NON- HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND CARDIOVASCULAR DISEASE IN PATIENTS WITH DIABETIC DYSLIPIDAEMIA

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Elevated levels of blood lipids are one of the major risk factors for cardiovascular (CV) disease in patients with type 2 diabetes mellitus. Diabetic dyslipidaemia is characterised by the presence of potentially atherogenic lipids, including high levels of plasma triglycerides (TGs), mild-to-moderately elevated levels of low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C). Statin therapy to reduce LDL-C levels is the mainstay of treatment practice to reduce CV risk. However, despite achieving targets for LDL-C, patients with diabetic dyslipidaemia remain at a high risk of residual CV events. Hence there is a need to target other components (i.e. elevated TGs) of the atherogenic dyslipidaemia that are not affected by treatment with statins. This review highlights the clinical benefits of using non-HDL-C, a single marker that includes all atherogenic lipoproteins, as a leading treatment target to reduce the residual CV risk.

KEYWORDS: cardiovascular risk; diabetic dyslipidaemia; fenofibrate; low-density lipoprotein cholesterol; non-high-density lipoprotein cholesterol; statins; triglycerides; omega-3 fatty acids

ХОЛЕСТЕРИН, НЕ СВЯЗАННЫЙ С ЛИПОПРОТЕИНАМИ ВЫСОКОЙ ПЛОТНОСТИ, И СЕРДЕЧНО-СОСУДИСТЫЕ ЗАБОЛЕВАНИЯ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ И ДИСЛИПИДЕМИЕЙ

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Повышенный уровень липидов в крови является одним из основных факторов риска развития сердечно-сосудистых заболеваний (ССЗ) у пациентов с сахарным диабетом 2 типа (СД2). Дислипидемия на фоне СД характеризуется наличием потенциально атерогенных липидов, включая высокие уровни триглицеридов (ТГ) в плазме, умеренно повышенным уровнем холестерина липопротеинов низкой плотности (ХС ЛПНП) и низким уровнем холестерина липопротеинов высокой плотности (ХС ЛПВП). Терапия статинами, направленная на снижение уровня ХС ЛПНП, является основным методом лечения с целью снижения риска развития ССЗ, обусловленных атеросклерозом. Однако, несмотря на достижение целевых уровней ХС ЛПНП, у пациентов с дислипидемией на фоне СД сохраняется высокий риск развития остаточных нежелательных явлений, связанных с заболеваниями сердечно-сосудистой системы. Следовательно, существует необходимость обращать внимание на другие компоненты (например, повышенные уровни ТГ) атерогенной дислипидемии, на которые не влияет терапия статинами. В этом обзоре подчеркнуты клинические преимущества использования уровня ХС не-ЛПВП как единственного маркера, который включает все атерогенные липопротеины, в качестве основной цели терапии, направленной на снижение риска развития остаточных явлений, связанных с заболеваниями сердечно-сосудистой системы.

КЛЮЧЕВЫЕ СЛОВА: риск развития сердечно-сосудистых заболеваний; дислипидемия на фоне сахарного диабета; фенофибрат; липопротеины низкой плотности; липопротеины, отличные от липопротеинов высокой плотности; статины; триглицериды; омега-3 жирные кислоты

DIABETIC DYSLIPIDAEMIA

A major risk factor contributing to an increased risk of cardiovascular (CV) disease and CV mortality in patients with type 2 diabetes mellitus (T2DM) is dyslipidaemia [1]. Diabetic dyslipidaemia is characterised by the presence of qualitative and quantitative atherogenic lipid abnormalities, including increased plasma triglycerides (TGs), low levels of high-density lipoprotein cholesterol (HDL-C), and mildly elevated levels of low-density lipoprotein cholesterol (LDL-C), with a predominance of small, dense LDL particles [2, 3].

STATINS AND CV RISK

The therapeutic choice for treating diabetic dyslipidaemia is primarily aimed at reducing the large burden of associated CV risk [4]. Evidence from randomised clinical trials (RCTs) [5-8], as well as from meta-analyses [9], has demonstrated that a reduction in LDL-C levels with statin therapy is associated with a marked reduction in CV events in patients with T2DM with or without prior CV disease. Therefore, guidelines recommend statins as the first-line lipid-lowering therapy in patients with diabetes, in combination with lifestyle modifications [10, 11]. The European

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Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines recommend an LDL-C target of <1.8 mmol/L in very-high-risk patients (the large majority of patients with diabetes) and <2.6 mmol/L in high-risk patients [10]. Addition of ezetimibe or, in selected cases, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, is recommended for patients who are unable to attain the LDL-C targets with the maximum tolerated dose of statins [12].

However, it is now known that even if the recommended LDL-C targets are met, a considerable residual CV risk remains [13]. A meta-analysis including >18,000 patients with diabetes from 14 RCTs revealed that despite an effective reduction in CV events per mmol/L reduction in LDL-C on statin therapy, 15.6% of patients with diabetes reported a CV event vs 13.7% of those without diabetes [9]. Similarly, in the TNT study, while 80 mg/day of atorvastatin demonstrated a 22% relative risk reduction in CV events compared with 10 mg/day of atorvastatin, cumulative incidence over 5 years showed that 1 in 11 patients experienced CV events [6]. Furthermore, results from landmark trials have shown that the rate of CV events in patients with diabetes on statins was much higher than those without diabetes treated with placebo (Table 1) [5, 7, 14-16].

The IMPROVE-IT trial showed that ezetimibe added to simvastatin resulted in an incremental decrease in LDL-C levels and improved CV outcomes in patients with diabetes, compared with those on simvastatin alone. However, despite having LDL-C levels at 1.4 mmol/L, treatment with simvastatin plus ezetimibe revealed a CV event rate of 30% at 5 years [17]. The FOURIER study also demonstrated that addition of a PCSK-9 inhibitor, evolocumab, to statin therapy lowered LDL-C levels to 0.78 mmol/L in patients with diabetes; however, these patients showed a greater CV risk compared with patients without diabetes at higher LDL-C levels (2.3 mmol/L) [18]. Taken together, these results suggest that the residual risk of CV disease is higher in patients with diabetes, indicating the need to target other components of atherogenic dyslipidaemia that are not affected by treatment with statins.

Table 1: Residual CV risk in patients with and without diabetes treated with lipid-lowering agents

Study name, Reference	Treatment	Events	Event rate without diabetes (%)		Event rate with diabetes (%)	
			Statin	Placebo	Statin	Placebo
HPS [5]	Simvastatin	CHD death, nonfatal MI, stroke, and revascularisation	19.8	25.7	33.4	37.8
CARE [7]	Pravastatin	CHD death, nonfatal MI, CABG, and PTCA	19.0	25.0	29.0	37.0
LIPID [14]	Pravastatin	CHD death and nonfatal MI	12.0	15.0	19.0	23.0
PROSPER [15]	Pravastatin	CHD death, nonfatal MI, and stroke	13.1	16.0	23.1	18.4
ASCOT-LLA [16]	Atorvastatin	CHD death and nonfatal MI	4.9	8.7	9.6	11.4
IMPROVE-IT [17]	Statin + Ezetimibe	CV death, nonfatal MI, unstable angina requiring rehospitalisation, revascularisation, and stroke	30.2	30.8	40.0	45.5
FOURIER [18]	Statin + Evolocumab		11.4	13.0	14.4	17.1

Notes: ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; CABG, coronary-artery bypass grafting; CARE, The Cholesterol and Recurrent Events; CHD, coronary heart disease; CV, cardiovascular; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HPS, Heart Protection Study; IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LIPID, The Long-term Intervention with Pravastatin in Ischaemic Disease; MI, myocardial infarction; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PTCA, percutaneous transluminal coronary angioplasty

EMERGING TARGETS FOR TREATING RESIDUAL CV RISK IN PATIENTS WITH DIABETES

The results from the ACCORD-Lipid study substantiated the effect of atherogenic dyslipidaemia on residual CV risk, where patients treated with simvastatin with controlled LDL-C levels had a >70% higher risk of CV events when the TG and HDL-C levels were not targeted [19, 20]. Genetic studies have also shown that elevated levels of TG-rich lipoproteins and remnant cholesterol (calculated as the difference of LDL-C plus HDL-C from total cholesterol [TC]) led to an increased risk of CV events and all-cause mortality. [21, 22] Hence, optimising secondary targets should be considered a top priority in patients at high CV risk despite achieving LDL-C targets [23]. Findings from population-based studies have drawn attention to non-HDL-C as a better predictor of CV risk compared with LDL-C alone among patients treated with statins [24, 25]. Non-HDL-C essentially represents the aggregate of all lipoproteins that have atherogenic potential, namely LDL-C, very low-density lipoprotein (VLDL) cholesterol, intermediate-density lipoprotein cholesterol, lipoprotein (a), chylomicrons and their TG-rich remnants [24, 26]. A meta-analysis including >60,000 statin-treated patients from 8 trials reported that patients who achieved LDL-C targets but not non-HDL-C goals had a 32% higher risk of CV events than those who met the non-HDL-C targets [25]. Therefore, there has been a renewed emphasis on the use of non-HDL-C as a potential target for the treatment of residual CV risk in patients with dyslipidaemia and specifically those with insulin-resistance [27].

Besides the simplicity of including all atherogenic lipoproteins into a single marker, the use of non-HDL-C is also more practical as it can be easily calculated (TC minus HDL-C) without the need for fasting samples and with no additional costs [26]. The International Atherosclerosis Society (IAS) and National Institute for Health and Care Excellence (NICE) guidelines have both recommended the use of non-HDL-C as a primary therapeutic goal for patients with CV risk [28, 29]. Conversely, the ESC/EAS, and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines recommend the use of non-HDL-C as a secondary goal in high-risk individuals once LDL-C goal is achieved. The recommended goal for non-HDL-C is the LDL-C goal plus 0.8 mmol/L [10, 11].

THERAPEUTIC APPROACHES TO TARGET NON-HDL-C

As aforementioned, the LDL-C component of non-HDL-C in high-risk patients can be treated with the highest tolerated dose of a statin or a statin plus ezetimibe (or a PCSK-9 inhibitor) combination [5, 17, 18]. The most commonly used therapies to target the remaining lipid components of the non-HDL-C focus mainly on TGs and include omega-3 fatty acids and fibrates [10].

Omega-3 fatty acids

Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been used to lower TG levels in patients with hypertriglyceridaemia. They act by reducing the production of hepatic VLDL and by increasing postprandial lipoprotein lipase levels [30]. Several RCTs have demonstrated that the addition of n-3 fatty acids (at 4 mg/day doses) to statin therapy is effective in lowering serum TG levels in patients with diabetes and other CV risk factors [31-33].

A recent study, REDUCE-IT, evaluated if highly purified EPA reduces ischaemic events in statin-treated patients with hypertriglyceridemia (1.52 to 5.63 mmol/L) and high CV risk. This double-blind, randomised, placebo-controlled trial enrolled >8000 patients who were followed-up for a median of 4.9 years. A 25% reduction in CV death, nonfatal myocardial infarction (MI), stroke, revascularisation, or unstable angina was seen in patients treated with EPA (2 mg twice daily)-statin therapy compared with those on placebo-statin therapy (P<0.001). A similar benefit was seen in patients with and without diabetes who constituted approximately 58% of the enrolled patients in each treatment arm. A 19.7% greater median reduction in TG levels from baseline was seen in the EPA group compared with the placebo group (P<0.001) [34].

Fibrates

Fibrates are agonists of the peroxisome proliferator-activated receptor-α, which act via transcription factors to control lipid metabolism and arterial function. Fibrates are highly effective in reducing plasma TGs and moderately increasing HDL-C levels [35].

Two prospective RCTs, ACCORD and FIELD, studied the clinical effects of fenofibrate in patients with diabetes. In the ACCORD study, a subgroup of patients (n=5518) on statin therapy were randomised to receive either fenofibrate or placebo. Although the primary endpoint (composite of nonfatal MI, nonfatal stroke, or death from CV causes) was not met, the clinical benefit of adding fenofibrate to statin therapy was evident in a prespecified subgroup of patients with atherogenic dyslipidaemia (high TG [≥2.3 mmol/L] and low HDL-C [≤0.9 mmol/L] levels). A 31% risk reduction in CV events was demonstrated with the combination therapy compared with statin monotherapy in patients with atherogenic dyslipidaemia, who constituted 17% of the overall study population [36]. Similarly, in the FIELD study, fenofibrate showed a 27% reduction in CV events in patients with diabetic dyslipidaemia but not in those without elevated TGs at baseline [37]. The CV benefit of fibrates was further confirmed by a meta-analysis of 5 placebo-controlled trials comparing the effect of different fibrates in patients with and without atherogenic dyslipidaemia. This analysis showed a 35% reduction in coronary events with fibrates specifically in patients with atherogenic dyslipidaemia [38]. A meta-regression analysis of fibrate-based trials demonstrated a reduction of 43% and 54% in coronary events per mmol/L reduction of TGs in patients with and without hypertriglyceridaemia, respectively [39].

The AACE guidelines therefore recommend the use of fibrates or omega-3 fatty acids (2–4 mg per day) in patients with severe hypertriglyceridaemia (TG >500 mg/dL) and to further reduce CV outcomes in patients with TG concentrations ≥200 mg/dL and HDL-C <40 mg/dL, on a background of optimised statin therapy [11]. The ESC/EAS guidelines recommend the use of fenofibrate in combination with statins for high-risk patients with TG levels >2.3 mmol/L despite optimised statin treatment [10].

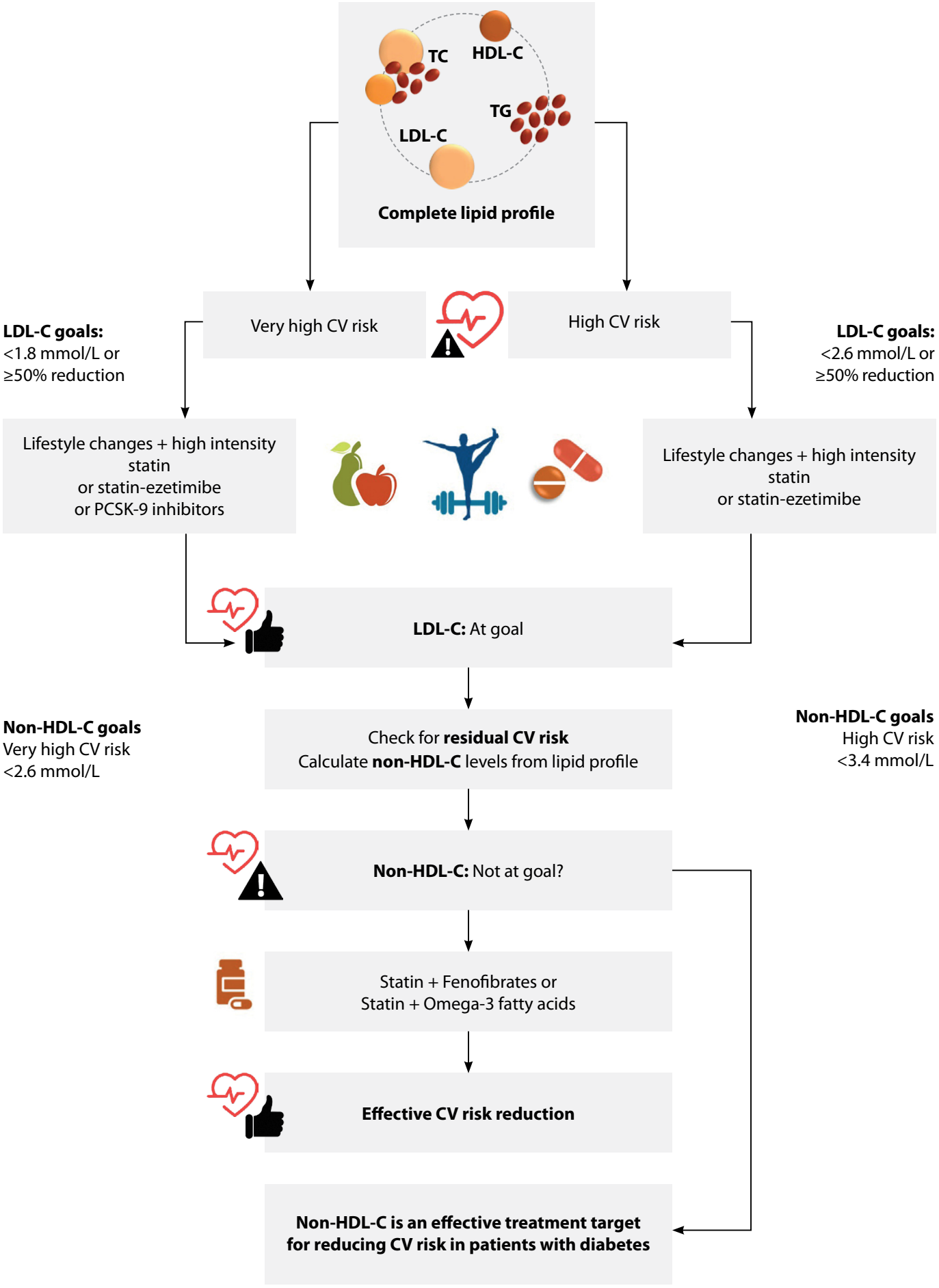

Figure 1: Treatment considerations to reduce CV risk in patients with diabetes: CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK-9, proprotein convertase subtilisin/kexin type 9; TG, triglycerides; TC, total cholesterol

SUMMARY

Statins are recommended as the first-line lipid-lowering therapy in combination with lifestyle modifications in patients with diabetes to reduce the risk of CV events. However, despite aggressive LDL-C lowering with statin therapy (±ezetimibe and PCSK9 inhibitors), a considerable residual CV risk remains specifically in patients with T2DM. Hence, there is a need for optimising secondary targets in patients who are at high CV risk despite achieving LDL-C goals. Non-HDL-C, a single marker that includes all atherogenic lipoproteins, has been recommended for use as a secondary target in high-risk individuals, as it provides a better measure of CV risk compared with LDL-C alone. Clinical benefits of using omega-3 fatty acids and fenofibrate in reducing the CV risk in patients with atherogenic dyslipidaemia has been well established. Therefore, the key to reducing CV risk in patients with diabetes is to use a comprehensive CV risk reduction approach of lifestyle optimisation, LDL-C management and treatment of all the atherogenic lipoproteins by targeting non-HDL-C (Figure 1).

ADDITIONAL INFORMATION

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