‘Goodnight, sweetheart’

Wake up to a new paradigm for lipid-lowering therapy

IAN R. HAMILTON-CRAIG MB BS, PhD, FRACP, FCANZ, FLS

A new paradigm for lipid-lowering therapy involves early initiation of upfront statin and ezetimibe combination therapy for patients at high or very high risk of cardiovascular disease. Because there is now substantial evidence for this strategy, it has been included in recent guidelines for lipid lowering.

It’s time to say ‘Goodnight, sweetheart’ to statin monotherapy for our patients at high risk of cardiovascular disease (CVD).

The recently published SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) study illustrated the benefits of using early, aggressive lipid-lowering therapy (LLT) in patients with acute coronary syndrome (ACS).[1,2] Those receiving early (within 12 weeks) upfront statin and ezetimibe combination therapy had improved outcomes for up to 12 years of follow up compared with patients receiving LLT within 12 to 16 months.[1,2] Further details of SWEDEHEART are discussed below.

This new paradigm for LLT involves early initiation of upfront statin and ezetimibe combination therapy for patients at high or very high risk of CVD. Because there is now substantial evidence for this strategy, it has been included in recent guidelines for LLT.[3-7] The strategy is also appropriate for patients without ACS, including those with familial hypercholesterolaemia.[8-10]

Guideline changes

The stepwise approach to lipid lowering was recommended in the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines of 2019.[11] In 2021, the International Lipid Expert Panel (ILEP) recommended the upfront approach, as did the Polish Lipid Association (PoLA) for patients at very high and extreme risk for whom maximum statin doses were unlikely to achieve target LDL-cholesterol (LDL-C) levels.[12] The rationale for this was to

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Key points

- **Removal of the PBS restrictions on ezetimibe in 2024 has enabled its coprescription with statins without the need for patients to have a prior eight-week period on statin monotherapy.**
- **Initiating lipid-lowering therapy with combination statin–ezetimibe (the ‘upfront’ approach) is now recommended by international guidelines rather than the traditional ‘stepwise’ approach.**
- **The upfront approach is particularly important in patients at high and very high risk of cardiovascular disease, especially those with acute coronary syndromes because it rapidly lowers LDL-cholesterol levels, stabilises atherosclerotic plaques and acutely reduces recurrent ischaemic events.**
- **Upfront ezetimibe–statin cotherapy may also be appropriate for initiating lipid-lowering therapy in patients at lower cardiovascular disease risk, as it allows lower doses of statins to be used with fewer side effects, improved compliance, fewer blood tests and clinic visits, and LDL-cholesterol lowering equivalent to that of maximum statin doses.**

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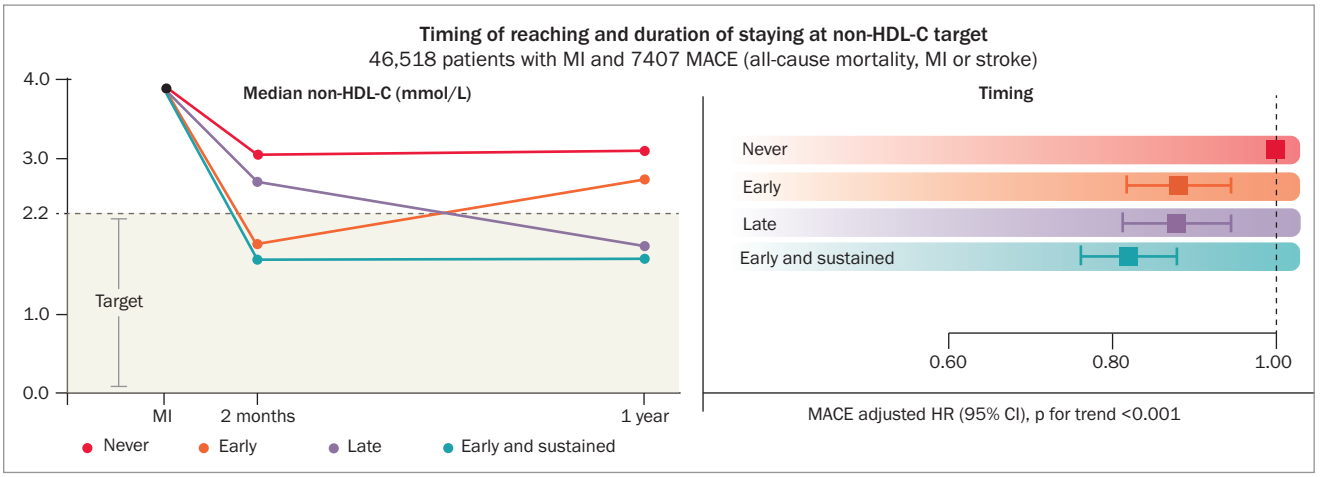

Figure 1. SWEDEHEART study: MACE in patients with MI according to time of reaching non-HDL-C target (<2.2 mmol/L) and timing of initiation of ezetimibe–statin LLT.[1]

Abbreviations: CI = confidence interval; non-HDL-C = non-HDL-cholesterol; HR = hazard reduction, LLT = lipid-lowering therapy; MACE = major adverse cardiovascular events; MI = myocardial infarction.

minimise cumulative exposure to LDL-C (a long-term strategy), in contrast to current recommendations for upfront therapy, which are oriented towards acutely reducing ACS events through plaque passivation and lower risk of plaque rupture.[12]

In 2023, the ESC guideline for patients with ACS stated that upfront LLT 'may be considered'.[13] In 2024, ILEP recommended upfront LLT for patients with established atherosclerotic CVD, and also for patients with ACS, triple upfront therapy with statins, ezetimibe and either proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or bempedoic acid (the latter is not currently available in Australia).[12] Single-pill combinations were also recommended to improve compliance.[12]

The PoLA is conducting an ACS registry of patients requiring angioplasty, with currently 72,050 enrolled in the study.[12] Routine upfront LLT is now recommended for these patients after preliminary findings reported a 47% reduction in all-cause mortality within 52 days.[12]

The 2025 ESC/EAS lipid management guidelines also recommended upfront statin–ezetimibe LLT during hospital admission for statin-naïve patients with ACS who are not expected to reach the LDL-C goal with statin monotherapy. Patients on statins before admission also require intensification of LLT.[11]

Estimating CVD risk

An important consideration for upfront combined LLT is that there are likely to be considerably more patients at high risk of CVD in our practices than currently recognised.[14-17] Such patients may be detected using risk factor algorithms, with the caveat that they often underestimate CVD risk and imaging techniques are more sensitive, reproducible and reliable.[18] Use of coronary artery calcium (CAC) measurement for detecting and quantifying asymptomatic subclinical atherosclerosis is a widely used and validated tool for improving prediction of coronary heart disease risk and is more accurate and cost-effective than using traditional risk factors.[19-24] Paradoxically, CAC assessment is not yet a Medicare item, although considerable effort is being made to address this situation.

SWEDEHEART findings

SWEDEHEART involved Sweden's nationwide registry of patients admitted to hospital with myocardial infarction between 2015 and 2022.[1,2] This registry had previously shown that on optimal statin monotherapy, only 20 to 25% of patients reached LDL-C goals. Using modelling of expected LDL-C levels from treatment escalation, this proportion doubled if ezetimibe were added. All patients reached LDL-C goals if PCSK9 inhibitors were added.[1,2] The authors hypothesised that patients who achieved the non-HDL-cholesterol (non-HDL-C) target of less than 2.2 mmol/L (equivalent to 1.4 mmol/L LDL-C) early after myocardial infarction and in whom the target was sustained would have the best outcomes compared with later or delayed achievement.[1,2]

SWEDEHEART enrolled over 56,000 patients and determined CVD outcomes after a mean of 5.4 years' follow up in relation to timing and intensity of non-HDL-C lowering (Figure 1).[1] Subjects were classified into three groups: those receiving ezetimibe early (within 12 weeks), late (13 weeks to 16 months) or not at all. At three years, there were 14% and 29% higher rates of overall CVD and 64% and 83% higher rates of CVD death in late or nil groups, respectively, compared with early LLT (Figure 1).[1]

The SWEDEHEART results strongly support the upfront strategy in all statin-naïve patients with ACS predischarge, with early review at two months and the addition of further oral or injectable LLT according to achieved LDL-C levels. Another approach is early

triple-therapy LLT with PCSK9 inhibitors, resulting in LDL-C levels less than 1 mmol/L in almost all cases and fewer CVD events.[4-6,25]

Currently in Australia about 14% of patients with ACS receive PCSK9 inhibitors due to PBS restrictions.[26] Use of PCSK9 inhibitors is likely to increase with demonstrable cost-efficacy, especially when oral PCSK9 inhibitors become available.[27]

In summary, patients on statin monotherapy independent of LDL-C levels could be routinely considered for combined statin and ezetimibe LLT to achieve even lower LDL-C levels and accelerate plaque regression and protection from CVD events.[28-35]

Explanation behind the upfront strategy

The outcomes of SWEDEHEART and other studies supporting the upfront strategy with combination LLT may be explained by the presence of a high load of unstable plaques in patients with ACS, which can be more effectively passified and less liable to rupture by earlier achievement of lower LDL-C levels.[28-35]

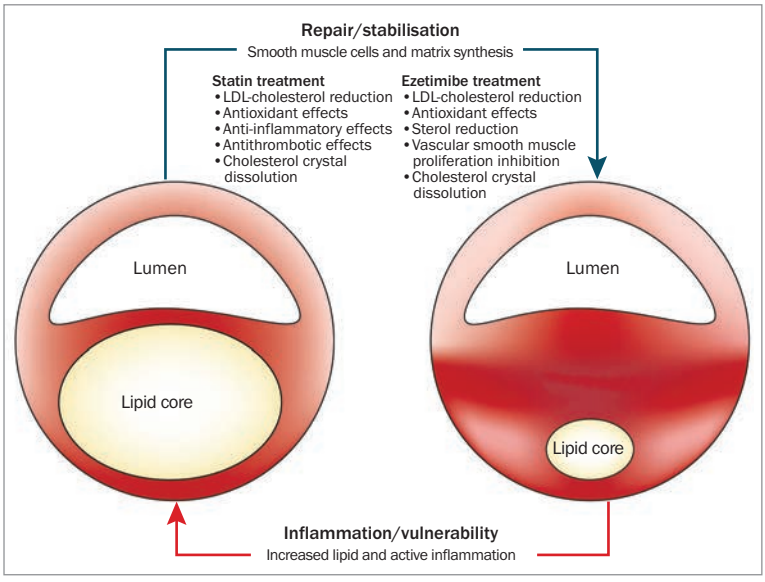

Figure 2. Plaque-stabilising effects of ezetimibe and statins.[29]

Unstable or high-risk plaques have features that can now be identified by imaging techniques, including the presence of a thin fibrous cap, a large lipid core and remodelling in which the arterial wall expands to conserve the lumen.[28-35] Unstable plaques have a high content of active inflammatory cells.[35] These secrete

Table 1. 2025 European Society of Cardiology guidelines: treatment goals for LDL-cholesterol according to CVD risk[11]

CVD risk	Risk factors	Target LDL-cholesterol level (mmol/L)
Low	• SCORE2/SCORE2-OP <2%	<3.0 mmol/L
Moderate	• SCORE2/SCORE2-OP ≥2% and <10% • Young patients (type 1 diabetes <35 years of age; type 2 diabetes <50 years of age) with diabetes duration <10 years without other risk factors	<2.6 mmol/L
High	• SCORE2/SCORE2-OP ≥10% and <20% • Markedly elevated single risk factors, particularly total cholesterol >8 mmol/L or LDL-cholesterol >4.9 mmol/L or BP ≥180/110 mmHg • Familial hypercholesterolaemia without other major risk factors • Moderate chronic kidney disease (eGFR 30 to 59 mL/min/1.73 m^2) • Diabetes mellitus without target organ damage, with diabetes duration ≥10 years or other additional risk factor	<1.8 mmol/L and ≥50% from baseline
Very high	• SCORE2/SCORE2-OP ≥20% • Atherosclerotic CVD (clinical or imaging) • Familial hypercholesterolaemia with atherosclerotic CVD or with another major risk factor • Severe chronic kidney disease (eGFR <30 mL/min/1.73 m^2) • Diabetes mellitus and target organ damage; ≥3 major risk factors; or early onset of type 1 diabetes of long duration (>20 years)	<1.4 mmol/L and ≥50% from baseline
Extremely high	• Atherosclerotic CVD and recurrent vascular events while on maximally tolerated statin-based therapy • Polyvascular (coronary or peripheral) arterial disease	<1.0 mmol/L and ≥50% from baseline

Abbreviations: BP = blood pressure; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; SCORE2 = Systematic Coronary Risk Evaluation 2; SCORE2-OP = Systematic Coronary Risk Evaluation 2 Older Persons.

Table 2. Efficacy of lipid-lowering monotherapy: percentage reduction in LDL-cholesterol levels with statins and nonstatins[9]

LDL-cholesterol reduction		
Low (<30%)	**Moderate (30 to 49%)**	**High (≥50%)**
• Simvastatin 5 to 10 mg • Fluvastatin 20 to 40 mg • Pravastatin 5 to 20 mg • Ezetimibe 10 mg • Plant sterols 1 g twice daily • Bile acid resins • EPA ethyl esters • Fenofibrate 145 mg	• Simvastatin 20 to 40 mg • Rosuvastatin 5 to 10 mg • Atorvastatin 10 to 20 mg • Bempedoic acid 180 mg*	• Rosuvastatin 20 to 40 mg • Atorvastatin 40 to 80 mg • PCSK9 inhibitors (inclisiran and monoclonal antibodies)

Abbreviations: EPA = eicosapentaenoic acid; PCSK9 = proprotein convertase subtilisin/kexin type 9.
* Bempedoic acid is currently available in Europe and the USA.

macrophage-activating cytokines, initiating foam cell formation, deposition of crystalline cholesterol and promotion of a pro-inflammatory cycle that contributes to plaque progression.[35] Central to this process is influx of plasma-derived LDL-C, its subsequent oxidation and evolution of the chronic inflammatory disease called atherosclerosis.[28-35] Plaques are metabolically active and capable of considerable regression through risk-factor control, particularly reduction of levels of LDL-C and other atherogenic lipoproteins.[28-35]

Like statins, ezetimibe has been shown to have antiatherosclerotic pleiotropic effects, in addition to LDL-C lowering (Figure 2).[29,36] Reduction in major cardiovascular events has been shown in several trials involving combination statin and ezetimibe LLT, including IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), EWTOPIA-75 (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older), SHARP (Study of Heart and Renal Protection), CLEAR OUTCOMES (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) and SWEDEHEART.[1,2,37-41] The RACING (Randomized Comparison of Efficacy and Safety of Lipid-Lowering With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-Risk Cardiovascular Diseases) trial showed no difference in events between moderate-intensity statin and ezetimibe cotherapy versus high-intensity statin therapy.[42]

Main points from SWEDEHEART and LLT trials

The main points from SWEDEHEART and other LLT trials are listed below.

- Ezetimibe, when used in combination with low- to moderate-statin doses, results in LDL-C lowering equivalent to maximal doses of statins. Therefore, a 'statin-sparing' approach may be used by initiating therapy with lower statin doses, which will hopefully improve compliance because of less severe and less frequent side effects from upfront combination statin and ezetimibe LLT.[43]
- The benefits of LDL-C levels depend on the extent of LDL-C reduction, its duration and the age at which patients begin LLT. The axiom, 'Sooner, Longer, Lower' summarises this paradigm.[44]
- Recent trials have emphasised the 'Lower is Better' approach with lower recommended target LDL-C levels (below

Table 3. Efficacy of combination LLT: percentage reduction in LDL-cholesterol levels with statin plus nonstatins[9]

LDL-cholesterol reduction			
Moderate (30 to 49%)	**High (50 to 59%)**	**Very high (60 to 79%)**	**Extremely high (80 to 84%)**
Oral drugs			
Ezetimibe + • simvastatin 10 mg or • fluvastatin 40 mg or • pravastatin 20 mg	Ezetimibe + • simvastatin 20 mg or • atorvastatin 10 to 20 mg or • rosuvastatin 5 to 10 mg	Ezetimibe + • atorvastatin 40 to 80 mg or • rosuvastatin 20 to 40 mg	–
Oral + subcutaneous drugs			
–	–	PCSK9 inhibitor (SC) + • atorvastatin 10 to 20 mg or • rosuvastatin 5 to 10 mg or • simvastatin 40 mg	PCSK9 inhibitor (SC) + ezetimibe + • atorvastatin 40 to 80 mg or • rosuvastatin 20 to 40 mg

Abbreviations: LLT = lipid-lowering therapy; PCSK9 = proprotein convertase subtilisin/kexin type 9 (includes monoclonal antibodies and inclisiran); SC = subcutaneous.

1.0 mmol/L) in patients at very high risk of CVD (Table 1).[11]
- The relationship between achieved LDL-C levels and coronary heart disease events is linear and continuous, with no threshold for lack of benefit to levels below 0.5 mmol/L using current therapy.[45] The same relationship applies to the regression of atherosclerotic lesions, with regression generally occurring more often than progression when LDL-C levels are less than 0.75 mmol/L.[46]
- LDL-C levels below 0.5 mmol/L are now possible using triple therapy with high-dose statins in combination with ezetimibe and PCSK9 inhibitors.[47] Clinicians can now decide quite accurately the LDL-C level they wish to achieve, by adjusting the doses of LLT (Tables 2 and 3).[9]
- Current LDL-C targets may therefore be regarded as conservative, with many cardiologists treating patients well below consensus guidelines for various categories of CVD risk. This paradigm for LDL reduction may be called 'Lowest is Better', using lower-than-recommended targets. Others prefer to use current guidelines, which do not yet recognise the 'Lowest is Better' approach until they can be established by randomised trials.

The 2025 National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand (CSANZ) comprehensive guidelines for patients with ACS still use the stepwise approach to LLT (Box).[48] These may be modified in the future to include the upfront strategy.[49]

'Combination LLT should be considered at the outset of therapy initiation to maximize LDL-C goal attainment and improve reduction in hard CVD end points.'[12]

Concluding comments: the bedtime story

At the August 2025 CSANZ annual scientific conference imaging and preventive cardiology were among the main themes. Imaging and LLT were linked as key drivers for identifying and treating high-risk patients in presentations such as: 'Are cardiovascular risk assessment tools predictive for coronary plaque burden?' The key speakers recommended changes to Medicare to allow greater access to CAC and CT coronary angiography for general practitioners, particularly in regional and remote areas, and use of the upfront LLT strategies described above.

A 2025 meta-analysis of the ILEP investigators that included 108,373 patients at very high risk of CVD showed that statin–ezetimibe cotherapy resulted in overall greater reduction in LDL-C, the same risk of adverse effects and significantly lower risk of all-cause mortality, major adverse cardiovascular events and stroke compared with statin monotherapy. Combination therapy reduced mean LDL-C levels by about 20% compared with monotherapy, and there were significant reductions in major cardiovascular events by 18%, stroke by 17% and all-cause mortality by 18%. Adverse events and the therapy discontinuation rate were comparable in the two groups. The investigators concluded: 'Combination LLT should be considered at the outset of therapy initiation to maximize LDL-C goal attainment and improve reduction in hard CVD end points.'[12] These issues are emphasised in the updated 2025 ESC/EAS guidelines.[11]

There are no longer PBS restrictions on ezetimibe prescribing, so ezetimibe can be coprescribed with a statin without the need for a prior eight-week period on statin monotherapy.[50] So, let's put to bed some of our older ideas for lipid lowering and wake up to the current paradigm of starting therapy for patients at high CVD risk with combined statin and ezetimibe LLT rather than statin monotherapy, and put this into practice to achieve lower LDL-C levels, greater plaque regression and improved protection from CVD events. **CT**

2025 Australian ACS guideline: lipid-modifying practice points[48]

Initial LLT
- Initiate or continue high-potency statin therapy (e.g. atorvastatin or rosuvastatin) as soon as possible during the patient's ACS admission, irrespective of baseline LDL-C level.
- For people on LLT before the index ACS admission, consider intensifying existing LLT.

Subsequent LLT
- Reassess total cholesterol and LDL-C levels about four to six weeks after initiating or intensifying treatment.
- Adjust statin therapy or add nonstatin therapy according to whether levels are at target values.
- Note that additional nonstatin therapies are often needed to achieve target LDL-C levels and prevent recurrent coronary events.

Familial hypercholesterolaemia
- In people with ACS (men <55 years of age and women <60 years of age), the Dutch Lipid Clinic Network score can guide the need for diagnostic genetic testing.
- If genetic predisposition to familial hypercholesterolaemia is confirmed, consider cascade testing, genetic counselling and initiating statin therapy in family members.

High triglyceride levels
- In people with ACS with triglyceride levels of 1.5–5.6 mmol/L and LDL-C 1.0–2.6 mmol/L despite statin therapy, consider adding icosapent ethyl.
- Note that the current PBS eligibility criteria for icosapent ethyl include a triglyceride level of 1.7 mmol/L.

Abbreviations: ACS = acute coronary syndrome; LDL-C = LDL cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction.

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A list of references is included in the online version of this article (www.cardiologytoday.com.au).

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