Management of elevated serum triglycerides in type 2 diabetes: A pragmatic approach

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In people with type 2 diabetes and elevated serum triglycerides, a healthy lifestyle and adequate adherence form the foundation of treatment (after secondary and iatrogenic causes of hypertriglyceridaemia [HTG] have been excluded). Because of the significant risk of pancreatitis, those with type 2 diabetes and triglyceride (TG) levels ≥10 mmol/L should be considered for referral to a specialist lipid clinic. Treatment with fenofibrate should be considered when TG levels are ≥4.5 to <10 mmol/L despite optimised statin therapy and diabetes control. If TG levels remain ≥4.5 mmol/L, pharmaceutical grade, highly concentrated, licensed omega-3 fish oils (PG omega-3 fish oils) should be prescribed in addition to fenofibrate and statins. PG omega-3 fish oils should be added to statins if fenofibrate is poorly tolerated or in those at risk of adverse events. TG levels ≥2.3 to <4.5 mmol/L, despite optimised statin therapy and diabetes control, should trigger consideration of dual therapy with statin plus fenofibrate, especially for those with concurrent established vascular disease or end-organ damage. Dual therapy with PG omega-3 fish oils may be considered for those with TG levels ≥2.3 to <4.5 mmol/L if fenofibrate is poorly tolerated or in young people following acute coronary syndrome. Here we describe pragmatic and, where possible, evidence-based guidelines to help improve the management of HTG in people with type 2 diabetes mellitus.

Article points

1. Treatment of elevated triglyceride (TG) levels in people with type 2 diabetes should be based on fasting TG levels.
2. Before starting therapy, clinicians should exclude secondary and iatrogenic causes and encourage individuals to follow a healthy lifestyle.
3. TG levels ≥10 mmol/L should trigger referral to a specialist lipid clinic, as there is a significant risk of pancreatitis.
4. TG levels between ≥4.5 and <10 mmol/L should be actively treated, including, as necessary, dual and triple therapy.
5. Treatment for TG levels between ≥2.3 and <4.5 mmol/L will depend on the presence of other risk factors, such as established vascular disease and end-organ damage.

Key words

- Dyslipidaemia
- Fenofibrate
- Hypertriglyceridaemia
- Omega-3 fish oils
- Triglycerides
- Type 2 diabetes

Authors' details can be found at the end of the article.

People with type 2 diabetes mellitus are at increased risk of cardiovascular disease (CVD; Donahoe et al, 2007; Sinclair, 2012). Several factors are associated with this risk, including hypertriglyceridaemia (HTG; NICE, 2008b). The management of severe HTG (triglyceride [TG] levels >10 mmol/L), which is a risk factor for pancreatitis, has been well described in recent papers (Sandhu et al, 2011; Schaefer et al, 2011). However, there is a need for further guidance regarding the management of elevated TG levels <10mmol/L. This article offers pragmatic suggestions and a practical algorithm to aid implementation of NICE guidance (NICE, 2008a; 2008b) and

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1. Lipid profiles that do not specifically measure TG levels may not capture fully the risks associated with dyslipidaemia in type 2 diabetes.
2. TG levels >1.7 mmol/L drive the production of more atherogenic particles in both the LDL and HDL subfractions, and the preponderance of small, dense LDL particles in people with type 2 diabetes confers a highly atherogenic phenotype at normal LDL-cholesterol concentrations.
3. Baseline and annual assessment of people with type 2 diabetes should therefore measure concentrations of TGs, HDL-cholesterol, LDL-cholesterol and total cholesterol.
4. A full lipid assessment should also be performed once individuals are optimised on statins to assess other aspects of dyslipidaemia that are associated with the residual cardiovascular disease risk, such as hypertriglyceridaemia (HTG).

encourage the appropriate identification and management of HTG as part of primary and secondary CVD prevention in type 2 diabetes.

Guideline development

This guideline was developed from a round-table discussion among professionals in diabetes, cardiology, lipidology, chemical pathology and general practice, chosen for their expertise and geographical spread across the UK. Where possible, suggestions were evidence based. Where evidence was lacking, the group agreed a suggested pragmatic approach.

Following these discussions, two drafts were circulated electronically to offer all authors the opportunity to comment. The meeting and guideline development was funded by an unrestricted educational grant from Abbott Healthcare Products and reviewed by Abbott for scientific accuracy only. However, Abbott Healthcare Products did not comment on, or contribute to, any stage of the guideline development.

Measuring serum triglycerides

Serum TGs measured by clinical biochemistry laboratory tests are present in all lipoprotein classes, but particularly in very-low-density lipoprotein (VLDL), which reflect hepatic TG synthesis (Schulze et al, 2004), and chylomicrons, which reflect absorption of dietary lipids. Chylomicrons are usually present in the blood for 3–6 hours after a meal and are metabolised following a fast of 10–12 hours (Lin et al, 2010). VLDL levels typically start rising substantially at TG concentrations ≥2.26 mmol/L (Schulze et al, 2004).

Lipid profiles that do not specifically measure TG levels may not capture fully the risks associated with dyslipidaemia in type 2 diabetes. As LDL, chylomicrons and VLDL carry one apoB molecule, LDL-cholesterol levels may be normal (Reiner et al, 2011) despite elevated TG levels (Miller et al, 2011). TG levels >1.7 mmol/L drive the production of more atherogenic particles in both the LDL and HDL subfractions (Chapman et al, 2011). Furthermore, the preponderance of small, dense LDL particles in people with type 2 diabetes confers a highly atherogenic phenotype at normal LDL-cholesterol concentrations (Miller et al, 2011). Baseline and annual assessment of people with type 2 diabetes should therefore measure concentrations of TGs, HDL-cholesterol, LDL-cholesterol and total cholesterol. A full lipid assessment should also be performed once individuals are optimised on statins to assess other aspects of dyslipidaemia that are associated with the residual CVD risk, such as HTG.

Screening for HTG can be performed in the fed or fasting state. Postprandial TG levels may predict CVD risk as accurately as fasting levels. However, differences in the time of postprandial blood sampling can markedly influence fasting TG levels (Kannel and Vasan, 2009). People with type 2 diabetes who have HTG in the fed state should therefore be reassessed after fasting for 10–12 hours, during which time they should drink only water, black tea or black coffee. They should take their normal evening dose of insulin and delay the morning dose until their post-test meal, and should miss the morning dose of any oral antidiabetes drug.

Managing HTG in type 2 diabetes

At present, there is no agreement between the Joint British Societies (JBS) and NICE on the TG concentration that is associated with an increased risk of CVD. The JBS guidelines recommend increasing the CVD risk score by a factor of 1.3 when TG levels are >1.7 mmol/L (JBS, 2005). NICE suggests considering adding a fibrate when TG levels are >2.3 mmol/L despite statins in people at high cardiovascular risk, such as those with type 2 diabetes (NICE, 2008a). The specialists' view summarised in this article and the algorithm (*Figure 1*) reflect NICE's recommendations.

Statins are the mainstay of hyperlipidaemia management in type 2 diabetes. However, considerable residual CVD risk remains despite the potency of statins in reducing LDL-cholesterol levels. In the HPS (Heart

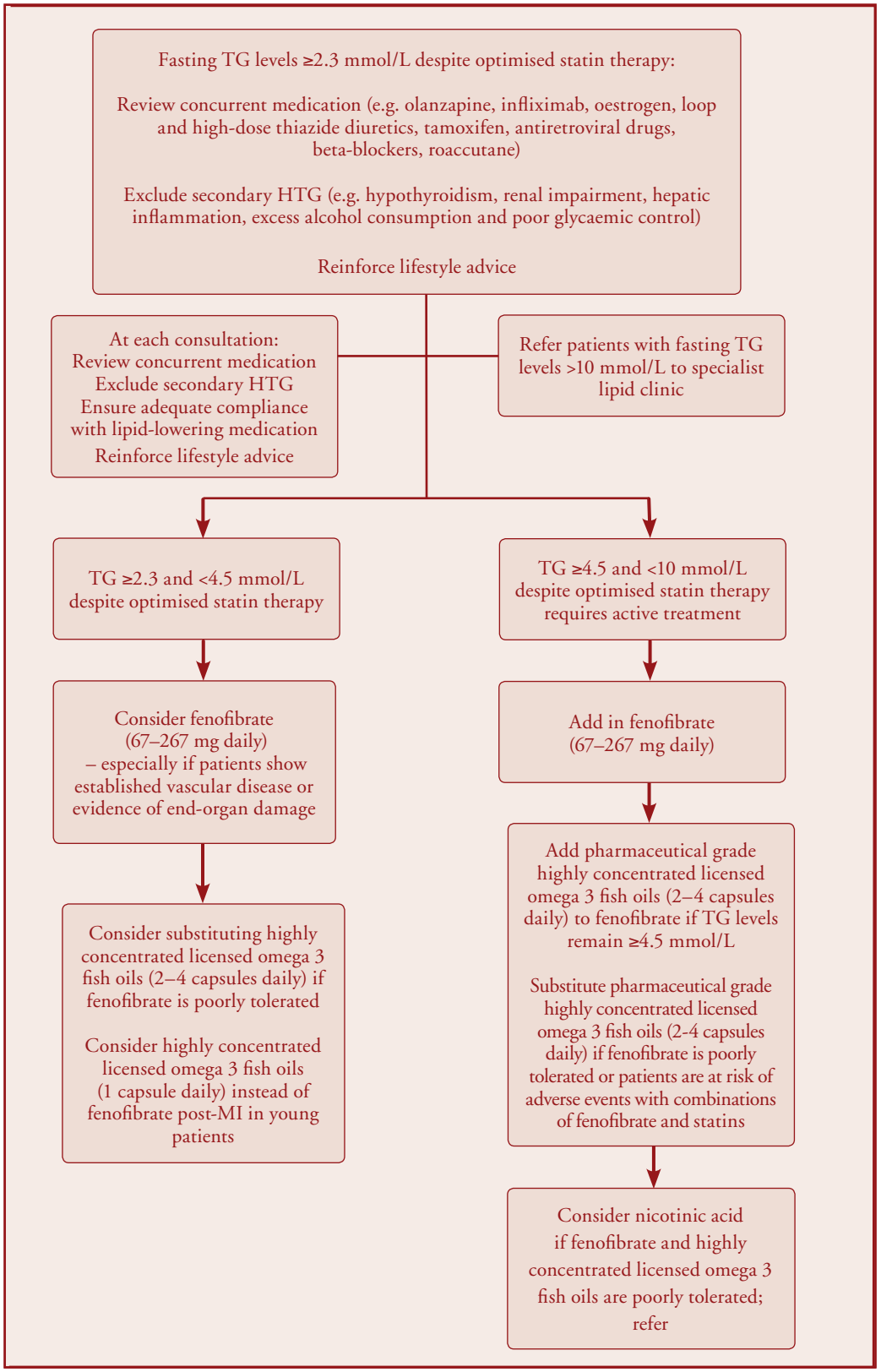

Figure 1. Pragmatic approach to the management of hypertriglyceridaemia (HTG) in type 2 diabetes mellitus to aid implementation of NICE recommendations. MI = myocardial infarction ; TG = triglyceride.

"At each consultation, clinicians should reinforce the importance of controlling body weight, taking regular physical activity, avoiding tobacco, eating low saturated fat, low sugar diets and avoiding excess alcohol, irrespective of pharmacological regimen."

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1. Before initiating hypertriglyceridaemia (HTG) treatment, clinicians should exclude and manage secondary and iatrogenic causes.
2. Secondary causes of HTG include hypothyroidism, renal impairment, excess alcohol consumption and poor glycaemic control.
3. Potential iatrogenic causes include olanzapine, infliximab, oestrogen, loop and high-dose thiazide diuretics, tamoxifen, antiretroviral drugs (and protease inhibitors in particular), beta-blockers and isotretinoin.
4. Whenever practicable, an alternative drug should be substituted and triglyceride levels re-evaluated after a few weeks.
5. At each consultation, clinicians should reinforce the importance of controlling body weight, taking regular physical activity, avoiding tobacco, eating a low-saturated-fat, low-sugar diet and avoiding excess alcohol, irrespective of pharmacological regimen.

Protection Study), statins reduced the event rate by 24%. Nevertheless, 19.8% of statin-treated participants, considering the whole cohort, experienced a major vascular event by 5 years' follow-up (HPS Collaborative Group, 2002). Indeed, exposure to 40 mg simvastatin or 80 mg fluvastatin daily is associated with a residual 10-year coronary risk of 33.8% (Krobot et al, 2012). Moreover, TG levels often remain elevated in statin-treated individuals in "real world" practice (Hamilton et al, 2011; Leiter et al, 2011), which may contribute to the residual risk.

Ezetimibe may reduce LDL-cholesterol levels when maximally tolerated doses of statins fail to reduce LDL-cholesterol to target levels, but seems to have relatively little effect on TG levels (Rotella et al, 2010). Ezetimibe is therefore not included in these recommendations.

Principles of management

Before initiating treatment for HTG, clinicians should exclude and manage secondary causes, including hypothyroidism, renal impairment, excess alcohol consumption and poor glycaemic control (Schaefer et al, 2011). Clinicians also need to exclude iatrogenic causes of HTG, such as:

- Olanzapine (Albaugh et al, 2011).
- Infliximab (Castro et al, 2011).
- Oestrogen (Lin et al, 2010).
- Loop and high-dose thiazide diuretics (Weidmann et al, 1992).
- Tamoxifen (Chang et al, 2009).
- Antiretroviral drugs, and protease inhibitors in particular (Montessori et al, 2004).
- Beta-blockers (Shaw et al, 1978).
- Isotretinoin (Zane et al, 2006).

Whenever practicable, clinicians should substitute an alternative drug and re-evaluate TG levels after a few weeks.

At each consultation, clinicians should reinforce the importance of controlling body weight, taking regular physical activity, avoiding tobacco, eating low-saturated-fat, low-sugar diets (Solano and Goldberg, 2006; Oh and Lanier, 2007) and avoiding excess alcohol, irrespective of pharmacological regimen. Furthermore, before changing pharmacological treatment, clinicians should ensure that patients adhere adequately (≥80%) to the maximum tolerated dose.

In a UK study, 41% of people with diabetes were taking >80% of their statin dose 5 years after the start of treatment. This is lower adherence than that found in the primary (70%) and secondary prevention trials (81–94%; Donnelly et al, 2008), suggesting that the improved outcomes associated with statins in these studies may not be realised in clinical practice. Clinicians should monitor patients as outlined in *Table 1*.

HTG >10 mmol/L

Severe HTG (TG level >10 mmol/L) is associated with an increased risk of acute pancreatitis (Sandhu et al, 2011; Schaefer et al, 2011). GPs should therefore refer individuals with TG levels >10 mmol/L to a specialist lipid clinic for urgent evaluation and treatment.

HTG between ≥4.5 and <10 mmol/L

People with diabetes and TGs between ≥4.5 and <10 mmol/L despite optimised statin therapy (with or without ezetimibe) and diabetes control should receive fenofibrate (67–267 mg daily). NICE noted that gemfibrozil is associated with more drug–drug interactions than fenofibrate. Furthermore, the cardiovascular evidence base supporting bezafibrate is weaker than that for fenofibrate. Bezafibrate also seems to have a less marked effect on TG levels than fenofibrate. Finally, few studies have evaluated ciprofibrate. NICE therefore regarded fenofibrate as the first-line fibrate (NICE, 2008a).

Fibrates reduce TG levels by up to 60% (Oh and Lanier, 2007). In the FIELD (Fenofibrate Intervention and Event Lowering) study, fenofibrate reduced the risk of a coronary event by 11% compared with placebo in people with type 2 diabetes. Although the difference was not statistically significant, rates of certain secondary endpoints – non-fatal myocardial infarction (MI; relative risk [RR], 0.76), total CVD events (RR, 0.89) and coronary revascularisation (RR, 0.79) – significantly declined in the fenofibrate arm (Keech et al, 2005).

Table 1. Monitoring suggestions for people with type 2 diabetes mellitus and hypertriglyceridaemia.

Pharmacological agent	Liver function tests (LFTs)	Creatine kinase test	Renal function
Atorvastatin Fluvastatin Pravastatin Rosuvastatin Simvastatin	Perform LFTs: • Before treatment • 12 weeks after the start of treatment or a dose increase • Periodically (e.g. every 6 months) thereafter. NICE does not recommend routine monitoring Perform LFTs in those who develop signs or symptoms consistent with hepatic injury People who show increased liver enzymes require close monitoring • Discontinue if AST or ALT persistently remain >3 times ULN	Routine CK monitoring is not required in asymptomatic individuals Measure CK before starting statins in the following situations: • Renal impairment • Hypothyroidism • Personal or family history of hereditary muscular disorders • History of muscular toxicity with a statin or fibrate • Previous history of liver disease • Substantial alcohol use Consider measuring CK level before starting statins in those aged >70 years with predisposing factors for rhabdomyolysis Consider measuring pretreatment CK level and monitoring during therapy where interactions or genetic background could increase statin plasma levels If baseline CK level is >5 times ULN, re-measure 5–7 days later. Do not start treatment if CK level remains >5 times ULN Measure CK level in those reporting muscle pain, cramps or weakness, especially when accompanied by malaise or fever. Cease treatment if CK level is >5 times ULN	Consider assessing renal function during routine follow-up of those treated with 40 mg rosuvastatin
Fenofibrate	Consider monitoring serum transaminases every 3 months during first 12 months of treatment • Interrupt treatment if AST or ALT >3 times ULN or increases by >100 IU		Measure creatinine level during first 3 months of treatment and periodically thereafter Interrupt treatment if creatinine level increases to >50% of ULN
Pharmaceutical grade, highly concentrated, licensed omega-3 fish oils	Regularly monitor AST and ALT in individuals with hepatic impairment, especially those taking 4 capsules daily		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK=creatine kinase; ULN=upper limit of normal.

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1. If triglyceride (TG) levels remain ≥4.5 mmol/L, the addition of 2–4 capsules of pharmaceutical grade, highly concentrated, licensed omega-3 fish oils to fenofibrate and statin therapy should be considered.
2. Each capsule of pharmaceutical grade, highly concentrated, licensed omega-3 fish oils contains 460 mg eicosapentaenoic acid ethyl ester and 380 mg docosahexaenoic acid ethyl ester.
3. Clinicians should be aware of the increased risk of myopathy when combining a fibrate and a statin.
4. Combining fish oil and a statin reduces TG levels by an additional 30% compared with statin monotherapy.

In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, fenofibrate reduced TG levels by approximately 26%, compared with approximately 10% with placebo, when added to simvastatin in people with type 2 diabetes. However, no significant difference emerged in rates of primary outcome (non-fatal MI, non-fatal stroke or cardiovascular death) between fenofibrate (2.2%) and placebo (2.4%; hazard ratio 0.92; ACCORD Study Group, 2010).

Both FIELD (Keech et al, 2007) and ACCORD (Ismail-Beigi et al, 2010) suggested that fenofibrate produced beneficial effects on microvascular disease in people with type 2 diabetes. FIELD suggested that fenofibrate reduced requirements for laser treatment of diabetic retinopathy (Keech et al, 2007). In ACCORD, intensive treatment (target HbA_{1c} level <42 mmol/mol [6.0%]) delayed the onset of albuminuria and the emergence of certain indices consistent with ocular complications and neuropathy. However, intensive treatment did not reduce the risk of advanced microvascular conditions (Ismail-Beigi et al, 2010).

If TG levels remain ≥4.5 mmol/L, clinicians could consider prescribing 2–4 capsules of pharmaceutical grade, highly-concentrated, licensed omega-3 fish oils (PG omega-3 fish oils) in addition to fenofibrate and statin. Each capsule contains 460 mg eicosapentaenoic acid (EPA) ethyl ester and 380 mg docosahexaenoic acid (DHA) ethyl ester.

Dual therapy with PG omega-3 fish oils plus statin is indicated if fenofibrate is poorly tolerated or individuals are at risk of adverse events with fenofibrate. For example, those taking a medication with a narrow therapeutic index that is metabolised by cytochrome (CYP) 2C19 (e.g. warfarin and several antiepileptic drugs), CYP2A6 (e.g. valproic acid) and especially CYP2C9 (e.g. warfarin and phenytoin) could be at risk of adverse events during treatment with fenofibrate. (Bezafibrate may offer an alternative to moving directly to PG omega-3 fish oils for some of those with poor tolerance of fenofibrate.) Clinicians should be cognisant of the increased risk of myopathy when combining a fibrate and a statin.

Combining fish oil and a statin reduces TG levels by an additional 30% compared with statin monotherapy (Oh and Lanier, 2007). During JELIS (Japan Eicosapentaenoic acid Lipid Intervention Study; Yokoyama et al, 2007), Japanese participants (16% of whom had diabetes) with total cholesterol ≥6.5 mmol/L received 1800 mg EPA daily added to a statin. After a mean of 4.6 years, TG concentrations decreased significantly from baseline by 9% in the EPA group and by 4% with statin monotherapy (controls).

The primary endpoint (any major coronary event) occurred in 2.8% of the EPA group and 3.5% of controls, a 19% relative reduction. The number of unstable angina cases and non-fatal coronary events declined by 24% and 19%, respectively. In participants with a history of coronary artery disease, EPA reduced the rate of major coronary events by 19% compared with controls (8.7% and 10.7%, respectively). In those without a history of coronary artery disease, EPA reduced major coronary events by 18% compared with statin monotherapy, although the difference was not statistically significant (1.4% and 1.7%, respectively; Yokoyama et al, 2007).

More recent studies (Alpha Omega [Kromhout et al, 2010], OMEGA [Rauch et al, 2010] and SU.FOL.OM3 [SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids; Galan et al, 2010]) failed to show that omega-3 polyunsaturated fatty acids (PUFAs) improved major cardiovascular outcomes. However, a greater proportion of participants received statins in these studies than in previous trials and participants were "very well treated" with antithrombotics and antihypertensives (Kromhout et al, 2012).

In contrast, in naturalistic practice, TG levels often remain elevated despite statin therapy (Hamilton et al, 2011; Leiter et al, 2011), suggesting that people with diabetes and elevated TG levels do not receive the "state of the art" treatment used in the recent studies (Kromhout et al, 2012). Consequently, the outcomes in the most recent studies of omega-3 PUFAs may not translate to general clinical practice.

Side effects associated with omega-3

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1. People with type 2 diabetes are at increased risk of cardiovascular disease (CVD), which is associated with several factors including hypertriglyceridaemia (HTG).
2. Despite the potency of statins in reducing LDL-cholesterol concentration, a considerable residual CVD risk remains and triglyceride (TG) levels are often elevated.
3. In line with the JBS guidelines, clinicians could consider thresholds for detailed clinical enquiry and possible treatment of TG levels >2.3 mmol/L in those at especially high risk according to their CV risk assessment scores.
4. The practical recommendations suggested in this article should aid implementation of NICE guidance, encourage GPs to identify and manage HTG proactively, and thus help to prevent CVD in people with type 2 diabetes.

PUFAs may include fishy aftertaste and mild gastrointestinal upset (Oh and Lainer, 2007). However, supplementation with up to 1 g of omega-3 PUFA daily is well tolerated, with the exception of dysgeusia, and does not increase bleeding risk (Kromhout et al, 2012).

Niacin potentially reduces TG levels by up to 50% (Oh and Lanier, 2007). However, side effects, including flushing, pruritus, nausea, hepatitis and triggering migraine, can prove dose limiting (Brunzell, 2007). The combination of nicotinic acid/laropirant (Tredaptive) is known to cause less flushing thus having a more favourable side-effect profile (Viljoen and Wierzbicki, 2010). It is recommended that GPs without a specialist interest should not prescribe nicotinic acid and derivatives.

HTG between ≥2.3 and <4.5 mmol/L

People with diabetes and TG levels between ≥2.3 and <4.5 mmol/L despite optimised statin therapy (with or without ezetimibe) and diabetes control should be considered for fenofibrate (67–267 mg daily), especially in the presence of concurrent established vascular disease or end-organ damage. For example, as mentioned above, fenofibrate reduces the risk of microvascular complications (JBS, 2005; Keech et al, 2007). In line with the JBS guidelines (JBS, 2005), clinicians could consider thresholds for detailed clinical enquiry and possible treatment of levels >2.3 mmol/L in those at especially high risk according to their CV risk assessment score.

Clinicians could consider prescribing 2–4 capsules of PG omega-3 fish oils in addition to optimised statin treatment if fenofibrate is poorly tolerated. It is also recommended that younger patients with a history of acute coronary syndrome and TG levels between ≥2.3 and <4.5 mmol/L despite optimised statin therapy should receive dual therapy with PG omega-3 fish oils.

This recommendation is based on NICE guidelines, which recommend eating ≥7 g of omega-3 PUFAs per week, from two to four portions of oily fish, as secondary prevention following an MI. NICE adds that people who suffered an MI within the last 3 months and who cannot consume sufficient fish could take ≥1 g daily of a formulation containing omega-3-acid ethyl esters licensed for secondary prevention post-MI. Treatment should last for up to 4 years (NICE, 2007).

Conclusion

People with type 2 diabetes are at increased risk of CVD, which is associated with several factors including HTG. Despite statins' potency at reducing LDL-cholesterol level, a considerable residual CVD risk remains and TG levels are often elevated. The practical recommendations suggested in this article should aid implementation of NICE guidance, encourage GPs to identify and manage HTG proactively, and thus help to prevent CVD in people with type 2 diabetes.

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Acknowledgements

The preparation of this review was supported by an unrestricted educational grant from Abbott Healthcare Products, who did not actively contribute to the discussions or comment on the recommendations. Abbott reviewed the final piece for scientific accuracy, but did not suggest any changes. The authors would like to acknowledge the editorial and logistical assistance of ROCK medical communications.

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