban đầu.

Statin liều trung bình giảm 5-15%, nhưng liều cao giảm 25-30% nồng độ TG.

Theo như ACC/AHA thì statin liều cao chỉ có Atorvastatin 40-80 mg, và Rosuvastatin 20-40 mg.

Thời điểm sử dụng: Thường vào buổi tối sau ăn hoặc trước khi đi ngủ do chuyển hóa lipid mạnh nhất vào buổi tối. Nhưng hiện tại, các thuốc thế hệ mới có tác dụng kéo dài, nên vẫn có thể uống buổi sáng được.

Table 1 Statin Dosing and ACC/AHA Classification of Intensity

Statin	Dosage		
	Low-intensity (LDL-C reduction <30%)	**Moderate-intensity (LDL-C reduction 30% to <50%)**	**High-intensity (LDL-C reduction >50%)**
Atorvastatin	NA	10 to 20 mg	40 to 80 mg
Fluvastatin	20 to 40 mg	40 mg 2×/day; XL 80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2 to 4 mg	NA
Pravastatin	10 to 20 mg	40 to 80 mg	NA
Rosuvastatin	NA	5 to 10 mg	20 to 40 mg
Simvastatin	10 mg	20 to 40 mg	NA

From ACC/AHA, 2013.[30] Dosages shown are total daily dosages; exceptions are noted.

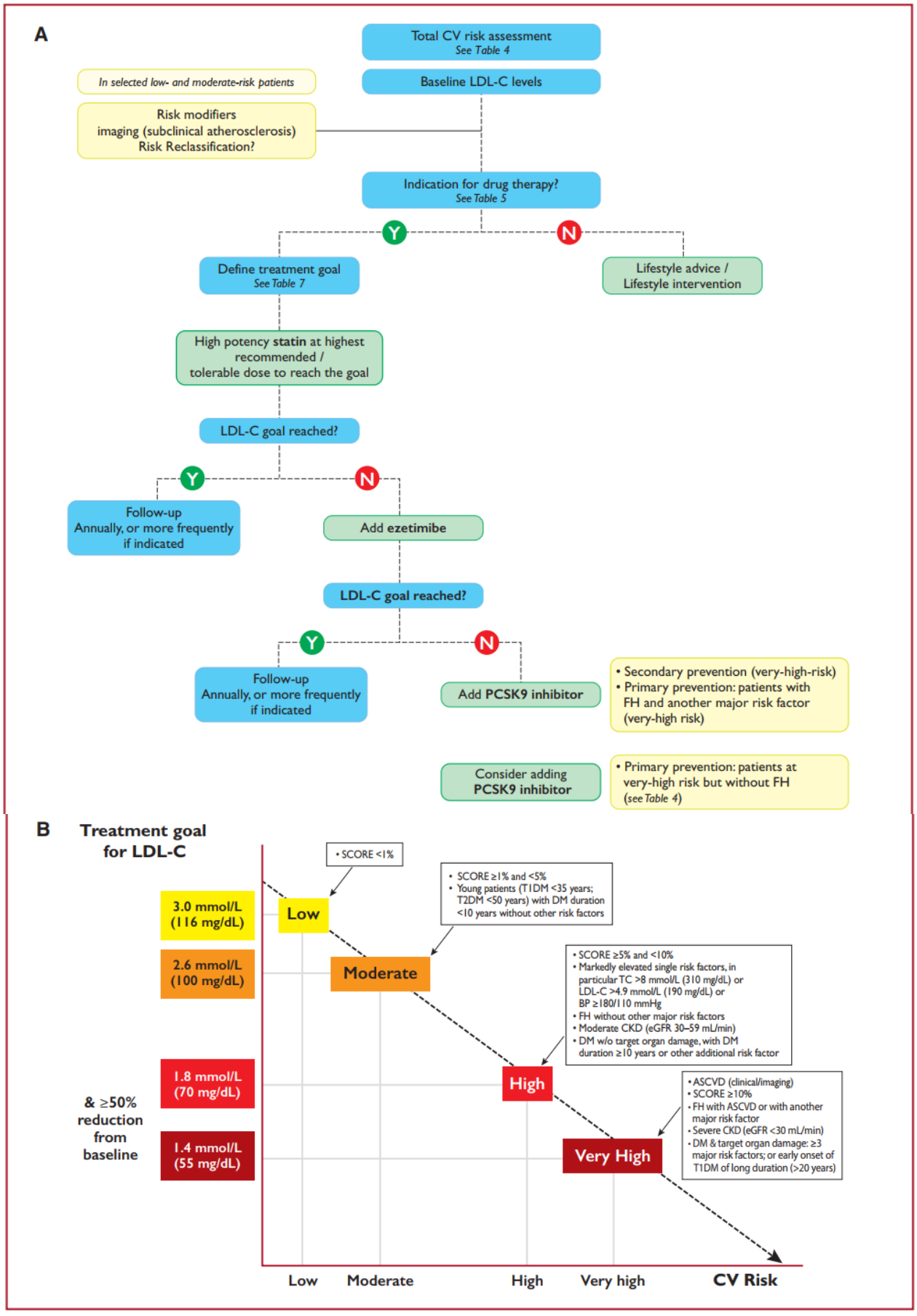
Table 1. Comparison of the effectiveness of statins

Statin	Changes in lipid levels (%)			
	↓ to whole cholesterol level	↓ to LDL cholesterol level	↑ to HDL cholesterol level	↓ to triglycerides
Lovastatin	16 – 34	21 – 42	2 – 10	6 – 27
Pravastatin	16 – 25	22 – 34	2 – 12	15 – 24
Simvastatin	19 – 36	26 – 47	8 – 16	12 – 34
Fluvastatin	16 – 27	22 – 36	3 – 11	12 – 25
Atorvastatin	25 – 45	26 – 60	5 – 13	17 – 53
Rozuvastatin	33 - 46	45 - 63	8 - 14	10 – 35

Properties of statins

Variable	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
LDL cholesterol reductions (dose range, mg)	38 to 54% (10 to 80)	17 to 33% (20 to 80)	29 to 48% (20 to 80)	31 to 41% (1 to 4)	19 to 40% (10 to 40)	52 to 63% (10 to 40)	28 to 41% (10 to 40)
Elimination half-life, hours	15 to 30	0.5 to 2.3	2.9	12	1.3 to 2.8	19	2 to 3
Bioavailability, %	12	19 to 29	5	51	18	20	5
Protein binding, %	80 to 90	>99	>95	99	43 to 55	88	94 to 98
Solubility	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Cytochrome P450 metabolism*	3A4	2C9	3A4	Limited	Limited	Limited	3A4
Active metabolites	Yes	No	Yes	Yes	No	No	Yes
Transmembrane transporters¶	OATP1B1/1B3 BCRP	OATP1B1/1B3	OATP1B1	OATP1B1/1B3	OATP1B1/1B3	OATP1B1/1B3 BCRP	OATP1B1/1B3
Effect of food on absorption of drug	None	Negligible	Increased absorption	Decreases	Decreased absorption	None	None
Optimal time of administration	Anytime	IR: evening (or morning and evening if taken twice daily) XR: anytime	IR: with evening meal (or with morning and evening meal if taken twice daily) XR: evening	Anytime	Anytime	Anytime	Evening
Renal excretion of absorbed dose, %	2	<6	10	15	20	10	13

Chống chỉ định: CK > 4*ULN, bệnh gan đang hoạt động, xơ gan mất bù, viêm gan cấp, phụ nữ có thai và cho con bú.



2. Khuyến cáo về điều trị tăng triglycerid:

• Bệnh nhân nguy cơ cao, có TG > 200 mg/dL thì statins vẫn là lựa chọn đầu tay để điều trị (IB).

• Có thể xem xét kết hợp statins với ***icosapent ethyl 2 x 2 g/day***, sau đó mới lựa chọn fibrate kết hợp với statins để điều trị TG cao.

• Các thuốc hạ lipid máu vẫn được khuyến cáo sử dụng dựa trên phân tầng nguy cơ tương tự người nhỏ tuổi hơn ở nhóm từ 66 đến 75 tuổi. Tuy nhiên, > 75 tuổi không khuyến cáo sử dụng nữa, có thể cân nhắc ở nhóm nguy cơ cao trở lên.

3. Xét nghiệm theo dõi:

(1) Theo dõi lipid:

- Nếu chưa đạt yêu cầu, ***thử lại trong khoảng 4-12 tuần*** để hiệu chỉnh đến khi đạt mục tiêu.

- Sau đó, mỗi năm 1 lần.

(2) ALT:

- Trước khi điều trị và sau khi điều trị/tăng liều 8-12 tuần:

- Nếu ALT < 3 ULN thì tiếp tục dùng, thử lại sau 4-6 tuần.

- Nếu ALT > 3 ULN thì ngưng thuốc, thử lại sau 4-6 tuần, nếu tiếp tục tăng thì đi tìm nguyên nhân khác.

(3) CK:

- Trước khi bắt đầu điều trị: Nếu CK > 4 ULN thì không khởi động thuốc, thử lại.

- Không theo dõi CK thường quy, chỉ thử khi bệnh nhân đau cơ.

What if CK becomes elevated in a person taking lipid-lowering drugs?

Re-evaluate indication for statin treatment.

If ≥4× ULN:

- If CK >10× ULN: stop treatment, check renal function, and monitor CK every 2 weeks.
- If CK <10× ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK between 2 and 6 weeks.
- If CK <10× ULN: if symptoms present, stop statin and monitor normalization of CK, before rechallenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

If <4× ULN:

- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider rechallenge with the same or another statin.
- Consider low-dose statin, alternate day or once/twice weekly dosing regimen, or combination therapy.

For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in *Supplementary Figure 4*.

Hạ lipid máu ở vài tình huống đặc biệt			
Hội chứng vành cấp có PCI	**Mục tiêu**	**Thuốc sử dụng**	**Thời gian dùng**
Kháng viêm Ổn định mảng xơ vữa Giảm tái nhồi máu	Giảm > 50% và < 55 mg/dL LDL-c, đối với người đã xử dụng trước đó thì mục tiêu < 40 mg/dL (~ 1mmol/L). Kiểm tra lại lipid máu sau 4-6 tuần.	Rosuvastatin 20 – 40 mg 1 v (u) Atorvastatin 40-80 mg 1 v (u) Ezetimab	Càng sớm càng tốt Trong vòng 1-4 ngày sau khi chẩn đoán. Sau 4-6 tuần, không đạt mục tiêu thì kết hợp với ezetimab.
Tăng triglycerid máu	**Mục tiêu**	**Thuốc sử dụng**	**Thảo luận**
ATP III: > 200 mg/dL là cao, ≥ 500 là rất cao. Hoặc: ≥ 150 mg/dL là điều trị	Nếu > 500 mg/dL (>850 mg/dL) thì cần hạ xuống < 500 mg/dL để giảm nguy cơ VTC.	Fenofibrate 145 mg 1 viên uống không liên quan đến bữa ăn. Gemfibrozil 600 mg x 2 trước ăn sáng và tối.	Fibrate giảm được tới 70% TG. Gemfibrozil tăng nguy cơ hoại tử cơ, nên nếu dự định dùng Statins sau này thì không nền sử dụng (như ở ACS, LDL-c cao).
	< 500 (<850 mg/dL)	Statins liều cao Icosapent ethyl	
Trong bệnh cảnh cấp tính như Viêm tụy cấp do tăng Triglycerides	Giảm < 500 mg/dL trong vòng 3-4 ngày	Lọc huyết tương Insulin Regular 0.1-0.3 UI/kg Fenofibrate 160 mg	