Managing dyslipidaemia in the context of diabetes

Mike Kirby

People with diabetes have an increased risk of cardiovascular complications, including acute coronary syndrome, stroke, heart failure and arrhythmias. The background to this risk for the development of cardiovascular complications is multifactorial and our understanding of the nature of atherosclerotic disease has progressed considerably. This article explores the latest thinking on the link between the various facets of dyslipidaemia and cardiovascular risk and reviews current evidence for lipid management in people with diabetes.

People with diabetes have an increased risk of cardiovascular complications, including acute coronary syndrome, stroke, heart failure and arrhythmias. Data suggest that people with diabetes, without prior cardiovascular disease, have the same rate of myocardial infarction as people without diabetes who have had previous events (Haffner et al, 1998; Malmberg et al, 2000; Donahoe et al, 2007). Chronic heart failure affects one in five patients with diabetes, which is four-fold greater than the general population (Rubler et al, 1972). In addition, while improvements have been seen in recent decades in mortality rates in people with diabetes, the progress has been limited to the male population (Gregg et al, 2007).

The background to this risk for the development of cardiovascular complications is multifactorial and our understanding of the nature of atherosclerotic disease has progressed considerably. The concept that atherosclerosis is a gradual process, leading to narrowing of the arteries until such a point that a thrombus forms and occludes a vessel, is naive. The concept was originally questioned by pathologists who showed that most myocardial infarctions are caused by low-grade stenosis (Falk et al, 1995). The current approach is to define atherosclerotic plaques as either: stable, which can lead to high grade obstruction; or unstable, which are vulnerable to rupture and show a high incidence of thrombi (Davies, 1996).

The initial phase of the development of atherosclerosis is endothelial dysfunction caused by hyperglycaemia with or without hypertension and dyslipidaemia and the adverse effect of adipose tissue-derived inflammatory cytokines. These include tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). The effect of this is to produce adhesion molecules, inflammatory mediators and cytokines that stimulate the involvement of inflammatory cells such as monocytes, which then enter the vessel wall and further stimulate the inflammatory response by interacting with oxidised low-density lipoproteins (LDLs). In addition to this, there is a reduction in the release of nitric oxide (NO), leading to vessel

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Learning objectives

After reading this article the participant should be able to:

1. Outline the underlying process in the development of atherosclerosis and its contribution to major adverse cardiovascular events.
2. Define the relationship between lipid levels and cardiovascular risk in people with diabetes.
3. Describe the merits of the various options for lipid management in people with diabetes.

Key words

- Cardiovascular risk
- Cholesterol
- Dyslipidaemia

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Page points

1. Plaques in people with diabetes are more likely to rupture, with consequent thromboembolic events, because of the inflammatory process within.
2. In addition to the effect on the arterial wall, there is a subset of people with diabetes who acquire diabetic cardiomyopathy during the course of this disease.
3. In diabetes, LDL cholesterol may not be significantly elevated compared with matched individuals without the disease, but is a smaller more dense and atherosclerotic particle.

constriction (Xu and Zou, 2009). Subsequently, the monocytes differentiate into macrophages and foam cells, which further stimulate the release of inflammatory mediators (Hansson, 2005). What can be seen at this stage is a fatty streak. The platelet hyperactivity that is present in diabetes probably contributes to the further development of lesions at this stage (Ross, 1999). Eventually, more complicated lesions occur and the core of the plaque becomes necrotic. This necrotic core is protected by a fibrous cap, and it is those lesions which have a thin and vulnerable fibrous cap that are likely to become unstable plaques (Hansson et al, 1988).

Plaques in people with diabetes are more likely to rupture, with consequent thromboembolic events, because of the inflammatory process within (Moreno et al, 2000). Recent techniques using intra-vascular ultrasound with virtual histology (IVUS-VH) have advanced our knowledge of plaque morphology (Lindsey et al, 2009).

In addition to the effect on the arterial wall, there is a subset of people with diabetes who acquire diabetic cardiomyopathy during the course of this disease. The nature of this process in not clearly defined, but there are functional and structural changes in the cardiac muscle that cause cardiac enlargement, increased stiffness and impaired diastolic function, which eventually leads to heart failure (Devereux et al, 2000). Heart failure is more common in the presence of poor glucose control, suggesting that hyperglycaemia may be an important contributor (Lind et al, 2011).

Clearly, good blood glucose control (i.e. reducing hyperglycaemia and avoiding hypoglycaemia in the process), particularly in the early stages of the disease, good blood pressure control throughout, and attention to dyslipidaemia is critically important in people with diabetes to prevent this atherosclerotic process (Colhoun et al, 2004; Holman et al, 2008).

Lipid levels and cardiovascular risk

In diabetes, LDL cholesterol may not be significantly elevated compared with matched individuals without the disease, but is a smaller more dense and atherosclerotic particle (Mazzone et al, 2008).

The well-established treatment approach is to focus on the use of LDL cholesterol-lowering drugs such as statins. Statin therapy reduces cardiovascular events by 25–50% (Collins et al, 2003; Colhoun et al, 2004); however, there still appears to be an excess residual cardiovascular risk among statin-treated people with diabetes compared with those without the disease (Costa et al, 2006). This residual risk may result from lipoprotein abnormalities that occur in diabetes and which are not adequately addressed by statin therapy (Mazzone et al, 2008).

Dyslipidaemia in type 2 diabetes is characterised by increased concentrations of triglyceride-rich lipoproteins, decreased concentrations of high-density lipoprotein (HDL) cholesterol and abnormalities in the composition of triglyceride-rich HDL and LDL lipoprotein particles (Garvey et al, 2003; Deeg et al, 2007). HDL is a very complex lipoprotein particle and changes in its composition may affect its atherosclerotic properties (Mazzone, 2007). The failure of cholesterol ester transfer protein inhibition with torcetrapib to protect against cardiovascular events suggests that HDL particle composition may be a more

Box 1. High-density lipoprotein cholesterol functionality: relevance to athero- and vasculoprotection (Chapman, 2011).

- Regulation of glucose metabolism
- Cholesterol homeostasis and cellular cholesterol efflux
- Endothelial repair
- Anti-inflammatory activity
- Anti-oxidative activity
- Anti-apoptotic activity
- Anti-thrombotic activity
- Anti-protease activity
- Vasodilatory activity
- Anti-infectious activity

important consideration than HDL cholesterol level in the reduction of cardiovascular risk (Barter et al, 2007). *Box 1* examines the relevance of HDL cholesterol functionality to athero- and vasculoprotection.

The case for non-HDL cholesterol

It is likely that combined dyslipidaemia may confer a higher magnitude of risk than elevated LDL cholesterol alone (Assman and Schulte, 1992). Triglycerides appear to be an independent risk factor (Austin et al, 1998), although they may be a marker of low HDL cholesterol. Non-HDL cholesterol may be defined as the difference between total and HDL cholesterol and thus represents cholesterol carried on all the potentially pro-atherogenic particles (Hsai, 2003; see *Figure 1*). The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommended non-HDL cholesterol as a secondary target in lipid lowering, after gaining adequate control of LDL cholesterol, if the triglycerides were elevated (≥200 mg/dL [2.3 mmol/L]; Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). By measuring total cholesterol and HDL cholesterol, and calculating non-HDL cholesterol, we can avoid the potential limitations of triglycerides as a marker of coronary heart disease (CHD) risk and instead measure something that directly reflects the cholesterol content of all the particles that may be pro-atherogenic. Another advantage of non-HDL cholesterol measurement is that it does not need to be done in the fasting state. Non-HDL cholesterol may be, therefore, a readily obtainable, inexpensive and convenient measure of CHD risk that may be superior to LDL cholesterol in many respects (Hsai, 2003).

A study by Lu et al (2003) highlighted the predictive value of non-HDL cholesterol for CHD and its potential role in the management of diabetic dyslipidaemia. It could therefore be considered a secondary target after achieving the total and LDL cholesterol targets as recommended by NICE: 4 and 2 mmol/L, respectively (NICE, 2009).

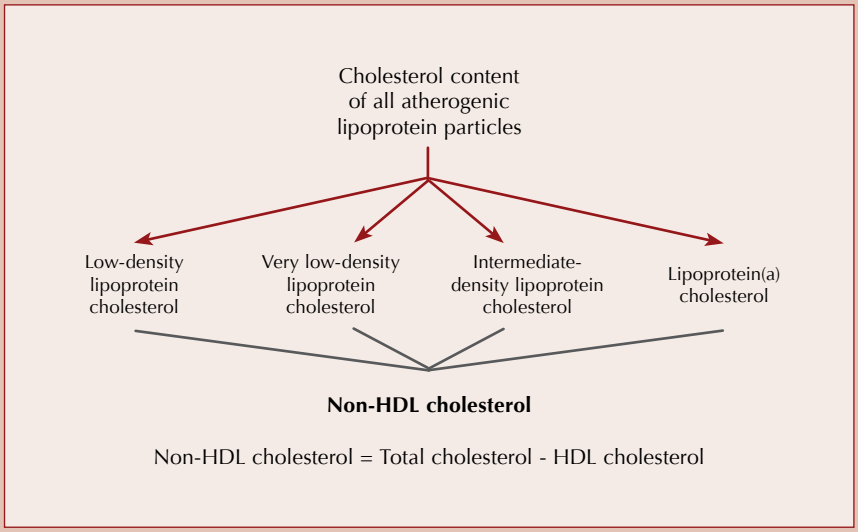

Figure 1. Components of non-high-density lipoprotein (non-HDL) cholesterol (redrawn with kind permission of the author from Virani, 2011).

Table 1. Hazard ratiors for major cardiovascular events by LDL and non-HDL cholesterol categories (Boekholdt et al, 2012).

LDL cholesterol level	Non-HDL cholesterol level	Hazard ratio	95% confidence interval
Not meeting target (2.6 mmol/L or higher)	Not meeting target (3.4 mmol/L or higher)	1.21	1.13–1.29
Not meeting target (2.6 mmol/L or higher)	**Meeting target** (under 3.4 mmol/L)	1.02	0.92–1.12
Meeting target (under 2.6 mmol/L)	Not meeting target (3.4 mmol/L or higher)	1.32	1.17–1.50
Meeting target (under 2.6 mmol/L)	**Meeting target** (under 3.4 mmol/L)	1.00*	

*Reference.

HDL=high-density lipoprotein; LDL=low-density lipoprotein.

Page points

1. Elevated levels of non-high-density lipoprotein cholesterol are manageable with available lipid-lowering agents combined with intensive lifestyle modification.
2. NICE guidelines provide treatment goals of a total cholesterol level <4 mmol/L and a low-density lipoprotein (LDL) cholesterol level <2 mmol/L.
3. The US National Cholesterol Education Program Guidelines go one step further than NICE by recommending a target LDL cholesterol of <1.8 mmol/L in people with diabetes and established cardiovascular disease.

A recent meta-analysis of individual patient data from randomised controlled statin trials, in which conventional lipids and apolipoproteins were determined in all study participants at baseline and 1-year follow-up, has been published in *JAMA*. The researchers used data from eight randomised trials in which nearly 40 000 patients received statins. One standard deviation increases from baseline levels of LDL, apolipoprotein B (apoB) and non-HDL at 1 year were all associated with increased risks of cardiovascular events but the differences between LDL and non-HDL were significant. Patients reaching the non-HDL target of under 130 mg/dL (3.4 mmol/L) but not the LDL target of under 100 mg/dL (2.6 mmol/L) were – assessed relative to patients achieving both targets – at lower excess risk than those reaching the LDL target but not the non-HDL target (Boekholdt et al, 2012; see *Table 1*).

Virani (2011), in the *Texas Heart Institute Journal*, has reviewed non-HDL cholesterol as a metric of good quality of care. Non-HDL cholesterol has been shown to be a better marker of risk in both primary and secondary prevention studies. In a recent analysis of data combined from 68 studies, non-HDL cholesterol was the best predictor among all cholesterol measures both for coronary artery events and for strokes (Emerging Risk Factors Collaboration, 2009). In the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trial, elevated non-HDL cholesterol and apoB levels were the best predictors after acute coronary syndrome of adverse cardiovascular outcomes in patients on lipid-lowering therapy (Kastelein et al, 2008).

Elevated levels of non-HDL cholesterol, in combination with normal levels of LDL cholesterol, identify a subset of patients with elevated levels of LDL particle number, elevated apoB concentrations and LDL of small, dense morphology (Ballantyne et al, 2001). The increase in the incidence of metabolic syndrome probably reduces the accuracy of risk prediction for vascular events when LDL cholesterol is used for that purpose, whereas non-HDL cholesterol has been shown to retain predictive capability in this patient population (Sattar et al, 2004).

Lipid management

Elevated levels of non-HDL cholesterol are manageable with available lipid-lowering agents combined with intensive lifestyle modification. All of the currently available lipid-lowering agents, including statins, fibrates, niacins, fish oil products and intestinally active agents such as ezetimibe, decrease non-HDL cholesterol levels.

As noted earlier, NICE guidelines provide treatment goals of a total cholesterol level <4 mmol/L and an LDL cholesterol level <2 mmol/L (NICE, 2009).

In line with the NICE-recommended "audit level" for total cholesterol of 5 mmol/L (based on the observation that more than half of patients will not achieve a total cholesterol level <4 mmol/L or an LDL cholesterol level <2 mmol/L; NICE, 2008), the total cholesterol Quality and Outcomes Framework indicator for people with diabetes is as follows (NHS Commissioning Board et al, 2013):

> "DM004. The percentage of patients with diabetes, on the register, whose last measured total cholesterol (measured within the preceding 12 months) is 5 mmol/l or less."

The US National Cholesterol Education Program Guidelines go one step further than NICE by recommending a target LDL cholesterol of <1.8 mmol/L in people with diabetes and established cardiovascular disease (Grundy et al, 2004). The American approach to hypertriglyceridaemia (defined as a triglyceride level of >2.2 mmol/L), which is present in many people with diabetes, is to target LDL cholesterol first and then use non-HDL cholesterol as a secondary target for treatment, with a goal 0.8 mmol/L higher than the LDL goal (Brunzell et al, 2008).

Contrary to the NICE guidelines, which recommend a fibrate when triglycerides are raised (NICE, 2009), the approach of many authorities in this situation is to use a non-HDL goal (0.8 mmol/L above the LDL goal) and intensify statin therapy, and if necessary add ezetimibe. Outcome data are now available for ezetimibe in combination

with statin therapy from SHARP (the Study of Heart and Renal Protection), confirming the benefit of lipid lowering in chronic renal disease (Baigent et al, 2011). The approach to very high triglycerides (>11 mmol/L) should also include a low-total-fat diet, a fibrate, and omega-3 fish oils (Hartweg et al, 2007; McEwan et al, 2010).

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial failed to demonstrate a benefit of adding fenofibrate to a statin compared with statin therapy alone in people with diabetes (ACCORD Study Group et al, 2010). There was a trend towards a reduction in adverse cardiovascular events in a predefined subgroup of patients with triglycerides ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol ≤34 mg/dL (0.8 mmol/L; *P*=0.057 for interaction).

Scott et al (2009) explored whether cardiovascular risk and the effects of fenofibrate differed in individuals with and without the metabolic syndrome and according to various features of the metabolic syndrome defined by the NCEP ATP III among people with type 2 diabetes in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. The findings were that more than 80% of FIELD participants met the ATP III criteria for metabolic syndrome. Each ATP III feature of the metabolic syndrome, apart from increased waist circumference, increased the absolute risk of cardiovascular events over 5 years by at least 3%. Those with marked dyslipidaemia (elevated triglycerides [≥2.3 mmol/L] and low HDL cholesterol) were at the highest risk of cardiovascular disease (17.8% over 5 years). Fenofibrate significantly reduced cardiovascular events in those with low HDL cholesterol or hypertension. The largest effect of fenofibrate in reducing cardiovascular risk was observed among individuals with marked dyslipidaemia, in whom a 27% relative risk reduction (95% confidence interval, 9–42%, *P*=0.005; number needed to treat, 23) was observed. Subjects with no prior cardiovascular disease had greater risk reductions than the group as a whole. The authors concluded that metabolic syndrome components identify higher cardiovascular risk in individuals with type 2 diabetes, and so the absolute benefits of fenofibrate are likely to be greater when metabolic syndrome features are present. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridaemia (Scott et al, 2009).

Recent data on niacin have been less encouraging. An outcomes trial comparing statin alone against statin plus niacin enrolled patients with established cardiovascular disease and atherogenic dyslipidaemia (LDL cholesterol ≤160 mg/dL (4.1 mmol/L) and HDL cholesterol <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women (ClinicalTrials.gov, 2011). The trial was halted prematurely, 18 months ahead of schedule, because niacin offered no additional benefits in this patient population (National Institutes of Health, 2011).

HPS2-THRIVE (the Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events; http://www.thrivestudy.org/ [accessed 15.05.13]) involved over 25 000 men and women aged at least 50 years with a history of heart attack, stroke or peripheral arterial disease. All study participants were given simvastatin and, if necessary, ezetimibe to ensure good control of LDL cholesterol. In addition, they were randomly allocated to receive extended-release niacin/laropiprant (Tredaptive™) or matching placebo tablets daily for approximately 4 years. The primary objective of the study was to investigate whether fewer participants given extended-release niacin/laropiprant had heart attacks, strokes or revascularisation procedures or died from coronary heart disease than those in the placebo arm. Professor Jane Armitage, HPS2-THRIVE Chief Investigator, said:

> "The preliminary HPS2-THRIVE results show that, when added to an effective statin-based treatment, the combination of extended-release niacin and laropiprant does not produce clinically meaningful reductions in the rate of major vascular events (such as heart attacks and strokes)."

Page points

1. The highest risk and greatest benefits of fenofibrate are seen among those with marked hypertriglyceridaemia.
2. An outcomes trial comparing statin alone against statin plus niacin enrolled patients with established cardiovascular disease and atherogenic dyslipidaemia but was halted prematurely, 18 months ahead of schedule, because niacin offered no additional benefits in this patient population.

Box 2. Case example one.

Narrative

Mr B is a 62-year-old man who has had type 2 diabetes for 6 years. He weighs 98 kg with a BMI of 30 kg/m^2 and his HbA_{1c} level is 60 mmol/mol (7.6%). His estimated glomerular filtration rate is 58 mL/min/1.73 m^2 and his blood pressure is 146/88 mmHg. He takes metformin 0.5 g twice daily and ramipril 5 mg daily and follows a healthy lifestyle programme diligently.

He had been on atorvastatin 40 mg but reported muscle pain and cramps in his legs. These disappeared when the statin was stopped but his lipid profile was unsatisfactory, with a cholesterol level of 5.4 mmol/L, high-density lipoprotein (HDL) cholesterol level of 0.9 mmol/L, triglyceride level of 2.7 mmol/L and low-density lipoprotein (LDL) cholesterol of 3.3 mmol/L.

His calculated 10-year risk of coronary heart disease (CHD) was 40.6%, fatal CHD 26.4%, stroke 15.2% and fatal stroke 2.5%.

Discussion

Mr B was subsequently started on pravastatin 40 mg. His muscle pains were no longer a problem but his targets (total cholesterol level of 4 mmol/L and LDL cholesterol level of 2 mmol/L) remained elusive until ezetimibe 10 mg was additionally prescribed. Amlodipine 5 mg was also added to his regimen to achieve a target blood pressure of less than 130/80 mmHg, and metformin was titrated up to 2 g.

MSD has advised clinicians to stop prescribing Tredaptive™ and to review patients on the drug in a timely fashion (Merck, 2013).

Case examples relating to managing dyslipidaemia in the context of diabetes are presented in *Box 2* and *Box 3*.

Box 3. Case example two.

Narrative

Mrs D, a teacher aged 48 years, attends for an NHS health check. She is overweight (96 kg), with central obesity and a waist measurement of 90 cm. Her blood pressure measures 150/88 mmHg. A random blood glucose test is performed in addition to tests for total cholesterol, high-density lipoprotein (HDL) cholesterol and estimated glomerular filtration rate.

Her cholesterol level was 5.8 mmol/L with HDL cholesterol at 0.95 mmol/L. Her glucose level was 7.1 mmol/L and her renal function was normal.

A subsequent glucose tolerance test confirmed type 2 diabetes with a fasting glucose level of 7.2 mmol/L and a 2-hour glucose level of 12 mmol/L. LDL cholesterol level was 3.57 mmol/L and triglycerides were 2.8 mmol/L. Her HbA_{1c} level was 8.2% (66 mmol/mol). No end organ damage was identified and there was no microalbuminuria.

Discussion

Mrs D was provided with lifestyle advice and started on simvastatin 40 mg and an angiotensin-converting enzyme inhibitor as her blood pressure remained high. Metformin will be introduced if the HbA_{1c} level fails to fall below 53 mmol/mol (7.0%) with the diet and exercise diabetes regimen.

Concluding remarks

The American Diabetes Association (2009) guidelines suggest that if lipid targets are not achieved on maximally tolerated doses of statins, combining a statin with other lipid-lowering therapy may be considered to achieve lipid targets. This recommendation is based on expert consensus. Randomised trials demonstrating reductions in adverse cardiovascular end points (myocardial infarction, stroke and death) are currently lacking.

We therefore must be pragmatic and attempt to deal with the residual risk in people with diabetes after appropriate LDL cholesterol lowering using non-HDL cholesterol as a secondary target. ■

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"We must be pragmatic and attempt to deal with the residual risk in people with diabetes after appropriate low-density lipoprotein cholesterol lowering using non-high-density lipoprotein cholesterol as a secondary target."

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1. Which of the following statements BEST explains current understanding of how atherosclerotic disease causes myocardial infarction? Select ONE option only.

   A. Atherosclerosis gradually leads to narrowing of coronary arteries
   B. Atherosclerosis causes an increased systemic thrombotic tendency
   C. Thrombus forms once coronary arteries become too narrow
   D. Unstable atherosclerotic plaques rupture

2. Which ONE of the following inflammatory cytokines has been clearly implicated in the INITIAL development of atherosclerosis? Select ONE option only.

   A. Insulin
   B. Interferon-gamma (IFN-gamma)
   C. Interleukin-2 (IL-2)
   D. Tumour necrosis factor-alpha (TNF-alpha)

3. Arterial constriction occurs in response to REDUCED release of which one of the following? Select ONE option only.

   A. Carbon dioxide
   B. Nitric oxide
   C. Nitrogen
   D. Oxygen

4. Which of the following haematological factors is MOST LIKELY associated with the progression of atherosclerosis in people with diabetes? Select ONE option only.

   A. Platelet hyperactivity
   B. Polycythaemia
   C. Thrombocythaemia
   D. All of the above
   E. None of the above

5. The presence of which of the following, if any, BEST explains why some people with diabetes develop diabetic cardiomyopathy? Select ONE option only.

   A. Hyperglycaemia
   B. Hyperlipidaemia
   C. Hypertension
   D. Hyperviscosity
   E. None of the above

6. According to research data, statin therapy in people with diabetes reduces the relative risk of cardiovascular events by which approximate percentage? Select ONE option only.

   A. 5–10
   B. 15–30
   C. 25–50
   D. 30–60
   E. 50–70

7. Which of the following activities is NOT a component of HDL's vasculo-protective functionality? Select ONE option only.

   A. Anti-constrictive
   B. Anti-infectious
   C. Anti-inflammatory
   D. Anti-protease
   E. Anti-thrombotic

8. According to NICE guidelines, which is the recommended TARGET for people with diabetes and dyslipidaemia? Select ONE option only.

	Total cholesterol (mmol/L)	HDL cholesterol (mmol/L)
A.	5	3
B.	5	2
C.	4	3
D.	4	2
E.	3	3
F.	3	2

9. "Non-HDL cholesterol" is BEST defined as the difference between which two of the following? Select ONE option only.

   A. HDL cholesterol and LDL cholesterol
   B. HDL cholesterol and triglycerides
   C. Total cholesterol and HDL cholesterol
   D. Total cholesterol and triglycerides

10. A 57-year-old man with type 2 diabetes has persistent hypertriglyceridaemia despite taking daily simvastatin 40 mg and addressing lifestyle factors.

    Which of the following is the LEAST effective management option? Select ONE option only.

    A. Add ezetimibe
    B. Add fenofibrate
    C. Increase simvastatin
    D. Switch to atorvastatin
    E. Switch to niacin