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Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia

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Fenofibrate–statin combination therapy

A panel of European experts on lipids and cardiovascular disease discussed clinical approaches to managing cardiovascular risk in clinical practice, including residual cardiovascular risk associated with lipid abnormalities, such as atherogenic dyslipidaemia (AD). A simplified definition of AD was proposed to enhance understanding of this condition, its prevalence, and its impact on cardiovascular risk. Atherogenic dyslipidaemia can be defined by high fasting triglyceride levels ($\geq$2.3 mmol/L) and low high-density lipoprotein cholesterol (HDL-c) levels ($\leq$1.0 and $\leq$1.3 mmol/L in men and women, respectively) in statin-treated patients at high cardiovascular risk. The use of a single marker for the diagnosis and treatment of AD, such as non-HDL-c, was advocated. Interventions including lifestyle optimization and low-density lipoprotein (LDL)-lowering therapy with statins ($\pm$ ezetimibe) are implemented by all experts. Treatment of residual AD can be performed with the addition of fenofibrate, since it can improve the complete lipoprotein profile and reduce the risk of cardiovascular events in patients with AD. Specific clinical scenarios in which fenofibrate may be prescribed are discussed, and include patients with very high triglycerides ($\geq$5.6 mmol/L), patients who are intolerant or resistant to statins, and patients with AD and at high cardiovascular risk. The fenofibrate–statin combination was considered by the experts to benefit from a favourable benefit–risk profile. Cardiovascular experts adopt a multifaceted approach to the prevention of atherosclerotic cardiovascular disease, with lifestyle optimization, LDL-lowering therapy, and treatment of AD with fenofibrate routinely used to help reduce a patient's overall cardiovascular risk.

Conversion factors

- Cholesterol mg/dL = mmol/L × 38.6
- Triglycerides mg/dL = mmol/L × 88.5
- Glucose mg/dL = mmol/L × 18

Introduction

Statin therapy has long been the cornerstone of cardiovascular disease (CVD) prevention for reducing levels of atherogenic low-density lipoprotein cholesterol (LDL-c). Recently, efforts have been directed at finding approaches to further reduce LDL-c levels, and consequently the risk of cardiovascular (CV) events, with either high doses of statins or the combination of statin therapy and a non-statin drug (e.g. ezetimibe in the IMPROVE-IT trial[1]). However, therapy solely directed at reducing LDL-c levels will not address other lipid abnormalities present [e.g. high levels of triglycerides (TGs) and/or low levels of high-density lipoprotein cholesterol (HDL-c)], which contribute to the presence of a residual risk of CV events.

A meeting of European experts in CVD and lipids was convened in Paris, France, on 10 November 2014 to discuss current understanding of atherogenic dyslipidaemia (AD) and its associated macrovascular CV risk. A summary of the experts' discussion on the role of fenofibrate–statin combination therapy in reducing CV risk in patients with AD has recently been published.[2] The present article discusses the expert panel's own clinical approaches to managing CV risk in practice, with a specific focus on residual CV risk associated with AD.

Atherogenic dyslipidaemia and residual cardiovascular risk

A number of factors, both non-lipid [e.g. age, gender, smoking, increased alcohol consumption, sedentary lifestyle, diabetes mellitus (DM), obesity, hypertension] and lipid (e.g. raised LDL-c levels, elevated TGs, and/or low HDL-c levels), contribute to the CV risk. While statin therapy, together with lifestyle optimization, successfully lowers LDL-c levels and reduces the rate of CV events for many patients, those with persistent lipid abnormalities may still experience such events. This remaining CV risk has been termed 'residual CV risk', a part of which is dependent on lipid abnormalities other than LDL-c levels (*Box 1*).

Box 1 Definition of residual risk according to the Residual Risk Reduction initiative[3]

Residual CV risk is defined as the risk of CV events that persists in people despite achievement of treatment goals for low-density lipoprotein (LDL) cholesterol, blood pressure, and glycaemia according to current standards of care.

CV, cardiovascular.

The first hurdle in treating residual CV risk due to dyslipidaemia, particularly AD (characterized by elevated TG and low HDL-c levels; *Box 2* and *Figure 1*) is a general lack of awareness of the incidence and impact that residual CV risk can have. Educational programmes are therefore needed to raise awareness of residual CV risk associated with AD and the importance of treatment beyond LDL-lowering therapy.

Box 2 Definition of atherogenic dyslipidaemia

- AD is defined by the Residual Risk Reduction initiative as 'the imbalance between proatherogenic triglyceride-rich apolipoprotein B-containing-lipoproteins and antiatherogenic apolipoprotein A-I-lipoproteins (as in high-density lipoprotein, HDL)'.[3]
- To help enhance understanding, the experts proposed a simplified definition of AD: **AD can be defined as the presence of high fasting TG levels (≥2.3 mmol/L) and low HDL-c levels (≤1.0 and ≤1.3 mmol/L in males and females, respectively) in high-risk patients[a] on maximally tolerated statin therapy.**
  - Although LDL-c levels are normal or moderately increased in AD, the LDL particles are typically smaller and more dense.
- AD is a prevalent condition, especially in individuals at high CV risk, with T2DM, MetS,[4,5] chronic kidney disease, with familial combined hyperlipidaemia,[6] overweight women,[7] or women with polycystic ovary syndrome.[8]
- There is clearly a need to address this unmet challenge, which is becoming even more important with the rise in obesity, MetS and T2DM in emerging economies in Africa, Asia, and the Middle East.[3]

AD, atherogenic dyslipidaemia; CV, cardiovascular; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; TG, triglyceride; T2DM, type 2 diabetes mellitus.

[a]CV risk defined according to the European Society of Cardiology/European Atherosclerosis Society guidelines.[9]

Furthermore, it was the experts' opinion that clear goals for treatment of AD and ways to achieve these should be set to ensure that physicians, whether in primary- or secondary-care settings, can identify and treat patients with residual CV risk.

Measuring lipids in clinical practice

Lipids measured in clinical practice usually consist of total cholesterol, LDL-c, fasting TGs, and HDL-c. LDL-c and non-HDL-c (calculated) are considered the most important parameters and therefore used as goals for dyslipidaemia treatment.

In addition to these, a number of markers and goals for treatment of residual CV risk are described in *Figure 2*.[9–15] The use of a single parameter, e.g. non-HDL-c, may be particularly useful, as it is easy to measure and already recognized by international guidelines. It is recommended as a secondary target for patients with high TGs and DM, metabolic syndrome, or chronic kidney disease by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias.[9] Of note, non-HDL-c is recommended as a primary treatment target in all patients by the National Institute for Health and Care Excellence Lipid modification guidelines.[16]

Global approach to cardiovascular risk

The multifactorial nature of atherosclerotic CVD (ASCVD) risk supports the need for a multifaceted approach to its prevention. The experts routinely follow the approach presented in *Figure 3*, which focuses on three key aspects: (i) lifestyle optimization, (ii) LDL-c lowering, and (iii) treatment of AD.

Lifestyle optimization

The importance of getting patients to improve their diet, increase physical exercise levels, limit alcohol intake, quit smoking, and monitor their sleep pattern should not be understated or underestimated. Lifestyle changes may help improve AD, with a 5–10% weight reduction often enough to see improvement. Glycaemic control in patients with type 1 DM is primarily achieved through insulin management rather than lifestyle factors, whereas lifestyle changes have a bigger impact on type 2 DM (T2DM).

Low-density lipoprotein cholesterol-lowering therapy

Lipid-lowering therapy is usually initiated at the same time as lifestyle changes in high-risk and very-high-risk patients. LDL-c goals are set in line with current guidelines and the individual patient's CV risk (<2.5 and <1.8 mmol/L for high-risk and very-high-risk patients, respectively, in the ESC/EAS guidelines[9]). The IMPROVE-IT trial recently showed that LDL-c lowering to 1.4 mmol/L with ezetimibe–simvastatin combination resulted in a greater reduction in the overall 7-year rate of CV events compared with simvastatin alone [32.7 vs. 34.7% reduction, respectively; absolute risk reduction of 2.0% and hazard ratio of 0.936 (95% confidence interval: 0.89, 0.99); $P = 0.016$].[1] The beneficial effects of the ezetimibe–simvastatin combination therapy were more pronounced in patients with DM, who had a greater relative and absolute benefit compared with patients without DM.[18]

These results indirectly reinforce the ESC/EAS guidelines' approach of targeting lipids, and LDL-c in particular (*Box 3*).[9] Therefore, the strong position of the US guidelines[19] cautioning against non-statin treatment will likely be revised, as well as the current Class IIb recommendation for ezetimibe (for the treatment of hypercholesterolaemia, either for statin-intolerant patients or if goals are not reached) in the ESC/EAS guidelines.[9] As a result, future guidelines are likely to encourage further lowering of LDL-c to 1.4 mmol/L in patients at very high CV risk, highlighting that lower LDL-c levels are associated with further clinical benefits.

The experts noted that intensifying statin treatment to reach lower LDL-c levels may be difficult in some patients, e.g. frail patients with multiple pathologies who are already receiving other drugs, and that the majority of patients in clinical practice may not reach LDL-c levels as low as 1.4 mmol/L. Furthermore, the IMPROVE-IT study was conducted in patients at very high CV risk and was carried out over 7 years,[1] with a number needed to treat (NNT) at 7 years of 50. For patients at high CV risk, this combination therapy targeting LDL-c may not be cost-effective. One-third of patients still experienced CV events, even with very low LDL-c values, thereby supporting the need to address other lipid abnormalities that can be associated with residual CV risk (i.e. TG/HDL-c abnormalities).

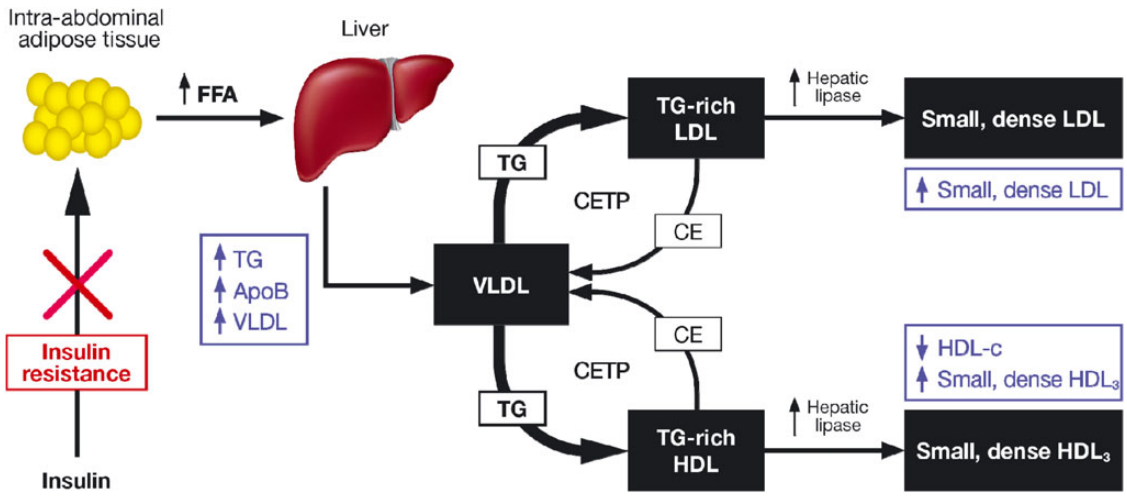

Figure 1 Pathophysiology of atherogenic dyslipidaemia in insulin resistance.[54] In adipose tissue, insulin resistance leads to impaired inhibition of TG hydrolysis and release of an increased amount of FFA, resulting in an increased production of TG and VLDL particles by the liver. CETP transfers TG from TG-rich VLDL to LDL (the resulting TG-rich LDL particles can undergo hydrolysis by hepatic lipase and lead to small, dense LDL particles) and HDL (with the hydrolysis of TG-rich HDL leading to lower levels of HDL cholesterol, increased proportion of small, dense HDL[3] and increased release of free Apo A-I). Apo, apolipoprotein; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.

Non-HDL-c

- Non-HDL-c (i.e. all the cholesterol carried by lipoproteins minus HDL-c) gives an assessment of the levels of atherogenic molecules, including LDL-c and TG-containing particles
- Non-HDL-c can be measured in both fasting and non-fasting states, thereby avoiding the variability associated with TG measurement. TGs are routinely measured in the fasting state; however, as non-fasting remnant TGs have been associated with an increase in all-cause mortality,[10] the experts noted that it is interesting to include this non-fasting element in the measure of non-HDL-c
- Although there is limited evidence supporting non-HDL-c as a better goal than LDL-c in non-diabetic patients, non-HDL-c levels may better predict CV risk than LDL-c in patients with T2DM, MetS, or chronic kidney disease[9]
- The experts noted that non-HDL-c is very easy to determine and captures the information of cholesterol carried by atherogenic ApoB-containing lipoproteins; however, it is still underused as a marker or goal for treatment of AD

Apolipoproteins (ApoA-I, ApoB, ApoA-I/ApoB ratio)

- ApoB was considered by the panel of experts as a better marker than LDL-c as it captures all the atherogenic particles (LDL, IDL, and VLDL)
- ApoA-I, ApoB, and their ratio may be particularly useful for situations where, based purely on LDL-c, TG, and HDL-c levels, physicians may not know whether lipid-lowering therapy should be initiated (e.g. in primary prevention) or intensified
- However, ApoB is not routinely assessed in clinical practice as it has not been standardized in some countries and, therefore, non-HDL-c is still the preferred marker used by the experts

Lp(a)

- Lp(a) is used as a marker of premature atherosclerosis, and should be measured once for CV risk assessment in patients at intermediate or high CV risk and with premature CVD, familial hypercholesterolaemia, family history of premature CVD, or recurrent CVD despite statin treatment.[11] However, Lp(a) is seldom measured in clinical practice, and is most often measured in hospital settings
- Reducing LDL-c and Lp(a) levels by lipoprotein apheresis was shown to improve CV outcomes in patients with Lp(a)-hyperlipoproteinemia and progressive CVD.[12] It was noted that intensification of lifestyle measures and lowering of LDL-c in these patients is crucial. There is also growing evidence associating Lp(a) with residual CV risk[13,14]

Remnants and small, dense LDL particles

- Remnants provide very important information for the progression of atherosclerosis in the coronary arteries.[15] A causal association between non-fasting remnant cholesterol contained in TG-rich lipoproteins and ischaemic heart disease has been shown[10]
- Remnants provide a key insight into the post-prandial phase, when most of the circulating lipoproteins are atherogenic. However, in clinical practice, remnants are not measured; in hospital settings, LpBC can be measured and this provides a better way of assessing remnants than the classical lipid analysis
- Remnants and small, dense LDL are a key focus in research, and remnants in particular could be used to assess residual CV risk in the future (and act as a treatment goal); however, remnants have not yet been evaluated as a marker for CV risk

Surrogate markers

- The experts noted that surrogate markers (e.g. carotid ultrasound) are used mainly in specialized clinics or lipid units and for research purposes. The use of coronary calcium score is increasing in clinical practice, mainly to help reclassify patients in terms of risk groups and to adjust treatment accordingly
- Other CV markers are C-reactive protein, urinary albumin excretion rate, plaques, or stenoses on CT coronary angiography or vascular echography, and arterial rigidity, which may be used to assess atherosclerosis, even in patients at LDL-c goals, and provide an indirect way of estimating remnants or non-HDL-c levels
- While these surrogate markers may help assess CV risk and provide a separate estimate from other classical risk factors, they will not evaluate the residual CV risk but could be used to analyze treatment efficacy

Figure 2 Experts' perspectives on the potential markers or goals for treatment of atherogenic dyslipidaemia and reducing residual cardiovascular risk. AD, atherogenic dyslipidaemia; Apo, apolipoprotein; CV, cardiovascular; CVD, cardiovascular disease; CT, computed tomography; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp, lipoprotein; LpBC, lipoprotein B-complex; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride; VLDL, very-low-density lipoprotein.

It will therefore be interesting to verify (i) whether the European guidelines will update their goals and, if so, what the new level will be; (ii) whether the American guidelines will change their recommendations and come back to goals; and (iii) what will happen with regard to recommendations for combination therapy.

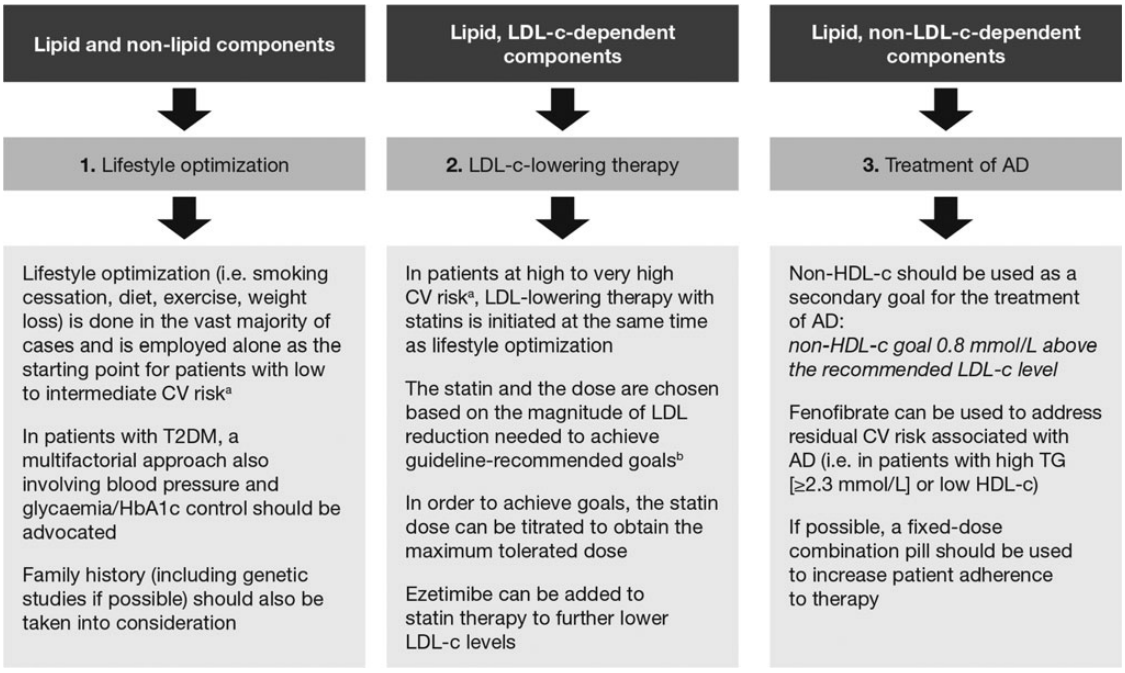

Figure 3 Global approach to cardiovascular risk taken by the experts. AD, atherogenic dyslipidaemia; CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus; TG, triglycerides. [a]CV risk as defined by the ESC/EAS guidelines[9]; [b]LDL goals (according to the ESC/EAS guidelines) are <2.5 mmol/L and <1.8 mmol/L for high-risk and very high-risk patients, respectively.[9]

Box 3 Guidelines

Experts tend to follow the ESC/EAS guidelines, which provide a comprehensive overview of the association between dyslipidaemia and increase in CV risk, and easy-to-follow guidance to provide a personalized treatment.[9] On the other hand, the US guidelines on the treatment of blood cholesterol to reduce atherosclerotic CVD in adults are not aimed at achieving goals for therapy, and are solely focused on LDL-c management.[17]

CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology.

Box 4 Why do we need to treat atherogenic dyslipidaemia?

Dyslipidaemias are one of the determinants of the risk of developing ASCVD.[9] In addition to LDL particles, which are often considered to be the most atherogenic lipoproteins, other ApoB-containing lipoproteins (e.g. TG-rich proteins and their remnants) contribute to intimal cholesterol deposition.[21] Lipoprotein size is a key determinant of atherogenesis, with remnants being able to penetrate the arterial intima and bind to and be retained by connective matrix tissue, thus directly contributing to plaque formation and progression.[21] This is particularly relevant to patients with AD, and provides the rationale that supports the use of additional treatment targeting AD, in combination with statins, for the modulation of residual CV risk.[22]

AD, atherogenic dyslipidaemia; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride.

Treatment of atherogenic dyslipidaemia

Analysis of the ACCORD-Lipid study reconfirmed the role of AD in residual CV risk, where patients receiving simvastatin and with controlled LDL-c levels had a 71% greater rate of major CV events if they also had TG/HDL abnormalities.[20] Thus, treatment of AD in high-risk patients (including patients with T2DM) could significantly reduce CV events (*Box 4*).

As a considerable proportion of high-risk patients cannot achieve recommended LDL-c goals, even with the highest tolerated dose of statin or with statin–ezetimibe, experts suggested that patients who achieve ≥50% reduction in LDL-c (as suggested by the ESC/EAS guidelines and the European guidelines on CVD prevention[9,23]) and who exhibit increased TG and/or decreased HDL-c levels are candidates for additional therapy targeting TG/HDL-c abnormalities. These have historically been treated with niacin or fibrates, including fenofibrate. Of note, fenofibrate has a most favourable pharmacological interaction with statins compared with another fibrate, gemfibrozil,[24] and is therefore more suited to use in combination with statins.

Use of niacin

Niacin is being phased out in Europe following results from the HPS2-THRIVE study, where niacin–laropiprant, in combination with statins, failed to reduce the rate of major CVD events vs. statins alone and increased the risk of serious adverse events.[25] Historical data and the

apparent benefit of niacin may have been due to its LDL-lowering action; however, in the era of potent LDL-lowering therapy with statins, niacin use may have become redundant.

Niacin's unfavourable benefit–risk ratio means that the experts often prefer other options, such as fenofibrate, especially in patients with T2DM. Some experts suggested that niacin may still be used in statin-intolerant patients, who have elevated lipoprotein a [Lp(a)] levels and isolated low HDL-c levels, or as an alternative to fenofibrate–statin therapy; albeit in both cases there is a lack of compelling evidence. Niacin side effects should be monitored, especially in Asian populations. Of note, agents currently undergoing Phase III clinical evaluation, e.g. proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, seem to exert a positive effect on Lp(a),[26] with many more positive effects on lipoprotein metabolism.

Use of fenofibrate

The benefit of fenofibrate–statin combination therapy in patients with AD was illustrated in the ACCORD-Lipid study,[20] where patients with T2DM and AD receiving fenofibrate–simvastatin benefited from a 31% risk rate reduction in CV death, myocardial infarction, or stroke compared with patients receiving simvastatin alone.[27] These findings contribute to the body of evidence supporting the benefits of combination therapy in reducing CV events in patients with AD.

The experts believe that the use of non-statin drugs, and especially fenofibrate, in the treatment of AD should be clarified in future guidelines. A barrier to this occurring to date may have been the lack of primary evidence from clinical trials. Although the benefit of fenofibrate–statin in patients with AD and T2DM is supported by indirect evidence from the pre-specified dyslipidaemic subgroup in the ACCORD-Lipid trial and a *post hoc* analysis from the FIELD trial,[20,28] lack of compelling new data on the impact of fenofibrate on CVD mortality and morbidity risk since the last version of the guidelines may mean that future guidelines may require further evidence before making a strong change in their recommendations.

Fenofibrate has a Class I recommendation for TG lowering in the ESC/EAS guidelines.[9] To avoid fluctuations in TG measurements, it may be beneficial to use non-HDL-c as the goal (at 0.8 mmol/L above the LDL-c goal) to initiate fenofibrate therapy. Likewise, the guidelines could state the level of residual CV risk above which fenofibrate should be considered, together with TG and/or HDL-c levels (i.e. the degree of AD) beyond which the NNT for benefit is low enough to recommend fenofibrate prescription. Of note, the 5-year NNT for fenofibrate for these patients was 20 in the ACCORD-Lipid trial[27] (*Box 5*).

Box 5 Experts' view on future guidelines

- The experts believe that future guidelines should focus on combination therapy in high-risk patients [e.g. highlighting the beneficial effects of ezetimibe–simvastatin combination (as seen in the IMPROVE-IT trial[1]) or PCSK9 inhibitors (as seen in OSLER and ODYSSEY studies[29])], as well as the need for combination treatment in patients with AD.
- The panel agreed that a clear message regarding the patient groups in which fenofibrate is approved is warranted. Notably, it should be stated that fenofibrate can also be used as a first-line treatment in patients with AD for whom statins are contraindicated or who cannot tolerate statins.

AD, atherogenic dyslipidaemia.

Importance of fixed-dose combination therapy

Fixed-dose combination (FDC) therapy may be key for improving patient adherence, as experienced in the field of hypertension and T2DM. The experts agreed that patient adherence to chronic therapies (and in particular to lipid-lowering therapies) is not optimal, especially in primary prevention. Adherence is crucial in secondary prevention, and adherence to CV drugs has been shown to result in a reduction in the rates of CV events.[30]

From experience, the experts felt that reducing the pill burden with FDC therapy would help improve adherence, particularly for patients with co-morbidity and concomitant drugs (e.g. patients with T2DM), although there is a lack of clinical data supporting this.

The favourable efficacy and safety profile of the fenofibrate–statin combination makes it particularly attractive,[31] especially in secondary prevention. Of note, statins may have drug–drug interactions with other fibrates. A strategy of alternate-day dosing may also be an effective therapeutic option in patients who are intolerant to statin or combination pills, as it was shown to be as effective as same-day dosing in controlling lipid parameters,[32] although its effects on long-term CV outcomes are not known. The experts also remarked that different dose options for statins should be available in combination pills.

Fenofibrate use in clinical practice

Fenofibrate is used by all members of the expert panel to treat residual AD (i.e. AD present in patients receiving statin therapy). While there is a lack of direct evidence from clinical trials on the effect of fenofibrate on ASCVD prevention, fenofibrate is widely used in clinical practice to help to reduce residual CV risk associated with AD in patients with and without diabetes (treatment of AD is not an end goal in its own right).

The approved indications for fenofibrate are captured in *Box 6*, with *Figure 4* outlining situations where fenofibrate can be prescribed in line with its licensed indications. Specific clinical scenarios in which the experts found that fenofibrate may be particularly useful are discussed in the next sections, based on a patient's lipid profile, T2DM status, concomitant therapies, and CV risk.

Which lipid abnormalities are routinely treated with fenofibrate?

A pooled analysis of three randomized Phase III trials conducted in patients with mixed dyslipidaemia evaluating fenofibric acid (the active metabolite of fenofibrate) in combination with the most powerful statins (simvastatin,

atorvastatin, and rosuvastatin) showed that combination therapy significantly improved the lipoprotein profile seen in AD.[34] A subgroup analysis of patients with T2DM also showed that combination therapy lead to a significantly greater improvement of the lipid profile compared with either monotherapy.[35] The lipid effects of fenofibrate (*Figure 5*) may help to reduce the macrovascular CV risk of patients with AD.

In addition to the scenarios given in *Figure 4*, fenofibrate therapy is sometimes considered by the experts in their clinical practice in patients who have not attained their LDL-c goal despite statin (or statin–ezetimibe) therapy, and who also have either elevated TG and low HDL-c levels or CVD and a high or very high CV risk (risk defined using the ESC/EAS guidelines[9]). The effects of fenofibrate on LDL-c lowering are minimal, although it may decrease atherogenic small, dense LDL particles; fenofibrate is largely prescribed to treat AD.

Box 6 Approved indications for fenofibrate[33]

Fenofibrate has been approved by the EMA as an adjunct to improving diet and lifestyle for the treatment of:

- Severe hypertriglyceridaemia, with or without low levels of HDL-c
- Mixed hyperlipidaemia, when a statin is contraindicated or not tolerated
- Mixed hyperlipidaemia in patients at high CV risk, in addition to a statin when triglycerides and HDL-c levels are inadequately controlled

CV, cardiovascular; EMA, European Medicines Agency; HDL-c, high-density lipoprotein cholesterol.

Is fenofibrate used as a first-, second-, or third-line treatment?

Fenofibrate may be used as monotherapy in patients with very high TGs ($\geq$5.7 mmol/L) in order to prevent acute pancreatitis (*Figure 4*). It may also be prescribed as a first-line intervention for the primary and secondary prevention of CV events in patients who are resistant or intolerant to statins but have moderately elevated TG levels, and are at very high CV risk. The recent EAS consensus paper on statin-associated muscle symptoms suggested to first decrease the statin dose in patients with muscle symptoms, adding ezetimibe $\pm$ fibrate (not gemfibrozil) only after the third re-challenge to obtain goal LDL-c levels.[36] Fenofibrate is used as a second- or third-line intervention, after lifestyle optimization and LDL-lowering therapy with statin $\pm$ ezetimibe.

In their clinical practices, the experts sometimes consider the use of fenofibrate in patients with AD and insulin resistance (i.e. without elevated LDL-c) as a first-line therapy in primary prevention. Many patients without a history of CVD but with AD and metabolic syndrome, abdominal obesity, or T2DM can also be considered to be at high CV risk and suitable for fenofibrate–statin therapy.[37]

Based on a patient's lipid profile	
High TG levels	• Patients with severe hypertriglyceridaemia (TGs ≥5.7 mmol/L) to prevent acute pancreatitis
Patients with AD	• High-risk primary or secondary prevention in patients with LDL-c on goal but with residual AD[a]
Based on a patient's concomitant therapies	
First line	• Patients with severe hypertriglyceridaemia (TGs ≥5.7 mmol/L) • Patients who are intolerant or resistant to statins and are at high or very high CV risk
Second line	• Patients treated with statins for LDL-c lowering and who have attained their LDL-c goal but have elevated TGs (>2.3 mmol/L after 3 months of statin therapy) or residual AD[a]
Third line	• Patients treated with statins and ezetimibe for LDL-c lowering, who have attained their LDL-c goal but have elevated TGs (>2.3 mmol/L after 3 months of statin–ezetimibe therapy) or residual AD[a]
Based on a patient's diabetes status	
Diabetic patient	• Primary or secondary prevention in patients with T2DM on statin treatment with high TGs (>2.3 mmol/L after 3 months of statin therapy) ± low HDL-c
Non-diabetic patient	• MetS and obese (visceral) patients in secondary prevention on statin with high TGs (>2.3 mmol/L after 3 months of statin therapy) and low HDL-c • Non-diabetic patient receiving high doses of statins, with residual AD, and who recently suffered from a myocardial infarction or stroke
Based on a patient's CV risk status	
High CV risk	• Patients at high CV risk, with goal LDL-c levels, but with high TGs (>2.3 mmol/L) after correction of modifiable causes of hypertriglyceridaemia
Very high CV risk	• Patients at very high CV risk on statin therapy with LDL-c on or close to goal levels, with high TGs (>2.3 mmol/L) ± low HDL-c

Figure 4 Experience regarding the use of fenofibrate in clinical practice. AD, atherogenic dyslipidaemia; CV, cardiovascular; HDL-c, high-density lipoprotein cholesterol; MetS, metabolic syndrome; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride. [a]That is, non-HDL-c goals not attained.

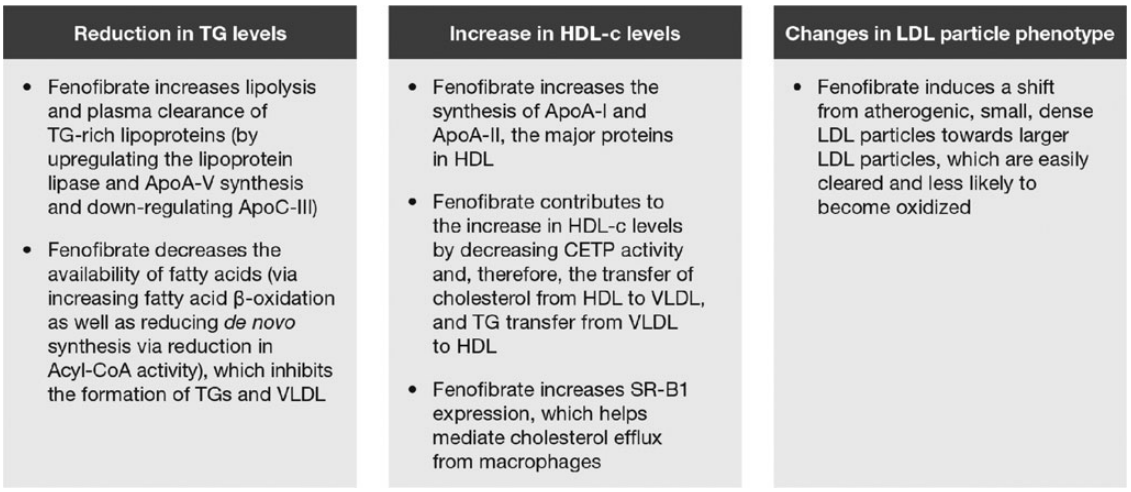

Figure 5 Lipid-modifying effects of fenofibrate.[55,56] Acyl-coA, acetyl coenzyme A; Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; HDL-c, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; SR-B1, scavenger receptor B-I; TG, triglyceride; VLDL, very-low-density lipoprotein.

Is fenofibrate used in diabetic as well as non-diabetic patients?

Diabetes is a coronary artery disease equivalent and increases CV risk, and, as such, patients with T2DM are considered at high or very high CV risk [ESC/EAS guidelines,[9] ESC and European Association for the Study of Diabetes (EASD) guidelines[38]]. It is key to control AD if a patient is concomitantly diabetic, which can be done with fenofibrate. Although fenofibrate use in T2DM is prevalent—diabetic patients often present with AD—it should be noted that fenofibrate use is independent from T2DM status but is associated with the presence of AD. Furthermore, the ESC/EAS guidelines recommend that drugs to lower TGs should be considered in subjects with high levels (>2.3 mmol/L) that cannot be lowered by lifestyle measures, and who are at high total CV risk[9]; in neither case is T2DM a requisite for combination therapy in selected patients. There is, therefore, a role for fenofibrate as an add-on to LDL-c-lowering therapy in patients with or without T2DM (*Figure 4*).

At the expert opinion level, fenofibrate is sometimes prescribed in patients with T2DM and AD, although there may not be any indications of subclinical atherosclerosis, or in patients with microvascular complications who are being treated with high doses of statins. Furthermore, although clinical evidence comes from the diabetic population, patients with insulin resistance, or those who are overweight or obese, may also benefit from fenofibrate treatment.[39,40] The meta-analysis conducted by Sacks *et al.*[41] clearly showed that patients with high TGs and low HDL-c who received fibrates experienced a reduction in CVD event rate. Fenofibrate may be especially beneficial in patients with high cardiometabolic burden. In animal models, fenofibrate peroxisomal proliferator-activated receptor-α (PPARα) activation-mediated actions reduced adiposity, improved peripheral insulin action, and exerted beneficial effects on pancreatic β-cells.[42]

Beyond its approved lipid-modifying benefits, fenofibrate is also valued by clinicians for its PPARα-mediated reductions of fibrinogen and pro-inflammatory markers levels, and improvements to the flow-mediated dilatation.[43] Evidence supports the fenofibrate-associated slowing of the progression of diabetic retinopathy (delaying the need for laser photocoagulation therapy), neuropathy (delaying the need for non-traumatic amputations), and albuminuria.[44–46] Fenofibrate has been approved for the reduction in the progression of diabetic retinopathy (in addition to blood pressure, glucose, and lipid control) in Australia.[47]

In which cardiovascular risk category is fenofibrate used?

Fenofibrate should be used in patients at high or very high CV risk, according to the ESC/EAS guidelines (*Table 1*) to specifically control TGs and HDL-c (*Figure 4*).[9] Lifestyle changes should be intensified in patients at low or intermediate CV risk, prior to considering the addition of a new drug.

The experts recommend the use of fenofibrate in patients with AD at high cardiometabolic risk, and also in patients with AD and proof of subclinical atherosclerosis. Of note, some experts are also using fenofibrate irrespective of the CV risk.

The experts stated that fenofibrate would be most useful and relevant in secondary prevention [e.g. for patients at LDL-c goals (or not) with maximum tolerated doses of statin (or statin–ezetimibe) therapy and with high TGs (±low HDL-c)], although it could be considered for primary prevention in patients with T2DM. Combination treatment to improve adherence would be particularly relevant in secondary prevention.

Several experts discussed the need to move away from using a different approach for primary and secondary prevention, and rather to assess the CV risk of a patient for the next 10 years. This approach is also encouraged by the European guidelines on CVD prevention in clinical practice, which considers categorization between primary and secondary prevention an arbitrary process that does not take

Table 1 High and very high cardiovascular risk definition[9,23]

High risk	Very high risk
• Markedly elevated single-risk factor (e.g. familial dyslipidaemia and severe hypertension) • T1DM or T2DM without CV risk factors or target organ damage • Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m^2) • Patients with a SCORE[a] 5–10%	• Patients with CVD • T2DM or T1DM with ≥1 risk factor and/or target organ damage • Severe chronic kidney disease (GFR <30 mL/min/1.73 m^2) • Patients with a SCORE[a] ≥10%

CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; GFR, glomerular filtration rate; SCORE, Systemic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
[a]SCORE is used as a risk assessment system and estimates the 10-year risk of a fatal atherosclerotic event.

into account the fact that atherosclerosis is a continuous and progressive process.[23] In the particular case of patients with T2DM, where calculating CV risk scores does not seem accurate, the ESC/EASD guidelines recommend classifying these as high or very high CV risk, depending on the presence of concomitant risk factor and target organ damage.[38]

Long-term clinical safety experience with fenofibrate

It was the experts' view that fenofibrate is a well-tolerated drug that is not associated with serious safety considerations. Fenofibrate appears to be better tolerated in combination with statins than gemfibrozil, which affects the pharmacokinetics of statins and increases risk of myotoxicity.[24]

Although fenofibrate has been associated with increased serum creatinine levels, controversy still exists as to whether these increases represent a true deterioration of renal function.[48] These increases are reversible upon cessation of the drug[49] and clinical trials have shown that fenofibrate was not associated with an increase in end-stage renal disease compared with placebo.[20] There is clinical evidence showing that fenofibrate-induced increases in homocysteine levels do not translate into increases in CV risk,[50] with patients benefiting from fenofibrate treatment despite the increase in homocysteine levels. Finally, fenofibrate can reduce uric-acid levels[51] (implicated in atherosclerosis, hypertension, and renal disease[52]) and also reduce the progression of micro- and macro-albuminuria.[20]

Overall, experts would avoid using fenofibrate in patients with end-stage renal failure, significant pancreatic disease (unless they have severe hypertriglyceridaemia), and history of gallstone disease, and they would exercise caution in patients with chronic renal disease (estimated glomerular filtration rate 15–60 mL/min); treatment should be discontinued if serum creatinine levels increase by >50% upper limit of normal.[53] They would monitor for myalgia, and hepatic and kidney functions[53]; experts also mentioned that they would monitor for gallstones and myopathy in patients with a history of symptoms associated with lipid-lowering therapy.

Conclusion

While lipid abnormalities such as AD (that can be present even in statin-treated patients at LDL-c goals) carry a residual CV risk, awareness of this condition is not optimal and can jeopardize efforts to reduce CV risk. In addition to building awareness of AD and its associated residual CV risk, the panel of experts agreed that clear markers and goals for treatment (such as non-HDL-c) need to be further established to ensure that the residual CV risk associated with TG/HDL-c abnormalities is appropriately treated.

With the recent advances in the field of CV prevention, and notably with the results from studies evaluating combination therapy of statins with non-statin drugs (e.g. ezetimibe in the IMPROVE-IT trial) or alternative LDL-lowering therapy with PCSK9 inhibitors, the experts suggested that the current statin-based approach to CVD prevention is likely to change. Indeed, as lower LDL-c levels are attained more easily, the meaning of residual CV risk may need to be amended as well as its treatment.

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