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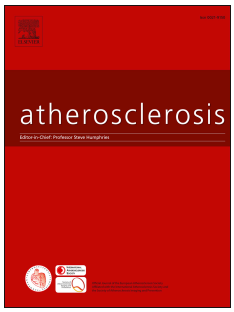

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From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients. A Statement from a European Atherosclerosis Society Task Force

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ABSTRACT

Background and aims: This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients.

Methods: Evidence-based review

Results: Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C and should be given upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels remain high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and <5.6 mmol/L [200 and <500 mg/dL) on statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus.

Conclusions: This guidance aims to improve real-world use of guideline-recommended combination lipid modifying treatment.

Key words: 2019 ESC/EAS Dyslipidaemia Guidelines; combination treatment; LDL cholesterol; triglycerides; lipid goals; high-risk

INTRODUCTION

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for dyslipidaemia management emphasized the need to lower low-density lipoprotein cholesterol (LDL-C) as much as possible to prevent atherosclerotic cardiovascular disease (ASCVD).[1] Replacing the 'and/or' approach taken in the 2016 guidelines,[2] LDL-C goals in high-risk and very-high-risk patients now involve consideration of the LDL-C level and at least 50% percent reduction from baseline LDL-C (**Box 1**). The elevated ASCVD risk in familial hypercholesterolaemia (FH) patients, particularly for those with recurrent events, was also recognized.[3] Beyond LDL-C, the guidelines updated recommendations for managing mild to moderately elevated triglycerides (TG), taking account of evidence from the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT).[4]

The guidelines underline the need for combination therapy to achieve LDL-C goals as early as possible. Despite this, there is a considerable shortfall with what is put into action. Real-world data show that poor LDL-C goal attainment is an issue across all categories of high and very-high-risk patients.[5,6] Limited uptake of high-intensity statin therapy,[6-10] and underuse of ezetimibe contribute.[6,11] Suboptimal treatment adherence is a major issue, due to various reasons including adverse effects (whether perceived or real), and clinician inertia.[12,13,9]

This EAS Task Force recognizes that the new LDL-C goals for high and very-high-risk patients with dyslipidaemia are even more demanding than previously; indeed, in real-world practice only about one-third attain LDL-C goal.[6] Therefore, combination lipid lowering therapy should become the standard of care for these patients. In practice, however, there is uncertainty about the most appropriate strategies for combination treatment, especially given

finite resources. This is especially pertinent for proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody therapy, which although highly efficacious in lowering LDL-C, is costly, with restricted or no reimbursement in many European countries. Added to this, clinicians are unclear regarding strategies for managing hypertriglyceridaemia, especially in the context of comorbidities. Consequently, this EAS Task Force aims to provide evidence-based practical guidance for the use of combination therapy to improve the management of elevated LDL-C and high TG in clinical practice. Importantly, and irrespective of the type of therapy, every effort should be made to improve patient adherence as this is a key determinant of response to lipid lowering therapy.

LDL-CHOLESTEROL MANAGEMENT

PHARMACOTHERAPY

Why is LDL-C the primary priority in lipid management? Does it matter how it is lowered?

There is incontrovertible evidence that LDL is causal for ASCVD.[14,15] In clinical practice, plasma LDL-C (either calculated or directly measured), a surrogate of LDL particle concentration, is used routinely for lipid testing and to evaluate therapeutic benefit. As there is no evidence for a threshold in LDL-C reduction for cardiovascular benefit, or for safety issues associated with very low LDL-C levels,[14,16] clinicians should aim to lower LDL-C levels as much as possible, especially in high and very-high-risk patients. It is also important that patients are at LDL-C goal as early as possible and as long as possible, preferably lifelong. Therefore, clinicians should always consider "*the lower the better*" together with "*the earlier the better*" and "*the longer the better*" management strategies.[17,18]

The cardiovascular benefit derived from LDL-C lowering is consistent for the available therapeutic strategies.[14] Mendelian randomization studies of polymorphisms in the genes encoding the targets of different LDL-C lowering treatments (i.e. *HMGCR*, the target of statins, *NPC1L1*, the target of ezetimibe, and *PCSK9*, the target of alirocumab and evolocumab), showed that each had a similar effect on the risk of coronary heart disease (CHD) per unit lower LDL-C.[19-21] Similar findings were reported in a study of genetic variants that mimic the effect of inhibiting ATP citrate lyase, the target of bempedoic acid.[22] Analyses of randomized clinical trials showed that for any LDL-C lowering strategy mediated via upregulation of LDL receptor expression (which applies to both statin and non-statin treatments including bile acid sequestrants, ezetimibe, bempedoic acid and PCSK9 inhibitors), there is a similar reduction in the risk of major vascular events (by 20-25%) per mmol/L lower LDL-C.[14,22,23]

How can treatment be optimized to achieve the LDL-C goals recommended by the 2019 ESC/EAS guidelines in practice?

To achieve best practice, a personalized approach to LDL-C management is needed in high and very-high-risk patients, including those at enhanced risk due to the presence of additional risk moderators and/or high LDL-C, as defined by a Joint ESC/EAS Task Force.[24] Two criteria are critical to decision-making: 1) the starting LDL-C level, i.e., how far the patient is from the recommended LDL-C goal, and 2) the average LDL-C reduction that is achievable with each treatment strategy (**Box 2**). Clinicians should be aware of individual variability in the LDL-C lowering response.[25] The practicalities of follow-up imply an important role for upfront combination treatment.

Patients with ASCVD

The key challenge for clinicians managing ASCVD patients is to reduce their risk of recurrent events and the associated burden of hospitalization, revascularization and intensive clinical management. While improving uptake of maximally tolerated high-intensity statin therapy is mandatory, non-statin LDL-C lowering therapy will often also be required to attain LDL-C goal, especially for patients at enhanced risk due to the presence of risk moderators and/or with high baseline LDL-C levels on statin monotherapy.[26,27] Therefore, this Task Force reinforces guideline recommendations for upfront high-intensity statin-ezetimibe combination therapy in ASCVD patients with baseline LDL-C levels ≥2.6 mmol/L (≥100 mg/dL) (**Figure 1**). Upfront combination therapy improves adherence and LDL-C goal attainment in the longer-term, as exemplified by the Treat Stroke to Target study, in which the combination of ezetimibe and statin therapy increased the proportion of patients at LDL-C goal by 3-fold.[28] The availability of a fixed combination of ezetimibe and a high dose of a more efficacious statin will likely improve patient adherence. For patients with statin intolerance and elevated LDL-C levels, upfront combination with ezetimibe and bempedoic acid reduces LDL-C levels by 40%; the availability of a fixed-dose combination has practical advantages.[29]

Add-on PCSK9 inhibitor treatment may be considered in patients not at LDL-C goal on statin-ezetimibe combination therapy who present with any of the risk moderators (**Figure 1**). Focused use of PCSK9 inhibitors in individuals at the highest risk with high LDL-C levels is likely to provide maximal clinical benefit,[30] supported by evidence from the FOURIER and ODYSSEY OUTCOMES trials,[31-40] as well as studies in FH patients,[41,42] and is cost-effective over the longer-term.[43] If there is no reimbursement for the use of PCSK9 inhibitors, addition of bempedoic

acid or a bile acid sequestrant is a viable alternative for very-high-risk patients with high LDL-C levels, providing incremental LDL-C reduction (by 20-25% and 16% on average, respectively).[44-47] The latter option also may improve glycaemic control in patients with type 2 diabetes mellitus (T2DM).[48]

A recurring concern among clinicians is the safety of very low LDL-C levels achievable with combination LDL-lowering therapy. Evidence to date, however, shows that even at LDL-C levels as low as 0.4 mmol/L (15 mg/dL), there was no adverse signal over 5-year exposure and, in the case of PCSK9 inhibitor therapy, no neutralizing antibodies.[49-51] Real-world pharmacovigilance data add further support, although further long-term exposure data are needed.[52]

Patients with familial hypercholesterolaemia without ASCVD

Patients with heterozygous FH without ASCVD are considered at high-risk, and the presence of additional risk moderators elevates this to very-high-risk.[24,53] Despite this, undertreatment of patients is common,[54] even with combination treatment with high-intensity (or maximally tolerated) statin and ezetimibe as the standard of care.[1] Consequently, this Task Force recommends adding a PCSK9 inhibitor in FH patients without clinically diagnosed ASCVD if LDL-C levels are >50% from LDL-C goal on combination statin-ezetimibe therapy. (**Figure 2**). This approach can also reduce the need for lipoprotein apheresis in patients with severe FH.[55,56]

Why upfront combination treatment with a statin and ezetimibe?

Patients with ASCVD, particularly those at enhanced risk with additional risk moderators, or FH without ASCVD and high LDL-C levels, are unlikely to attain LDL-C goal with intense statin monotherapy. Therefore, this Task Force recommends upfront combination high-intensity statin-ezetimibe treatment in these patients. This approach has practical advantages in avoiding repeated follow-up, allowing patients to be on target as early as possible, with favourable impact on cardiovascular outcome.

NUTRACEUTICALS

Beyond pharmacotherapy, nutraceuticals, targeted functional foods or dietary supplements of plant or microbial origin, may have a role in lowering LDL-C at the interface of lifestyle and pharmacotherapeutic intervention. The available nutraceuticals may lower LDL-C levels by 5-25%,[57] and could aid attainment of LDL-C goal. There are three main patient categories where LDL-C lowering nutraceuticals may be considered (**Box 3**).[58,59] For high and very-high-risk patients, these agents should be considered adjunctive to lifestyle intervention and should not replace more effective guideline-recommended pharmacotherapies.

What is the evidence that nutraceuticals lower LDL-C?

There is extensive support for the LDL-C lowering effects of whole foods such as nuts, pulses, oat cereal, psyllium, or foods supplemented with 2-3 g/day phytosterols (plant sterols or stanols), directly related to baseline LDL-C levels.[1] These should be encouraged simultaneously, as their combination in daily servings, as in the Portfolio diet, provides the LDL-C lowering

equivalent of low dose statin therapy.[60,61] However, clinical evidence for a single LDL-C-lowering nutraceutical is variable. The most studied in relation to efficacy and safety are foods fortified with plant sterols or stanols, which lower LDL-C by 9-12% at doses of 2-3 g/day,[62] red yeast rice (RYR) with monacolin K (i.e., natural lovastatin), which at a dose of 3-10 mg/day lowers LDL-C by 15-25%, and berberine, which lowers LDL-C by 10-20%.[57] Data for other single nutraceuticals, including soy derivatives and policosanol, are less conclusive.[1,63]

Can different nutraceuticals be combined?

Combinations of nutraceuticals with confirmed lipid-lowering may enhance their effects.[64] In randomized clinical trials, the combination of berberine, policosanol and RYR achieved LDL-C lowering of up to 25%, similar to low-dose statins.[58] Plant sterol/stanol fortified foods are also effective as add-on therapy to statins, ezetimibe and fibrates.[62]

What other considerations are relevant?

Safety, variability in the purity of preparations, and cost need to be weighed in discussions with patients. Long-term safety is an issue for all nutraceuticals, as regulatory requirements are less stringent than for pharmacotherapeutics. Safety has been specifically queried with RYR given the primary active ingredient is monacolin K, but evidence does not suggest any increase in the incidence of adverse events compared with lovastatin.[65-67] The variable purity of agents such as RYR and berberine is also problematic.[1,66] Finally, clinicians need to bear in mind that these nutraceuticals are likely to be more costly than generic statins, which may adversely impact long term patient adherence.

Does LDL-C lowering with nutraceuticals translate to cardiovascular benefit?

With the exception of RYR (for which there is a single low quality Chinese study[68]) and nuts studied in the context of the Mediterranean diet in the PREDIMED study,[69] there are no clinical trials of LDL-C lowering nutraceuticals that demonstrated cardiovascular hard endpoint benefit. Future trials are also unlikely. This should not, however, discourage their use given extensive evidence from randomized controlled trials that LDL-C lowering is associated with lower cardiovascular event rates in direct proportion to the extent of LDL-C reduction.[14]

Key points relating to LDL-C management are summarized in **Box 4**.

MANAGEMENT OF ELEVATED TRIGLYCERIDES

Even when LDL-C levels are at goal or lower, high and very-high-risk patients still experience ASCVD events, highlighting the need to target other modifiable risk factors. Among potential lipid targets, attention has focused on TG-rich lipoproteins and their remnants – for which plasma TG are a marker - as contributors to this residual cardiovascular risk. For mild to moderately elevated TG (up to 5.6 mmol/L or 500 mg/dL), therapeutic intervention is associated with ASCVD benefit, whereas at higher TG levels, intervention is needed to reduce the risk of pancreatitis (1).

Hypertriglyceridaemia is often associated with low plasma levels of high-density lipoprotein cholesterol (HDL-C), especially in patients with insulin-resistant conditions including T2DM.[70] Despite some inconsistency,[71] there is extensive observational data showing that low HDL-C associates with cardiovascular risk,[72] supporting its inclusion in SCORE global risk assessment. However, the lack of evidence from genetic studies for a protective role of HDL-C

in humans,[73] together with the failure of different therapeutic approaches targeting HDL-C to reduce cardiovascular events,[74-78] cast doubts on causality.

What is the evidence that some patients with controlled LDL-C levels remain at high cardiovascular risk due to persistently elevated TG-rich lipoproteins?

Findings from epidemiologic and genetic studies, and analyses from randomized controlled trials, support a role for TG-rich lipoproteins in the causal pathway for the development of atherosclerosis.[79] Several analyses of randomized controlled trials showed an association between TG levels and the risk for recurrent events in statin-treated patients with ASCVD.[80,81] This was especially the case for statin-treated T2DM patients, as shown by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, as elevated TG (and low HDL-C) increased cardiovascular risk compared with patients without this dyslipidaemia,[82] and this was also evident during continued follow-up in the ACCORDION study.[83]

Insights from Mendelian randomization studies and genetic analyses that investigated the impact of mutations in key genes encoding proteins that regulate TG-rich lipoprotein metabolism strengthen the evidence for a link between TG-rich lipoproteins, their remnants and ASCVD risk.[79,84] Loss-of-function mutations in the genes encoding apolipoprotein(apo) C-III (with certain exceptions) and angiopoietin-like proteins (ANGPTL) 3 and 4 were associated with lifelong lower plasma TG levels and a reduced risk of coronary artery disease.[85-89]

Are TG-rich lipoproteins more or less atherogenic than LDL?

Both TG and cholesterol are carried in the plasma by apoB-containing particles, which include LDL and TG-rich lipoproteins (chylomicrons, very low-density lipoproteins [VLDL] and

their remnants). Each of these lipoproteins carries a single apoB molecule. In effect, the concentration of circulating apoB particles determines the number of particles trapped within the arterial wall, the key driver of the initiation and progression of atherosclerosis.[90]

Mendelian randomization analyses compared the association of genetic scores for TG-lowering variants in the *LPL* gene and LDL-C-lowering variants in the *LDLR* gene with the risk of cardiovascular events based on data from over 650,000 subjects in cohort or case-control studies. The odds ratio per 10 mg/dL decrement in apoB-containing lipoproteins was 0.771 (95% CI, 0.741-0.802) for a genetic risk score based on TG-lowering variants in the *LPL* gene versus 0.773 (95% CI, 0.747-0.801) for a genetic risk score based on LDL-C lowering variants in the LDLR gene.[91] Thus, it was concluded the atherogenic risk from TG-rich VLDL particles and their remnants approximates that from an LDL particle per unit apoB particle.

What other features are associated with high TG?

Inflammation, coagulation and lipid accumulation in the arterial intima also associate with elevated TG-rich lipoproteins.[79] Products of LPL-mediated catabolism of TG-rich lipoproteins, such as oxidized free fatty acids, elicit inflammation in the arterial wall and at a multicellular level and promote endothelial dysfunction.[92-94] TG-rich lipoproteins also activate the coagulation cascade and upregulate the expression of plasminogen activator inhibitor-1.[95] Together these processes enhance platelet aggregation and thrombus formation, thereby exacerbating the underlying proatherothrombotic phenotype associated with elevated TG.[96] Additionally, there is evidence that microvascular disease is associated with higher levels of plasma TG and lower levels of HDL-C among T2DM patients with well controlled LDL-C.[97]

What is the evidence that lowering TG (a marker for TG-rich lipoproteins and remnants) reduces cardiovascular risk?

While there is strong epidemiologic and genetic evidence that TG-rich lipoproteins have a causal role in the ASCVD pathway, information from clinical trials that TG lowering reduced cardiovascular risk is limited. In respect of the fibrate trials, this is largely due to failure to recruit patients with sufficiently high TG levels. For example, in the ACCORD-Lipid trial, the median TG level at baseline was 1.8 mmol/L (interquartile range 1.3 to 2.6 mmol/L).[82] Post hoc analyses of the fibrate trials did, however, indicate benefit in individuals with elevated TG and low HDL-C.[98] For omega-3 fatty acids the evidence is more conflagrated. Whereas lowering TG levels by 18% with 4 g daily of icosapent ethyl, a purified eicosapentaenoic acid (EPA) ethyl ester, reduced cardiovascular events in REDUCE-IT,[4] STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridaemia) showed no benefit from TG lowering (to a similar extent) with 4 g daily of a carboxylic acid formulation of EPA and docosahexaenoic acid (DHA),[99] as discussed below. It should, however, be noted that a meta-regression analysis of trials of TG-lowering interventions (both fibrates and omega-3 fatty acids), showed that TG-lowering was associated with a reduced risk of cardiovascular events, even after adjustment for LDL-C lowering.[100]

Why did REDUCE-IT and STRENGTH differ in their findings?

The discrepant results of the REDUCE-IT and STRENGTH trials raise many questions. Both studies enrolled statin-treated patients at high cardiovascular risk with elevated TG levels at baseline (median 2.4 mmol/L [212 mg/dL] in REDUCE-IT and 2.7 mmol/L [240 mg/dL] in STRENGTH); patients in STRENGTH also had low HDL-C (median 36 mg/dL).[4,99] REDUCE-IT

showed a significant 25% reduction in major adverse cardiovascular events with high dose EPA compared with a mineral oil comparator after treatment for a median of 4.9 years.[4] This clinical benefit was higher than that predicted by the magnitude of TG-lowering (18%), implying that non-lipid pleiotropic mechanisms of EPA must be implicated. Furthermore, the EVAPORATE trial, which also compared high-dose EPA with the same mineral oil comparator, showed slowing of plaque progression and reduction in plaque volume over 18 months.[101] In contrast, the STRENGTH trial comparing high-dose EPA/DHA with corn oil, was stopped prematurely for futility after 42 months, despite 18% TG reduction as in REDUCE-IT.[4,99]

Several reasons have been proposed to explain these contrasting findings. First, a key difference is the choice of comparator. The mineral oil comparator in REDUCE-IT (and EVAPORATE) increased apoB, LDL-C, and high-sensitivity C-reactive protein levels,[4,101] whereas corn oil used in STRENGTH was a truly neutral comparator.[99] Thus it is possible that the positive results of REDUCE-IT may be due to the choice of an inappropriate placebo comparator which exaggerated the effects of EPA.[102] Second, the different formulations may be a factor, as there is evidence to suggest that EPA and DHA may have contrasting biological effects.[103] Moreover, on-treatment EPA blood levels were higher in REDUCE-IT than in STRENGTH (144 versus 89.6 μg/mL at 12 months).[4,99] Third, differences in the patient populations may be a factor, as REDUCE-IT enrolled a higher proportion of patients with established coronary artery disease (71% versus 56% in STRENGTH).[4,99] Therefore, a note of caution is necessary before endorsing high-dose omega-3 fatty acid preparations for cardiovascular risk reduction. Importantly, both trials showed that the incidence of atrial fibrillation was higher on omega-3 fatty acid treatment than in the comparator arm.[4,99]

Is it possible to compare the cardiovascular effects of lowering TG or lowering LDL-C?

In Mendelian analyses, the benefit from lowering TG or LDL-C levels, quantitated in terms of apoB reduction, a unifying metric of cardiovascular risk, was proportional to the absolute change in apoB.[91] To achieve a similar reduction in cardiovascular risk by lowering LDL-C levels by 40 mg/dL, TG levels must be lowered 5-fold or by approximately 200 mg/dL. This may explain why ACCORD Lipid failed to demonstrate cardiovascular benefit, as baseline TG levels were less than planned and thus the combination of statin and fenofibrate led to only modest reduction in apoB-containing lipoproteins.[82]

How to manage elevated TG in high- and very-high-risk patients?

Lifestyle intervention (losing weight, increasing physical activity, and limiting alcohol intake, as well as avoiding fructose and high carbohydrate foods) is fundamental to the management of elevated TG.[1] The magnitude of TG elevation is also relevant to therapeutic approaches. Patients with very high TG levels (>10 mmol/L or >800 mg/dL), are likely to have a multifactorial or polygenic predisposition to hypertriglyceridaemia and are at high risk of pancreatitis. These patients should be managed with a low-fat diet (< 10% of calories from fat) with high-dose omega-3 fatty acids, although fibrates may prove useful in polygenic chylomicronaemia.[104]

For mild to moderate hypertriglyceridaemia (<5.6 mmol/L or <500 mg/dL), the guidelines recommend statin treatment if TG are >2.3 mmol/L or >200 mg/dL.[1] Additional therapy with either a fibrate or omega-3 fatty acids should take into account the benefit versus risk of each treatment (**Figure 3**). Guideline recommendations for high-dose omega-3 fatty acids for ASCVD prevention relate to icosapent ethyl based on the results of REDUCE-IT.[4]

Caution is needed in the light of the lack of benefit evident in STRENGTH[98] and the increased risk for AF in both studies.

For T2DM patients with elevated TG despite maximally tolerated LDL-C lowering therapy, effects beyond macrovascular benefit may be relevant to treatment decisions. In both the ACCORD Lipid and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) studies, fenofibrate treatment was shown to prevent progression of diabetic microvascular complications, notably diabetic retinopathy,[105,106] all of which pose a substantial burden. Therefore, this Task Force recommends that the combination of statin (± ezetimibe) and fenofibrate may be considered in T2DM patients (with or without ASCVD) with TG >200 mg/dL or 2.3 mmol/L on statin treatment. Clinicians should be aware of the propensity for elevation in serum creatinine with fenofibrate,[107] which is usually transient and resolved by temporarily stopping treatment (**Box 5**).

UNANSWERED QUESTIONS

This practical guidance aims to simplify the use of combination treatment in high and very-high-risk patients with elevated levels of LDL-C and/or TG. The Task Force recognizes, however, that several outstanding questions remain, particularly regarding the role of high-dose omega-3 fatty acid preparations for cardiovascular risk reduction.

Another area of uncertainty relates to the future role of innovative LDL-C lowering treatments in combination strategies. Inclisiran, a small interfering RNA therapeutic targeting hepatic synthesis of PCSK9, provides a convenient approach to lowering LDL-C in combination with statin therapy, as dosing is infrequent (twice-yearly subcutaneous injections), thereby much improving patient adherence. Phase 3 trials have demonstrated durable LDL-C lowering

by about 50% in high and very-high-risk patients, including those with ASCVD and heterozygous FH.[108,109] Treatment was also well tolerated in the long-term.[110]

Furthermore, several novel treatments that target different sites of TG-rich lipoprotein metabolism are also in development and may offer potential for the management of hypertriglyceridaemia. The most advanced of these is pemafibrate, a selective peroxisome proliferator-activated receptor alpha modulator or SPPARMα. The PROMINENT study (Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN diabetic patiENTs), which is evaluating pemafibrate (on top of statin treatment) in 10,000 T2DM patients with elevated TG (≥2.3 mmol/L and <5.6 mmol/L), is a critical test of whether lowering elevated TG-rich lipoproteins reduces cardiovascular events.[111] The answer to this fundamental question is anticipated in the next 2-3 years.

Finally, for all innovative lipid modifying therapies, the long-term net benefit and cost remain priority issues.

CONCLUSION

This Task Force statement provides evidence-based practical guidance for the use of guideline-recommended combination lipid-modifying therapy in high and very-high-risk patients to prevent ASCVD events. Integration of these approaches into routine practice has the potential to improve the implementation of guideline-recommended management of high LDL-C and TG levels, and ultimately to favourably impact the trajectory and burden of ASCVD.

Conflict of interest

The authors declare the following financial interests/personal relationships outside the submitted work.

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Figure legends

Figure 1. Algorithm for managing high LDL-C levels in ASCVD patients

Abbreviations: CABG: coronary artery bypass graft; FH: familial hypercholesterolaemia; HI high-intensity; LDL-C low-density lipoprotein cholesterol; Lp(a) lipoprotein(a); PAD peripheral artery disease; *on high-intensity (HI) or maximally tolerated statin therapy

Figure 2. Algorithm for managing high LDL-C levels in FH patients without ASCVD

Abbreviations: CAC coronary artery calcium (score); HI high-intensity; LDL-C low-density lipoprotein cholesterol; Lp(a) lipoprotein(a); * high intensity (HI) or maximally tolerated statin therapy

Figure 3. Suggested algorithm for high and very-high-risk patients with elevated TG

Abbreviations: ASCVD atherosclerotic cardiovascular disease; HI high intensity statin therapy; LDL-C low-density lipoprotein cholesterol; TG triglycerides

Box 1. 2019 ESC/EAS Guideline-recommended LDL-C goals in high and very-high-risk patients

Definitions of high- and very-high risk are from the 2019 ESC/EAS guidelines.[1]

Patient category	**LDL-C goals**
Very-high-risk defined as: • Documented ASCVD, clinical or on imaging • Calculated SCORE ≥10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor • Severe chronic kidney disease (eGFR <30 mL/min/1.73 m^2) • Diabetes mellitus (DM) with target organ damage*, ≥3 major risk factors or early onset of type 1 DM of long duration (>20 years)	<1.4 mmol/L (<55 mg/dL) AND at least 50% reduction from baseline <1.0 mmol/L (<40 mg/dL) may be considered for ASCVD patients with a second event within 2 years while on maximally tolerated statin therapy
High-risk, defined as: • Markedly elevated single risk factors, in particular total cholesterol >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or blood pressure ≥180/110 mmHg • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD • Patients with FH without other major risk factors • Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2)	<1.8 mmol/L (<70 mg/dL) AND at least 50% reduction from baseline

* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

Box 2. Average LDL-C reduction with each treatment.

Values are derived from the 2019 ESC/EAS guidelines.[1]

Treatment	Average LDL-C reduction
Statin	
- Moderate-intensity	up to 30%
- High-intensity	up to 50%
High-intensity statin + ezetimibe	up to 65%
PCSK9 inhibitor	up to 60%
PCSK9 inhibitor + high-intensity statin	up to 75%
PCSK9 inhibitor + high-intensity statin + ezetimibe	up to 85%

Box 3. Patients for whom LDL-C lowering nutraceuticals may have a role

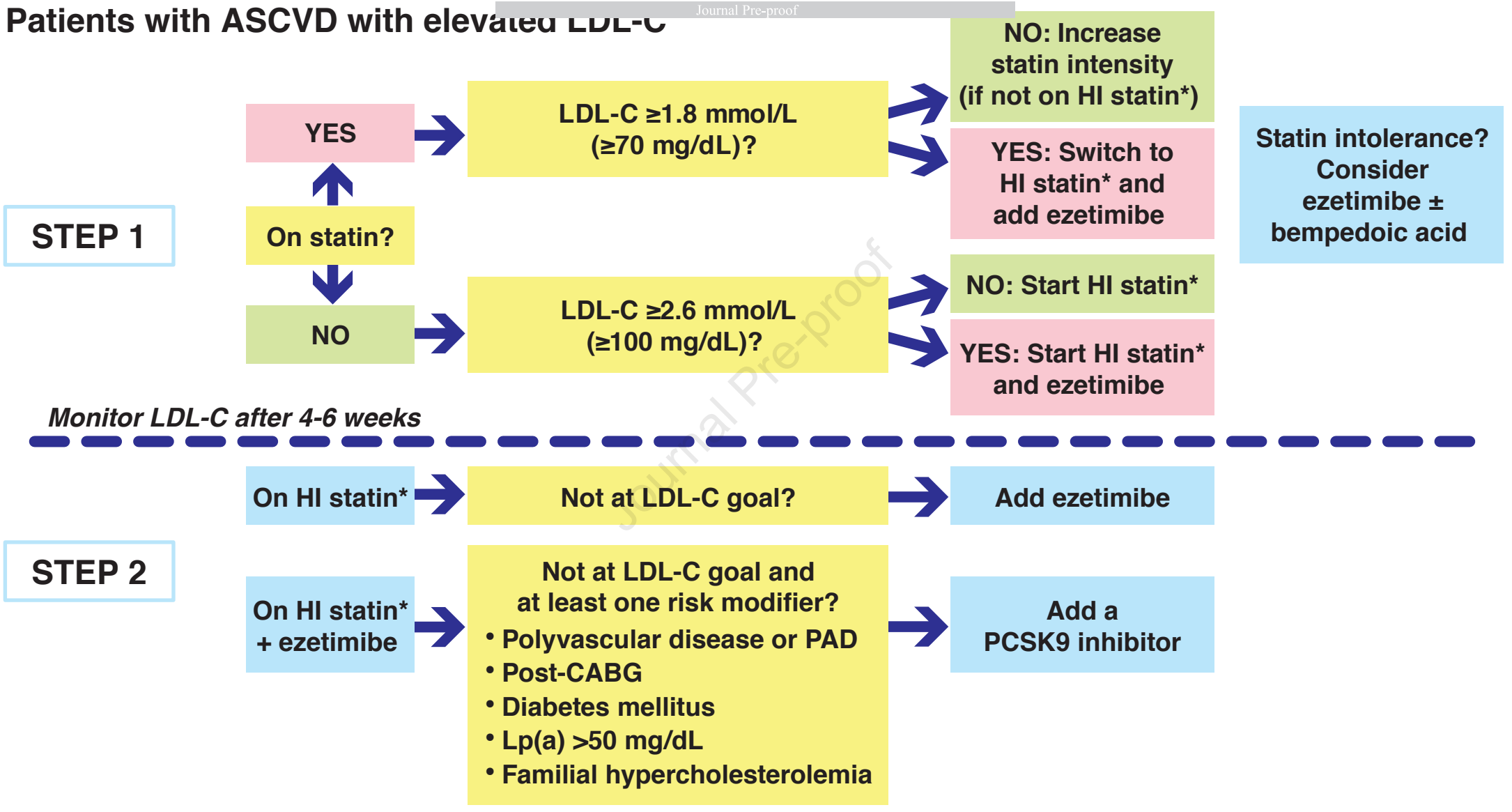
- Patients with mild to moderately elevated LDL-C levels not on pharmacotherapy and at low global ASCVD risk.
- Patients on statin therapy who are unwilling or unable (as in the case of statin intolerance) to increase the statin dose or intensity, or add non-statin LDL-C lowering therapy, irrespective of global ASCVD risk.
- Patients unwilling to consider LDL-C lowering pharmacotherapy, irrespective of global ASCVD risk.

Box 4. Key points: LDL-C management

- The first priority for all high-risk and very-high-risk patients is improving uptake of maximally tolerated high-intensity statin therapy.
- Add-on ezetimibe is the first choice in ASCVD patients not at LDL-C goal, with upfront combination in those with high LDL-C unlikely to reach the goal with a statin. A PCSK9 inhibitor may be added to attain LDL-C goal, depending on local rules.
- In FH adults without ASCVD, combination with maximally tolerated high-intensity statin and ezetimibe is the standard of care. A PCSK9 inhibitor is recommended with elevated LDL-C levels and/or indices of risk severity.
- LDL-C lowering nutraceuticals may help in attainment of LDL-C goal, always in the context of lifestyle management. These do not replace pharmacotherapy.

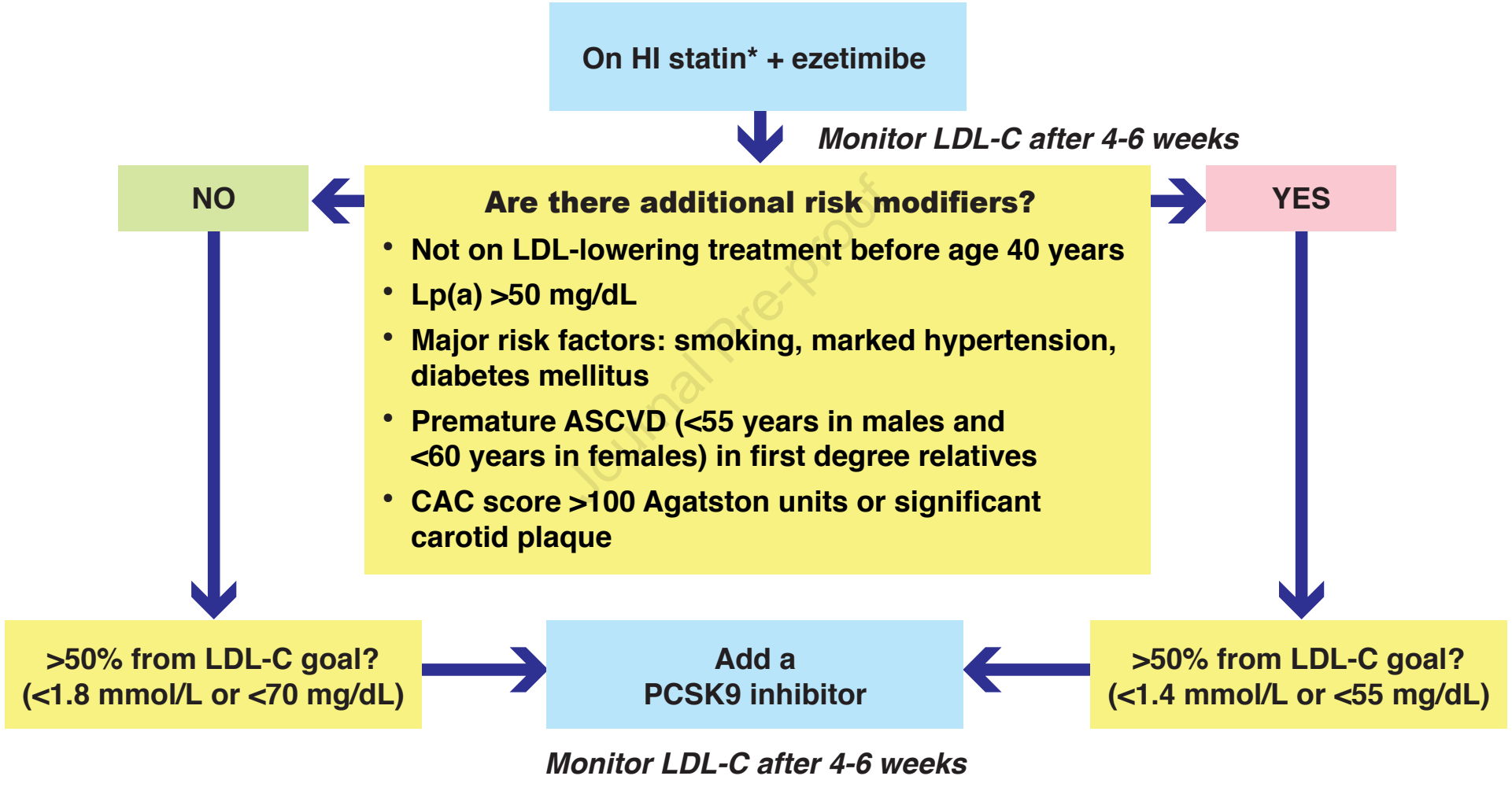
Box 5. Key points: Managing elevated TG-rich lipoproteins

- Elevated TG-rich lipoproteins associate with increased cardiovascular risk, even if patients are at LDL-C goal.
- Contemporary evidence suggests that the atherogenic risk derived from TG-rich particles and their remnants approximates the risk from an LDL particle.
- In type 2 diabetes mellitus patients with elevated TG on LDL-lowering therapy, fenofibrate may be considered for beneficial macro- and microvascular effects.
- High-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks of treatment.



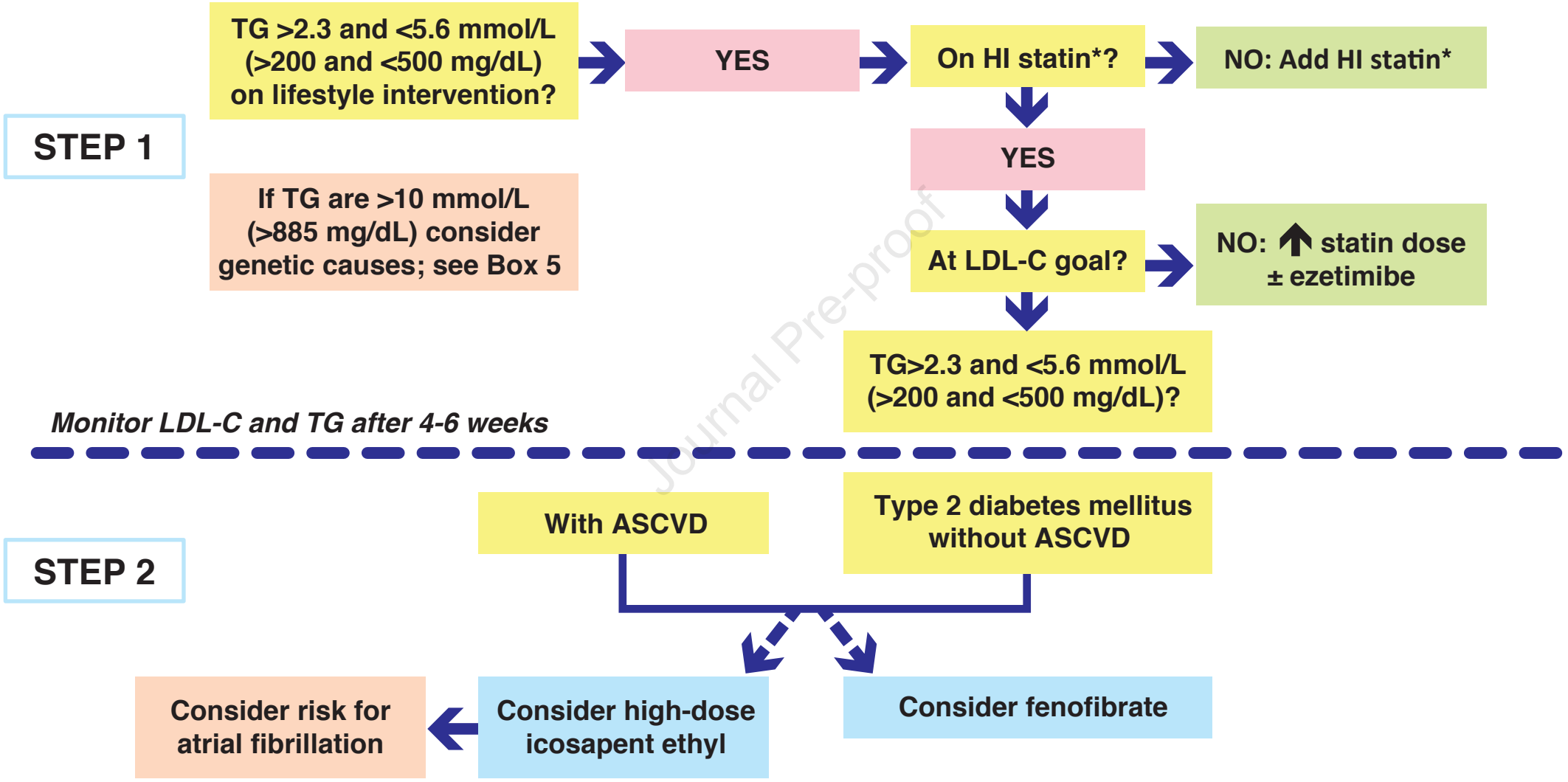
* HI statin: high-intensity statin or maximally tolerated statin therapy

Primary prevention adult patients with familial hypercholesterolemia



* HI statin: high-intensity statin or maximally tolerated statin

High-risk and very-high-risk patients with elevated TG



* HI statin: high-intensity statin or maximally tolerated statin therapy

HIGHLIGHTS

- This EAS Task Force gives practical guidance for combination lipid lowering therapy in high-risk and very-high-risk patients.
- Statin-ezetimibe is the first choice for managing elevated LDL-C; this should be upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in familial hypercholesterolaemia patients. A PCSK9 inhibitor may be added if LDL-C levels remain high.
- For type 2 diabetes mellitus patients with persistently high triglycerides on statin therapy, fenofibrate may be considered for both macro- and microvascular benefits.
- High-dose omega-3 fatty acids may be considered for managing elevated triglycerides (>2.3 mmol/L) on statin treatment, weighing the benefit versus risks.

Conflict of interest

The authors declare the following financial interests/personal relationships outside the submitted work.

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