MIMS DOCTOR

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Optimizing intensive lipid-lowering strategies in patients with high or very high CV risk

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Optimizing intensive lipid-lowering strategies in patients with high or very high CV risk

Dyslipidaemia treatment guidelines emphasize the importance of prompt and sustained achievement of lower target levels of LDL-cholesterol (LDL-C) especially in patients with high and very high cardiovascular (CV) risk. In an interview with *MIMS Doctor*, Dr Chiu-Lai Fu, Specialist in Cardiology in private practice in Hong Kong, reviewed key points from current dyslipidaemia management guidelines and how first-line combination regimens (eg, ezetimibe plus atorvastatin [Atozet®, Organon]) may benefit higher-risk patients with hypercholesterolaemia.

Risk stratification and target LDL-C levels

Dyslipidaemia management guidelines issued by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) in 2019 recommend more aggressive LDL-C lowering strategies for higher CV risk patients because there is an almost linear relationship between lower LDL-C levels and reduced CV events. [*Eur Heart J* 2020;41:111-188; *Atherosclerosis* 2021;325:99-109]

"For very-high-risk patients, the target LDL-C level is <1.4 mmol/L," said Fu. "This group includes patients with documented atherosclerotic CV disease [ASCVD], severe chronic kidney disease [CKD], diabetes mellitus [DM] with target organ damage or with ≥3 major risk factors or early onset of type 1 DM of long duration [>20 years], familial hypercholesterolaemia [FH] with ASCVD or another major risk factor, or a calculated Systematic Coronary Risk Estimation [SCORE] of ≥10 percent for 10-year risk of fatal CV disease [CVD]." (Table) [*Eur Heart J* 2020;41:111-188]

Meanwhile, the target LDL-C level for high-risk patients is <1.8 mmol/L. These include patients with markedly elevated single risk factors (ie, total cholesterol >8 mmol/L, LDL-C >4.9 mmol/L, or blood pressure ≥180/110 mm Hg), FH without other major risk factors, moderate CKD, DM without target organ damage with DM duration ≥10 years or another additional risk factor, or a calculated SCORE ≥5 percent and <10 percent for 10-year risk of fatal CVD. (Table) [*Eur Heart J* 2020;41:111-188]

Each 1.0 mmol/L absolute reduction in LDL-C is associated with approximately 20 percent reduction in the risk of CV events. Thus, in both high- and very-high-risk patients, the 2019 ESC/EAS guidelines stress the need to reduce LDL-C levels by ≥50 percent from baseline. These aggressive treatment goals are primarily aimed at reducing patients' atherosclerotic risk, with larger LDL-C reductions recommended for higher-risk patients. [*Eur Heart J* 2020;41:111-188]

Assessment of response to therapy

"Target LDL-C levels should be achieved as quickly as possible and maintained for as long as possible, especially in higher risk patients," stressed Fu. [*Atherosclerosis* 2021;325:99-109]

"Typically, response may be assessed at 6–8 weeks after initiation of therapy," she explained. "We can also re-evaluate lipid levels sooner, at 4–6 weeks in patients with acute coronary syndromes, to determine whether treatment goals have been achieved and to check for any safety issues so that prompt therapeutic adjustments can initiated." [*Eur Heart J* 2020;41:111-188]

Table. Patients with high and very high CV risk and corresponding LDL-C target levels

Risk category	Criteria	Target LDL-C goals
Very high risk	1. Documented ASCVD, clinical or on imaging (ie, ACS [MI or unstable angina], stable angina, coronary revascularization [eg, PCI, CABG], stroke and TIA, and PAD) 2. FH with ASCVD or with another major risk factor 3. Severe CKD (eGFR <30 mL/min/1.73 m²) 4. DM with target organ damage (ie, microalbuminuria, retinopathy or neuropathy) or ≥3 major risk factors, or early onset of type 1 DM of long duration (>20 years) 5. Calculated SCORE ≥10% for 10-year risk of fatal CVD	<1.4 mmol/L and ≥50% reduction from baseline* <1.0 mmol/L may be considered for ASCVD patients with a second event within 2 years while on maximally tolerated statin-based therapy
High risk	1. Markedly elevated single risk factors: total cholesterol >8 mmol/L, LDL-C >4.9 mmol/L, or BP ≥180/110 mm Hg 2. FH without other major risk factors 3. Moderate CKD (eGFR 30–59 mL/min/1.73 m²) 4. DM without target organ damage, with duration ≥10 years or with another additional risk factor 5. Calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD	1.8 mmol/L and ≥50% reduction from baseline*

*Baseline refers to the LDL-C level in patients not taking any LDL-C–lowering medication. In those who are taking LDL-C–lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C–lowering efficacy of the given medication or combination of medications.
ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; TIA = transient ischaemic attack
Adapted from Eur Heart J 2020;41:111-188.

Once target LDL-C levels are achieved, subsequent follow-up monitoring may be done every 6–12 months. [*Eur Heart J* 2020;41:111-188]

Role of combination lipid-lowering therapy in higher risk patients

"With more aggressive lipid-lowering targets recommended by ESC/EAS in 2019 vs previous guidelines, achieving recommended LDL-C levels in higher-risk patients have become more challenging even with maximally tolerated doses of high-intensity statins," noted Fu. [*Eur Heart J* 2020;41:111-188; *Eur Heart J* 2016;37:2999-3058]

"In my experience, only about 50 percent of high-risk patients are able to achieve LDL-C levels <1.8 mmol/L with maximally tolerated high-intensity statin alone," she commented. "Meanwhile, approximately 60–70 percent of my patients with very high risk are unable to achieve LDL-C levels <1.4 mmol/L with statins alone."

"Aside from inadequate reductions in LDL-C levels, many patients are also hesitant to receive or intolerant of high-intensity statin therapy at maximum recommended doses," shared Fu. "Although intolerance may be managed with statin dose reductions or temporary discontinuation, efficacy may be compromised. A useful alternative is to add a nonstatin lipid-lowering drug such as ezetimibe, which may allow for a lower statin dose without compromising efficacy."

The average LDL-C reduction achieved with a high-intensity statin is approximately 50 percent. By combining a high-intensity statin with ezetimibe, the average LDL-C reduction is estimated to increase to 65 percent. [*Eur Heart J* 2020;41:111-188]

In a randomized, double-blind, placebo-controlled trial of 628 patients with hyperlipidaemia not on lipid-lowering therapies, the combination of ezetimibe (10 mg) and atorvastatin (10 mg) reduced mean LDL-C levels by 53 percent ($p<0.01$) vs baseline levels. This was similar to the LDL-C reduction achieved with the highest dose of atorvastatin (80 mg) and is also consistent with the 2019 ESC/EAS recommendations of achieving ≥50 percent reduction in LDL-C levels from baseline for high- and very-high-risk patients. [*Circulation* 2003;107:2409-2415; *Eur Heart J* 2020;41:111-188]

"In my practice, using a fixed-dose combination pill containing ezetimibe plus atorvastatin helps further reduce LDL-C levels by 20–25 percent vs statin monotherapy," said Fu. "Clinically, we also find that the lipid-lowering response to this regimen is quite fast and sustained in our higher-risk patients."

"Furthermore, using a fixed-dose combination of ezetimibe plus atorvastatin is more convenient, especially for elderly patients, since polypharmacy due to multiple comorbidities is common in this population," said Fu. "Reducing their pill burden may help improve adherence and may make it easier to add other lipid-lowering agents in the remaining patients who are still unable to achieve target LDL-C levels."

"Since achieving LDL-C goals as early as possible is crucial, especially in higher risk patients, upfront statin/ezetimibe combination may be considered in these patients, especially if they are unlikely to reach target LDL-C goals with statin monotherapy," she continued. This is consistent with a statement by the EAS Task Force, which suggests upfront use of statin/ezetimibe combination therapy for patients with ASCVD, particularly if additional risk factors are present, and those with FH with high LDL-C levels without ASCVD, to help achieve LDL-C target as early as possible. [*Atherosclerosis* 2021;325:99-109]

Summary

"For high- and very-high-risk patients with dyslipidaemia, the aim is to achieve greater LDL-C reductions, reach target LDL-C levels as quickly as possible, and maintain these levels as for long as possible," reiterated Fu. "In these patients, first-line statin/ezetimibe combination may be considered to achieve treatment goals promptly and reduce their CV risk."

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RRR=Relative Risk Reduction

*A composite of CV death, non-fatal MI, hospital admission for UA, coronary revascularization (≥30 days after randomization), or non-fatal stroke

Study Design: The **IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)** was a randomized, double-blind study involving 18,144 patients who had been hospitalized for an ACS within the preceding 10 days and had LDL-C levels of 1.3–2.6mmol/L if they were receiving LLT or 1.3–3.2mmol/L if they were not receiving. The combination of ezetimibe (10mg) and simvastatin (40mg) was compared with simvastatin (40mg) alone and placebo. The primary endpoint was a composite of CV death, non-fatal MI, unstable angina requiring rehospitalization, coronary revascularization ≥30 days after randomization, or non-fatal stroke. The median follow-up was 6 years.

CV=cardiovascular; MI=myocardial infarction; UA=unstable angina; IMPROVE-IT=IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; ACS=acute coronary syndrome; LDL-C=low-density lipoprotein cholesterol; LLT= lipid-lowering therapy

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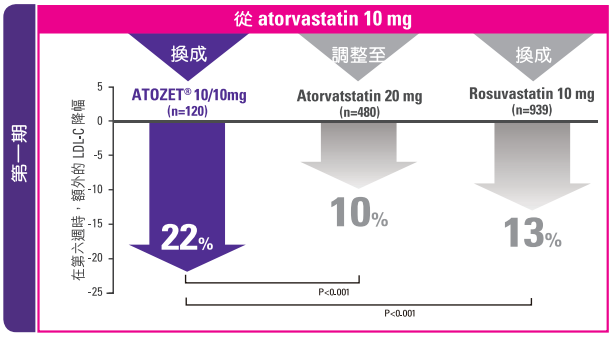

Hypercholesterolemic patients (n =1,547) at high atherosclerotic cardiovascular disease risk with low-density lipoprotein cholesterol (LDL-C) levels ≥100 and ≤160 mg/dl while treated with atorvastatin 10 mg/day entered a multicenter, randomized, double-blind, active-controlled, clinical trial using two 6-week study periods. Period I compared the efficacy/safety of (1) adding ezetimibe 10 mg (ezetimibe) to stable atorvastatin 10 mg, (2) doubling atorvastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160 mg/dl) after period I, entered period II; subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin 20 mg, or uptitrated their atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated their rosuvastatin to 20 mg.
The primary efficacy end point variable was the percent change from treated baseline in LDL-C levels at the end of period I

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Statin-ezetimibe合併治療是極高風險患者控制LDL-C的理想方案。[4]

圖示僅供參考

參考資料：1. Hong Kong Product Circular (ATOZET®). 2. Cannon, C.P. et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372 (25):2387-2397. 3. Bays, H.E. *et al.* Efficacy and safety of ezetimibe added on to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. *Am J Cardiol.* 2013;112:1885-1895. 4. Averna, M et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis 325 (2021) 99–109

Selected Safety information on ATOZET®

Indications: ***Prevention of Cardiovascular Events*** ATOZET® is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. ***Hypercholesterolaemia*** ATOZET® is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate - patients not appropriately controlled with a statin alone - patients already treated with a statin and ezetimibe ***Homozygous Familial Hypercholesterolaemia (HoFH)*** ATOZET® is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis). ***Contraindications:*** • Hypersensitivity to the active substances or to any of the excipients. • Therapy with ATOZET® is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. • ATOZET® is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). • ATOZET® is contraindicated in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir. ***Precautions:*** • Myopathy/Rhabdomyolysis ▷ In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. - Also, ATOZET® contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. ▷ A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. ▷ Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET® • Liver Enzymes ▷ Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET® is recommended. • Hepatic Insufficiency ▷ Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET® is not recommended. • Interstitial lung disease ▷ If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued. • Diabetes mellitus ▷ Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. • Excipients ▷ ATOZET® contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. ***Adverse events:*** • Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. • In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET®. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. • Please consult the full prescribing information for detailed adverse events.

Before prescribing, please consult the full prescribing information.

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