Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

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Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

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Aims
To critically evaluate the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles.

Methods and results
Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1–6 h after habitual meals are not clinically significant: +0.3 mmol/L (26 mg/dL) for triglycerides; −0.2 mmol/L (8 mg/dL) for total cholesterol; −0.2 mmol/L (8 mg/dL)
for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; −0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol; concentrations of HDL cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein(a) are not affected by fasting/non-fasting status. In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, while fasting sampling may be considered when non-fasting triglycerides ≥ 5 mmol/L (440 mg/dL). For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides ≥ 2 mmol/L (175 mg/dL), total cholesterol ≥ 5 mmol/L (190 mg/dL), LDL cholesterol ≥ 3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥ 0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol ≥ 3.9 mmol/L (150 mg/dL), HDL cholesterol ≤ 1 mmol/L (40 mg/dL), apolipoprotein A1 ≤ 1.25 g/L (125 mg/dL), apo-lipoprotein B ≥ 1.0 g/L (100 mg/dL), and lipoprotein(a) ≥ 50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides ≥ 1.7 mmol/L (150 mg/dL). Life-threatening concentrations require separate referral when triglycerides > 10 mmol/L (880 mg/dL) for the risk of pancreatitis, LDL cholesterol > 13 mmol/L (500 mg/dL) for homozygous familial hypercholesterolemia, LDL cholesterol > 5 mmol/L (190 mg/dL) for heterozygous familial hypercholesterolemia, and lipoprotein(a) > 150 mg/dL (99th percentile) for very high cardiovascular risk.

**Conclusion**

We recommend that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should flag abnormal values on the basis of desirable concentration cut-points. Non-fasting and fasting measurements should be complementary but not mutually exclusive.

**Keywords**

Lipids • Lipoproteins • Cardiovascular disease • Stroke • Reference values • Normal values

### Introduction

Most individuals consume several meals during the day and some consume snacks between meals; the postprandial state therefore predominates over a 24 h period. Nonetheless, in clinical practice, the lipid profile is conventionally measured in blood plasma or serum obtained after fasting for at least 8 h, and therefore may not reflect the daily average plasma lipid and lipoprotein concentrations and associated risk of cardiovascular disease.1,2

Interestingly, evidence is lacking that fasting is superior to non-fasting when evaluating the lipid profile for cardiovascular risk assessment. However, there are advantages to using non-fasting samples rather than fasting samples for measuring the lipid profile.3–7 Since 2009, non-fasting lipid testing has become the clinical standard in Denmark, based on recommendations from the Danish Society for Clinical Biochemistry that all laboratories in Denmark use random non-fasting lipid profiles as the standard, while offering clinicians the option of re-measuring triglyceride concentrations in the fasting state if non-fasting values are >4 mmol/L (350 mg/dL).8,9 Furthermore, the UK NICE guidelines have endorsed non-fasting lipid testing in the primary prevention setting since 2014.10

The most obvious advantage of non-fasting rather than fasting lipid measurements is that it simplifies blood sampling for patients, laboratories, general practitioners, and hospital clinicians and is also likely to improve patient compliance with lipid testing.3–7 Indeed, patients are often inconvenienced by having to return on a separate visit for a fasting lipid profile and may default on essential testing. Also, laboratories are burdened by a large volume of patients attending for tests in the morning. Finally, clinicians are burdened by having to review and make decisions on the findings in the lipid profile at a later date. This situation may also require an additional phone call, email, or even a follow-up clinic visit, placing extra workloads on busy clinical staff.

Perceived limitations to adopting non-fasting lipid measurements include the following: (i) fasting before a lipid profile measurement is believed to provide more standardized measurements; (ii) non-fasting lipid profiles are perceived as providing less accurate measurements and may make calculation of low-density lipoprotein (LDL) cholesterol via the Friedewald equation invalid; (iii) as fasting has been the clinical standard, it is unclear what values should be flagged as abnormal when using non-fasting rather than fasting plasma lipid profiles. These perceived limitations will be addressed in this paper.

The aims of the present joint consensus statement are to critically evaluate the use of non-fasting rather than fasting lipid profiles, and the clinical implications of this question with a view to providing appropriate guidance for laboratory and clinicians. Based on evidence from large-scale population studies and registries and on consensus of expert opinions, the European Atherosclerosis Society/European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFLM) joint consensus statement proposes recommendations on (i) situations when fasting is not required for a lipid profile and (ii) how laboratory reports should flag abnormal lipid profiles to improve compliance of patients and clinicians with concentration goals used in guidelines and consensus statements on cardiovascular

### Table 1 Key recommendations

| Recommendation                                                                                           |
|----------------------------------------------------------------------------------------------------------|
| Fasting is not required routinely for assessing the plasma lipid profile.                                  |
| When non-fasting plasma triglyceride concentration > 5 mmol/L (440 mg/dL), consideration should be given to |
| repeating the lipid profile in the fasting state.                                                       |
| Laboratory reports should flag abnormal values based on desirable concentration cut-points.            |
| Life-threatening or extremely high concentrations should trigger an immediate referral to a lipid clinic or|
| to a physician with special interest in lipids.                                                        |
disease prevention.11–15 This joint consensus statement is aimed at internists, general practitioners, paediatricians, cardiologists, endocrinologists, clinical biochemists, laboratory professionals, public health practitioners, health service planners, other health professionals, healthcare providers, and patients worldwide. Key recommendations are given in Table 1.

Constituents of the plasma lipid profile

A standard lipid profile includes measurements of plasma or serum concentrations of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (Figure 1).

Total cholesterol, HDL cholesterol, and triglycerides are measured directly, while LDL cholesterol can either be measured directly or calculated by the Friedewald equation if triglycerides are <4.5 mmol/L (<400 mg/dL): total cholesterol minus HDL cholesterol minus triglycerides/2.2 (all in mmol/L; or minus triglycerides/5 with values in mg/dL).16 with direct measurement of LDL cholesterol at triglyceride concentrations ≥4.5 mmol/L (400 mg/dL). Traditionally, the Friedewald equation has been applied to a fasting lipid profile; however, calculated LDL cholesterol determined with this equation at triglyceride concentrations <4.5 mmol/L (400 mg/dL) is similar to LDL cholesterol measured directly on both fasting and non-fasting lipid profiles (Figure 2).17,18 These four measurements can, without additional cost, be supplemented with remnant cholesterol and non-HDL cholesterol.

Remnant cholesterol (=triglyceride-rich lipoprotein cholesterol) is calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol, using non-fasting or fasting lipid profiles; if LDL cholesterol is also calculated, then remnant cholesterol is equivalent to triglycerides/2.2 in mmol/L and to triglycerides/5 in mg/dL. Calculated remnant cholesterol is a strong causal risk factor for cardiovascular disease.19–21 Non-HDL cholesterol is calculated as total cholesterol minus HDL cholesterol and is equivalent to LDL cholesterol, remnant cholesterol and lipoprotein(a) cholesterol combined (Figure 1). The use of non-HDL cholesterol for cardiovascular disease risk prediction has been emphasized in several guidelines and consensus papers.12–15

The most important additional measurement for inclusion for cardiovascular disease risk prediction is lipoprotein(a) [Lp(a)]. This genetic, causal cardiovascular risk factor11,22 should be measured at least once in all patients screened for cardiovascular risk;11 it is noteworthy that Lp(a) concentrations vary little over time (<10%) in any individual. The determination of Lp(a) should not, however, be included in repeated lipid profile measurements in the same patient, unless therapeutic intervention is aimed at reducing Lp(a) concentrations or in selected circumstances. Importantly, the cholesterol content of Lp(a), corresponding to 30% of Lp(a) total mass,23 is included in total, non-HDL, and LDL cholesterol values and its apolipoprotein B content in the apolipoprotein B value.

Finally, measurements of apolipoprotein B and apolipoprotein A1 can be used as alternatives to non-HDL and HDL cholesterol measurements, respectively (Figure 1),13–15,24 but these determinations come at extra cost.

Why has fasting been the standard?

Venipuncture is a universal practice involved in testing the lipid profile with the purposes of predicting cardiovascular risk and/or monitoring responses to lipid-lowering therapy. Some guidelines continue to promulgate the conventional practice of measuring the lipid profile in the fasting state,25 although other organizations endorse non-fasting lipid profiles.8,10 The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not require fasting for atherosclerotic cardiovascular disease risk estimation; however, they do recommend a fasting lipid panel before statin initiation to calculate LDL cholesterol and for individuals with non-HDL cholesterol ≥5.7 mmol/L (220 mg/dL) or triglycerides ≥5.7 mmol/L (500 mg/dL), as these may be clues to genetic and/or secondary causes of hypertriglyceridaemia.25 One reason among others for preferring fasting lipid profiles is the increase in triglyceride concentration seen during a fat tolerance test;26,27 however, the increase in plasma triglycerides observed after habitual food intake in most individuals is much less than that observed during a fat tolerance test.3,4,8,9,28–31 As a fast-food meal consisting of e.g. a burger, a shake, and fries might be considered a fat tolerance test, in areas where fast-food consumption is especially high patients may be advised to avoid high-fat, fast-food meals on the day of lipid profile testing. Also, as LDL cholesterol is often calculated by the Friedewald equation, which includes the triglyceride concentration,
calculated LDL cholesterol has been thought to be affected substantially by food intake; however, directly measured and calculated LDL cholesterol values are similar using both fasting and non-fasting lipid profiles (Figure 2).

If this Friedewald equation is employed, there may be some underestimation of LDL cholesterol when chylomicrons are present, which may even be circumvented if a modification of this equation is used. Also, many randomized lipid-lowering trials have used fasting lipid measurements and, in order to follow evidence-based practice, fasting blood sampling has often been the standard in everyday risk assessment. However, numerous population-based studies and at least three major statin trials used random, non-fasting blood sampling (Table 2), providing a robust evidence base for a change in the conventional practice of using fasting samples.

**Influence of food intake on the plasma lipid profile**

Several large-scale, population-based studies and registries including children, women, men, and patients with diabetes have now established that plasma lipids and lipoproteins change only modestly in response to habitual food intake (Figures 3 and 4, Table 3); this applies to the majority of individuals, but rarely some exhibit exaggerated responses. These studies were the Women’s Health Study from the USA, the Copenhagen General Population Study from Denmark, the National Health and Nutrition Examination Survey from the USA (Figure 3), and the Calgary Laboratory Services from Canada (Figure 4). Among all studies comparing non-fasting with fasting lipid profiles, minor increases in plasma triglycerides and minor decreases in total and LDL cholesterol concentrations were observed, with no change in HDL cholesterol concentrations. These minor and transient changes in lipid concentrations appear to be clinically insignificant; however, Langsted et al. observed a transient drop in LDL cholesterol concentration of 0.6 mmol/L (23 mg/dL) at 1–3 h after a meal in diabetic patients, which could be of clinical significance, particularly if this is used as an argument to withhold statins in a given patient. Of note, the reduction in total and LDL cholesterol at 1–3 h after the last meal observed in individuals with and without diabetes became statistically insignificant after adjusting for plasma albumin concentration as a marker of fluid intake; therefore, such a drop in total and LDL cholesterol is

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**Figure 2** Comparison of calculated low-density lipoprotein cholesterol using the Friedewald equation with low-density lipoprotein cholesterol measured directly using random non-fasting and fasting lipid profiles. Only lipid profiles with triglycerides <4.5 mmol/L (400 mg/dL) were included, as low-density lipoprotein is typically measured using a direct low-density lipoprotein cholesterol assay when triglycerides are ≥4.5 mmol/L. Mes, measured; Cal, calculated using the Friedewald equation (low-density lipoprotein cholesterol = total cholesterol − high-density lipoprotein cholesterol − triglycerides/2.2; all values in mmol/L; if values are in mg/dL then use triglycerides/5). Figure designed by Prof. B.G. Nordestgaard and Dr A. Langsted based on unpublished data from individuals participating in the Copenhagen City Heat Study 2001–2003 examination.
unrelated to food intake, noting that a similar drop may even be observed in a fasting lipid profile, since water intake is allowed ad libitum before a fasting blood test. Thus, the only way to prevent this drop in LDL cholesterol concentrations using either fasting or non-fasting lipid profiles is to forbid water intake before lipid profiles testing, while so-called fasting sampling will not remove this phenomenon. Importantly, in patients with diabetes, a fasting lipid profile may further disguise postprandial triglyceride increases that may be particularly important in the diabetic state.

For the purpose of the present joint consensus statement, we updated the analyses of Langsted et al.3,34 (Figure 5), based on the Copenhagen General Population Study and including 92 285 men and women from the Danish general population. As in previous reports (Table 3),3,4,9,29,30,34 the maximal mean changes at 1–6 h after habitual meals were considered clinically insignificant at +0.3 mmol/L (26 mg/dL) for triglycerides, −0.2 mmol/L (8 mg/dL) for total cholesterol, −0.2 mmol/L (8 mg/dL) for LDL cholesterol, +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol, and −0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol, while concentrations for HDL cholesterol, apolipoprotein A1, apolipoprotein B, and Lp(a) remained unchanged (Figure 5). Naturally, the corresponding changes in concentrations in individual patients will differ from the mean changes seen in Table 3 and in Figures 3–5, exactly as concentrations will differ from one fasting measurement to another in the same individual.

**Influence of food intake on the prediction of cardiovascular risk**

We exist mostly in the non-fasting state, which therefore reflects our habitual physiological status. However, blood samples typically measured after an 8–12 h fast have been the standard for assessing the plasma lipid profile.1,2 Postprandial effects do not appear to

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**Table 2** Population-based studies and statin trials that have employed non-fasting plasma lipid profiles to assess cardiovascular disease risk and trial outcomes, respectively

| Population-based studies totalling >300 000 non-fasting individuals | Statin trials totalling 43 000 non-fasting individuals |
|---|---|
| Tromsø Heart Study | Heart Protection Study |
| Norwegian National Health Service | Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm |
| British Population Studies | Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine |
| European Prospective Investigation of Cancer—Norfolk | |
| Northwick Park Heart Study | |
| Apolipoprotein-related Mortality Risk | |
| Copenhagen City Heart Study | |
| Women’s Health Study | |
| Nurses’ Health Study | |
| Physicians’ Health Study | |
| National Health and Nutrition Examination Survey III | |
| Circulatory Risk in Communities Study | |
| Copenhagen General Population Study | |
| The global 52-country case-control INTERHEART study | |

**Figure 3** Mean concentrations of lipids and lipoproteins as a function of the fasting period following the last meal in children from the US general population. The last meal simply represents what the particular child chose to eat at that particular day before blood sampling, with no information or requirement on amount or type of food eaten. Based on 12 744 children from the National Health and Nutrition Examination Survey.30
diminish, and may in fact enhance, the strength of the associations between plasma lipid, lipoprotein, and apolipoprotein concentrations and risk of cardiovascular disease.

Since the 1970s, numerous reports from well-conducted, large, representative, and mostly prospective studies with medium- to long-term follow-up have consistently found that non-fasting lipids suffice for screening of cardiovascular disease risk. These studies have examined clinical outcomes ranging from incident cardiovascular disease events (myocardial infarction, stroke, and revascularization) to cardiovascular or all-cause mortality, with consistent associations for non-fasting lipid profiles with cardiovascular disease risk. Furthermore, studies that included fasting and/or non-fasting individuals have found generally similar or sometimes superior cardiovascular disease risk associations for non-fasting compared with fasting lipid profiles, including for triglycerides. The challenge of taking small amounts of alcohol during non-fasting hours of the day and its influence on lipid profile values has often not been studied. Prospective studies that have assessed non-fasting lipid profiles are shown in Table 2.

A meta-analysis from the Emerging Risk Factors Collaboration that analysed the association of lipid profiles and risk of coronary heart disease events from 68 prospective studies, and included over 300 000 individuals, equally found no attenuation of the strength of the association between plasma lipid and lipoprotein concentrations and incident cardiovascular events in the 20 studies that used non-fasting blood samples; indeed, non-fasting non-HDL cholesterol and non-fasting calculated LDL cholesterol were superior to fasting measurements for predicting cardiovascular risk (n = 103 354; number of events 3829). Furthermore, at least three large clinical trials of statin therapy (Heart Protection Study, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) involving nearly 43 000 participants used non-fasting lipid profile measurements (Table 2).
Finally, for the purpose of this joint consensus statement and based on the Copenhagen General Population Study including 92 285 men and women from the Danish general population, we examined the risk of ischaemic heart disease and myocardial infarction for the highest vs. lowest quintile of random non-fasting lipids, lipoproteins, and apolipoproteins as part of standard and expanded lipid profiles (Figure 6); all lipids, lipoproteins, and apolipoproteins were associated strongly with the risk of both endpoints.

Hence, numerous prospective cohorts have found significant associations for non-fasting lipids, lipoproteins, and apolipoproteins with cardiovascular disease risk, and several landmark clinical trials of statin therapy have used non-fasting lipids for trial entry criteria and for monitoring the efficacy of lipid-lowering therapy. Collectively, these observations suggest that non-fasting blood sampling is highly effective, practical, and advantageous in assessing lipid-mediated cardiovascular disease risk and treatment responses.

### Recommendations on the use of non-fasting lipid profiles

To improve patient compliance with lipid testing, we therefore recommend that non-fasting lipid profiles be used in the majority of patients (Table 4), while with non-fasting plasma triglyceride >5 mmol/L (440 mg/dL), fasting sampling may be considered.

However, as lipid profile measurements often are taken repeatedly in the same patient, a single, spurious, non-fasting very high triglyceride concentration due to a very high fat intake preceding blood sampling will be followed by other measurements with lower concentrations.

Fasting can be a barrier to population screening, is unpopular with children, is often unsuitable for patients with diabetes, and counters the use of point-of-care testing, and fasting requirements can add to the overall costs of lipid testing. Non-fasting tests are also used to assess other metabolic disorders, such as haemoglobin A1c in diabetes. The collective sources of evidence reviewed above have therefore led to the notion that fasting samples are not essential for evaluation of cardiovascular risk.

Arguments against the use of non-fasting samples also merit consideration. There is evidence that the non-fasting condition may lower plasma LDL cholesterol concentrations owing to liberal intake of fluids (Table 3), and therefore lead to a potential minor misclassification of cardiovascular risk, as well as to error in initiating or altering lipid-lowering medication; although not all studies agree, this risk is small and may chiefly apply to diabetic subjects. While a non-fasting sample is sufficient to diagnose an isolated hypercholesterolaemia, such as familial hypercholesterolaemia, or elevated Lp(a), it can possibly confuse the distinction between familial hypercholesterolaemia and genetic forms of high triglycerides. Since non-fasting may therefore impair the accuracy

| Study population | Triglycerides | Total cholesterol | LDL cholesterol | HDL cholesterol |
|------------------|--------------|------------------|-----------------|-----------------|
| Mora et al. (2008) | ↑ 0.2 mmol/L | ↓ 0.1 mmol/L | ↓ 0.2 mmol/L | No change |
| Langsted et al. (2008) | ↑ 0.3 mmol/L | ↓ 0.2 mmol/L | ↓ 0.2 mmol/L | ↓ 0.1 mmol/L |
| Steiner et al. 2011 | ↑ 0.1 mmol/L | ↑ 0.1 mmol/L | ↑ 0.1 mmol/L | No change |
| Langsted and Nordestgaard (2011) | ↑ 0.2 mmol/L | ↑ 0.4 mmol/L | ↑ 0.6 mmol/L | No change |
| Sidhu and Naugler (2012) | ↑ 0.3 mmol/L | ↑ 0.2 mmol/L | ↑ 0.3 mmol/L | No change |

Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides.

No longer statistically significant after adjustment for reduction in plasma albumin concentrations; thus this drop in total and LDL cholesterol is due to fluid intake, not to food intake. In other words, as water intake is allowed during the up to 8 h fasting before lipid profile testing,2 this reduction in total and LDL cholesterol will also occur for fasting lipid profiles.

Langsted et al. observed a drop in LDL cholesterol of 0.6 mmol/L (23 mg/dL) at 1–3 h after a meal in diabetics, which could be of clinical significance,33 particularly if this precluded initiating or altering lipid-lowering medication; although not all studies agree, this risk is small and may chiefly apply to diabetic subjects.34 While a non-fasting sample is sufficient to diagnose an isolated hypercholesterolaemia, such as familial hypercholesterolaemia, or elevated Lp(a), it can possibly confuse the distinction between familial hypercholesterolaemia and genetic forms of high triglycerides. Since non-fasting may therefore impair the accuracy
in diagnosing some forms of hyperlipidaemia, we recommend that laboratories should also offer measurement of fasting triglycerides according to clinical context and indications, as in the case of very high non-fasting triglyceride concentration. Plasma lipids can be highly variable in children and a precise diagnosis of a lipid disorder that requires drug therapy may necessitate at least a second sample in the fasting state. From an evidence-based perspective, fasting and non-fasting samples have never been tested head-to-head in a clinical trial to assess how the corresponding lipid profiles alter clinical management and the disposition of patients, and what the relative cost-effectiveness of both approaches is. It is most unlikely that such a study will ever be funded, however.

What pragmatic recommendations can be made? First, non-fasting and fasting measurements of the lipid profile must be viewed as complementary and not mutually exclusive (Table 4). Common sense must prevail and a distinction made between their use in screening, assessment, and diagnosis. Fasting is less critical for first-stage screening, but may be more important when trying to establish a phenotypic diagnosis of genetically determined dyslipidaemias. Further, one circumstance where fasting may be especially valuable is getting a baseline lipid determination for those about to start medications that cause severe hypertriglyceridaemia in a genetically predisposed individual. Noting that fasting triglycerides are elevated can thus be useful before, e.g., steroid, oestrogen, or retinoid acid therapy. Also, fasting lipids have been used to follow the course of those recovering from hypertriglyceridaemic pancreatitis. Nevertheless, non-fasting blood samples can routinely be used for assessment of plasma lipid profiles in most situations (Table 4).
Potential for risk misclassification

It is important to consider whether transferring from fasting to non-fasting lipid profiles could lead to misclassification of cardiovascular risk and error in initiating statin therapy. Importantly, since statin treatment is decided on the basis of an individual’s global cardiovascular risk, including the presence of cardiovascular disease, familial hypercholesterolaemia and diabetes, and not just on plasma lipid values in both European and US guidelines, minor changes in the lipid profile from fasting to non-fasting conditions (Figures 3–5, Table 3) will affect only a few individuals regarding the decision to start a statin or not. However, most guidelines use LDL cholesterol to monitor pharmacological treatment and as goals for treatment. In individuals with borderline LDL cholesterol, the lower LDL cholesterol observed 1–6 h after a habitual meal, particularly in diabetic patients (due to hypoglycaemic risk) and in the elderly, needs to be considered when using non-fasting lipid profiles with no restrictions on water intake.

Novel findings from experience in Denmark

In 2009, the Danish Society for Clinical Biochemistry recommended that all laboratories in Denmark use random non-fasting lipid profile measurements rather than fasting profiles. It was believed that a single spurious, non-fasting very high triglyceride concentration due to high fat intake preceding blood sampling would be followed by other measurements with lower concentrations. However, it was also recommended that laboratories should have the option of re-measurement of triglyceride concentrations in the fasting state, if non-fasting triglyceride values were at >4 mmol/L (435 mg/dL).

This change in blood sampling was easy to implement in Denmark: after adoption of the non-fasting strategy by major university hospitals in Copenhagen and subsequent corresponding reports in written and electronic media nationwide, patients and clinicians in the entire country pushed for similar changes at their local clinical biochemical laboratory. Only a few laboratories refused initially to follow this new practice, but by 2015 practically all laboratories in Denmark use non-fasting lipid profiles.
To illustrate the consequences of implementing this new blood sampling policy and for the purpose of the present joint consensus statement, we retrieved results for all triglyceride measurements at Herlev Hospital, Copenhagen University Hospital in the period April 2011 through April 2015: of ~60,000 triglyceride measurements, only 10% were measured in the fasting state. Further, among the 5538 patients with both a non-fasting and a fasting triglyceride measurement, concentrations were very similar fasting and non-fasting measures overall as well as when stratified by triglyceride concentrations and the presence or absence of diabetes (Figure 7, top). In groups stratified for triglyceride concentrations, the interquartile ranges were wider for fasting than for non-fasting triglycerides, which is explained by regression dilution bias as the initial groups were made based on non-fasting concentrations and then fasting concentrations were compared afterwards. Thus, if groups were made initially based on fasting concentrations, then the confidence intervals for non-fasting triglycerides were wider than for fasting triglycerides (data not shown). In other words, the variation in fasting and non-fasting triglyceride concentrations measured in the same individuals at two different occasions is similar, as is also clear for the value in all 5538 individuals combined (Figure 7, top). Results were also similar for LDL cholesterol comparing non-fasting and fasting values (Figure 7, bottom).

### Recommendations on laboratory reporting of abnormal non-fasting and fasting lipid profiles

We recommend that laboratory reports should flag abnormal values based on desirable concentration cut-points, defined by guidelines and consensus statements, and for non-fasting samples, flag abnormal concentrations as triglycerides $\geq 2$ mmol/L (175 mg/dL) \[^{10,11}\] (corrected for endogenous glycerol), total cholesterol $\geq 5$ mmol/L (190 mg/dL), LDL cholesterol $\geq 3$ mmol/L (115 mg/dL), calculated remnant cholesterol $\geq 0.9$ mmol/L (35 mg/dL), calculated non-HDL cholesterol $\geq 3.9$ mmol/L (155 mg/dL), HDL cholesterol $\leq 1$ mmol/L (40 mg/dL) (sex-specific cut-points can be used for HDL cholesterol), apolipoprotein A1 $\leq 1.25$ g/L (125 mg/dL), apolipoprotein B $\geq 1.0$ g/L (100 mg/dL), and Lp(a) $\geq 50$ mg/dL (80th percentile) (Table 5); for fasting samples, abnormal concentrations should be triglycerides $\geq 1.7$ mmol/L (150 mg/dL), remnant cholesterol $\geq 0.8$ mmol/L (30 mg/dL), and non-HDL cholesterol $\geq 3.8$ mmol/L (145 mg/dL) while other measurements should use identical cut-points as for non-fasting values.

The majority of these cut-points correspond to desirable concentrations from guidelines and consensus statements. However, a desirable concentration cut-point for non-fasting triglycerides has

### Table 5 Abnormal plasma lipid, lipoprotein, and apolipoprotein concentration values that should be flagged in laboratory reports based on desirable concentration cut-points

| Abnormal concentrations | Non-fasting | Fasting |
|-------------------------|-------------|---------|
|                        | mmol/L      | mg/dL*  | g/L     | mmol/L | mg/dL*  | g/L     |
| Triglycerides*          | $\geq 2$    | $\geq 175$ | $\geq 1.75$ | $\geq 1.7$ | $\geq 150$ | $\geq 1.50$ |
| Total cholesterol       | $\geq 5$    | $\geq 190$ | $\geq 1.90$ | $\geq 5$   | $\geq 190$ | $\geq 1.90$ |
| LDL cholesterol         | $\geq 3$    | $\geq 115$ | $\geq 1.15$ | $\geq 3$   | $\geq 115$ | $\geq 1.15$ |
| Remnant cholesterol\(^{c}\) | $\geq 0.9$ | $\geq 35$ | $\geq 0.35$ | $\geq 0.8$ | $\geq 30$ | $\geq 0.30$ |
| Non-HDL cholesterol\(^{d}\) | $\geq 3.9$ | $\geq 150$ | $\geq 1.50$ | $\geq 3.8$ | $\geq 145$ | $\geq 1.45$ |
| Lipoprotein(a)\(^{e}\) | *           | $\geq 50$ \(^{f}\) | $\geq 0.50$ | *         | $\geq 50$ \(^{f}\) | $\geq 0.50$ |
| Apolipoprotein B        | $\geq 100$ | $\geq 1.00$ | $\geq 1$    | $\geq 100$ | $\geq 1.00$ | $\geq 1$    |
| HDL cholesterol\(^{g}\) | $\leq 1$    | $\leq 40$ | $\leq 0.40$ | $\leq 1$    | $\leq 40$ | $\leq 0.40$ |
| Apolipoprotein A1       | $\leq 125$ | $\leq 1.25$ | $\geq 0.125$ | $\leq 125$ | $\leq 1.25$ | $\geq 0.125$ |

*These values for flagging in laboratory reports are in some instances higher than corresponding to recommended desirable values in high and very high risk patients (Tables 6 and 7). We recommend to use SI units (e.g., mmol/L for lipids and g/L for apolipoproteins); however, as these values are not used in all countries, we also provide cut-points for other commonly used units.

\(^{a}\)LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein.

\(^{b}\)Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides, followed by rounding to nearest 5 mg/dL; for total cholesterol, we used 5 mmol/L and 190 mg/dL, as these are the two desirable concentration cut-point typically used in guidelines.

\(^{c}\)Triglyceride cut-points based on assays with correction for endogenous glycerol. In most laboratories, however, triglycerides are measured without subtraction of the glycerol blank; thus, triglycerides may wrongly be flagged as abnormal in rare individuals with very high plasma glycerol. That said, not accounting for the glycerol blank in outpatients rarely affected the triglyceride concentration.

\(^{d}\)High endogenous glycerol is seen e.g. during intravenous lipid or heparin infusion.

\(^{e}\)Remnant cholesterol is used when non-HDL cholesterol is used.

\(^{f}\)Calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol, that is, VLDL, IDL, and chylomicron remnants in the non-fasting state and VLDL and IDL in the fasting state.

\(^{g}\)Calculation as total cholesterol minus HDL cholesterol.

\(^{h}\)Apolipoprotein(a) should represent $\geq 80$th percentile of the specific apolipoprotein(a) assay.

\(^{i}\)Sex-specific cut-points can be used for HDL cholesterol.
been documented only recently,\textsuperscript{40,41} we therefore choose to recommend flagging of abnormal concentrations of non-fasting triglycerides as \( \geq 2.0 \text{ mmol/L (175 mg/dL)} \), according to the recent study from the Women’s Health Study that found that this cut-point was optimal for cardiovascular risk prediction. Interestingly, this is almost identical to the cut-points previously suggested by the EAS and by the Athens Expert Panel.\textsuperscript{12,24,42} A concentration cut-point for fasting triglycerides at 1.7 \text{ mmol/L (150 mg/dL)} was taken as 0.3 \text{ mmol/L} lower than for non-fasting triglycerides, corresponding to the mean maximal increase of triglycerides following habitual food intake (Figure 5, Table 3). Interestingly, this cut-point is identical to those proposed previously for fasting triglycerides by the AHA\textsuperscript{14} and the EAS.\textsuperscript{12}

Usually, in laboratory medicine, results of measured parameters are considered to be abnormal if they exceed the age- and sex-specific reference interval (\( = 2.5\text{th to 97.5\text{th percentiles}} \)). All results below or above these recommended cut-points are flagged with a character to show at a glance that this value deserves attention. Also automatic validation and flagging are used in many laboratories. Depending on the laboratory, this labelling can vary. Theoretically, the reference intervals should be established by each laboratory, but in most cases they are taken over from the general information provided by the manufacturer in the package insert. Due to wide-spread unhealthy life style, in most populations the average concentrations are always much above a common decision cut-point, as the presence or absence of co-morbidities (atherosclerotic cardiovascular disease, diabetes, chronic kidney disease) and other risk factors (age, gender, hypertension, smoking). This personalized reporting of desirable values is difficult to implement in laboratory reports because usually the clinical conditions and risk factors of the individual patient are not known to the laboratory professional. We therefore propose a simplified system of flagging abnormal values based on desirable concentration cut-points for moderate risk only, which may be complemented by more detailed information on risk stratified cut-offs in footnotes on the laboratory report or by references to web-based information of the same laboratory. Using such flagging emphasizes the importance of harmonization and standardization in laboratory medicine, and the responsibility of EAS and EFLM to communicate to laboratories when updates of cut-points are necessary as guidelines for cardiovascular disease prevention are revised.

According to the flagging of abnormal values based on desirable concentration cut-points proposed in Table 5, the following percentages of adults in the general population of a typical Western or Northern European country will have flagged test results in non-fasting lipid profiles: 27% will have triglycerides \( \geq 2 \text{ mmol/L (175 mg/dL)} \), 72% total cholesterol \( \geq 5 \text{ mmol/L (190 mg/dL)} \), 60% LDL cholesterol \( \geq 3 \text{ mmol/L (115 mg/dL)} \), 27% calculated remnant cholesterol \( \geq 0.9 \text{ mmol/L (35 mg/dL)} \), 50% calculated non-HDL cholesterol \( \geq 3.9 \text{ mmol/L (150 mg/dL)} \), 20% Lp(a) \( \geq 50 \text{ mg/dL (80\text{th percentile})} \), 59% apolipoprotein B \( \geq 1.0 \text{ g/L (100 \text{mg/dL})} \), 10% HDL cholesterol \( \leq 1 \text{ mmol/L (40 \text{mg/dL})} \), and 9% will have apolipoprotein A1 \( \leq 1.25 \text{ g/L (125 \text{mg/dL})} \) (Figure 8).

**Life-threatening plasma lipid concentrations—what to do?**

Life-threatening or extremely abnormal test results deserve special attention and reactions of the clinical biochemical laboratory. In this regard, the following extreme hyperlipidaemias should be noted: triglycerides \( > 10 \text{ mmol/L (880 \text{mg/dL})} \) because of risk of acute pancreatitis,\textsuperscript{24} LDL cholesterol \( > 5 \text{ mmol/L (190 \text{mg/dL})} \) in adults or \( > 4 \text{ mmol/L (155 \text{mg/dL})} \) in children and particularly \( > 13 \text{ mmol/L (500 \text{mg/dL})} \) because of suspicious heterozygous and homozygous familial hypercholesterolaemia,\textsuperscript{43–45} respectively, and Lp(a) \( > 150 \text{ mg/dL (99th percentile)} \) for very high risk of myocardial infarction and aortic valve stenosis\textsuperscript{11,46,47} (Table 8). As such concentrations are always much above a common decision cut-point,

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**Table 6** Treatment goals for prevention of cardiovascular disease according to current European Atherosclerosis Society/European Society of Cardiology guidelines\textsuperscript{13}

| Cardiovascular disease risk | LDL cholesterol | Non-HDL cholesterol | Apolipoprotein B |
|-----------------------------|-----------------|---------------------|-----------------|
|                             | \text{mmol/L}   | \text{mg/dL}        | \text{mg/dL}    | \text{g/L}    |
| Very high                   | \(< 1.8\)       | \(< 70\)             | \(< 2.6\)       | \(< 80\)     |
| High                        | \(< 2.5\)       | \(< 100\)            | \(< 3.3\)       | \(< 100\)    |
| Moderate                    | \(< 3.0\)       | \(< 115\)            | \(< 3.8\)       | \(< 145\)    |

**Table 7** Definition of hypertriglyceridaemia by European Atherosclerosis Society consensus statement\textsuperscript{24}

| Hypertriglyceridaemia        | \text{mg/dL}    | \text{mmol/L}       |
|------------------------------|-----------------|---------------------|
| Severe hypertriglyceridaemia | \( > 10 \text{ mmol/L (880 \text{mg/dL})} \) |
| Mild-to-moderate hypertriglyceridaemia | \( 2–10 \text{ mmol/L (180–880 \text{mg/dL})} \) |
Figure 8 Proportion of non-fasting individuals in the general population with flagged abnormal concentrations in laboratory reports using desirable concentration cut-points as shown in Table 5. Of all participants, 12% were receiving statins. Figure designed by Prof. B.G. Nordestgaard and Dr. A. Langsted based on unpublished data on 92,285 non-fasting individuals from the Copenhagen General Population Study recruited in 2003 through 2014.

Table 8 Life-threatening and extremely abnormal concentrations with separate reporting and consequent direct referral to a lipid clinic or to a physician with special interest in lipids

| Life-threatening concentrations | Refer patient to a lipid clinic or to a physician with special interest in lipids for further assessment of the following conditions |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Triglycerides                  | Chylomicronaemia syndrome with high risk of acute pancreatitis<sup>24</sup>                                               |
| LDL cholesterol                | Homozygous familial hypercholesterolaemia with extremely high cardiovascular risk<sup>44</sup>                           |
| LDL cholesterol                | Heterozygous familial hypercholesterolaemia with high cardiovascular risk<sup>43</sup>                                   |
| LDL cholesterol in children     | Heterozygous familial hypercholesterolaemia with high cardiovascular risk<sup>45</sup>                                   |
| Lipoprotein(s)                 | Very high cardiovascular risk, i.e. for myocardial infarction and aortic valve stenosis<sup>11,46,47</sup>              |
| LDL cholesterol                | Genetic abetalipoproteinemia                                                                                        |
| Apolipoprotein B               | Genetic hypoalphalipoproteinemia (e.g. lecithin cholesterol acyltransferase deficiency)                               |
| HDL cholesterol                |                                                                                                                        |
| Apolipoprotein A1              |                                                                                                                        |

<sup>a</sup>Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides, followed by rounding to nearest 5 mg/dL.
They should be flagged with special symbols to quickly initiate further diagnostic and possibly therapeutic actions, preferably with direct referral to a lipid clinic or to a physician with special interest in lipids. It is also important to refer patients with very low concentrations of LDL cholesterol, apolipoprotein B, HDL cholesterol, or apolipoprotein A1 to a specialist lipid clinic for further evaluation of a major monogenic disorder of lipid metabolism (Table 8).

Implementation of recommendations

Each country, state, and/or province in individual countries should adopt strategies for implementing routine use of non-fasting rather than fasting lipid profiles as well as flagging of abnormal values based on desirable concentration cut-points rather than using traditional reference intervals. Ideally, there should be one standard for reporting lipid profiles in each country as also accreditation bodies should be aware of the present consensus statement. Figure 9 suggests implementation strategies; however, the strategy might differ from country to country based on existing local practice in relation to use of non-fasting lipid profiles and flagging of abnormal values based on desirable concentration cut-points used for assessing cardiovascular risk, making diagnoses, and for initiating lipid-lowering drug therapy. Finally, within countries with differing ethnic groups, the policy on non-fasting might need to be further refined. Indeed, e.g. individuals of South Asian or Latin American descent are more likely to have severe triglyceride elevations when compared with individuals of non-Hispanic white and black descent. This could be another reason to have a caveat about avoiding a high-fat, fast-food meal on the day of lipid profile testing.

Authors’ contributions

EAS/EFLM Joint Consensus Panel members were nominated by EAS, EFLM, and the Co-chairs B.G.N. and M.L., to represent expertise across clinical and laboratory management and research in lipids from across the world. The Panel met twice, organized and chaired by M.L. and B.G.N. The first meeting critically reviewed the literature while the second meeting reviewed additional literature and scrutinized the first draft of the joint consensus statement. All Panel members agreed to conception and design, contributed to interpretation of available data, suggested revisions for this document, and approved the final document before submission.

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References

1. Rifi N, Warnick GR. Lipids, lipoproteins, apolipoproteins, and other cardiovascular risk factors. In: Burts CA, Ashworth ER, Bruns DE (eds), Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ed. Philadelphia: Elsevier Saunders; 2006. pp 903–982.

2. Simundic AM, Cornes M, Grankvist K, Lippi G, Nybo M. Standardization of collection requirements for fasting samples: for the Working Group on Preanalytical Phase (WG-PA) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). Clin Chem 2014; 60:33–137.

3. Langsted A. Fasting and non-fasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation 2008; 118:2047–2056.

4. Mora S, Rifi N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation 2008; 117:1001–1007.

5. Watts GF, Cohn JS. Whither the lipid profile: feast, famine, or no free lunch? Clin Chim Acta 2011; 363–365.

6. Gaziano JM. Should we fast before we measure our lipids? Arch Intern Med 2012; 172:1703–1706.

7. Khera AV, Mora S. Fasting for lipid testing: is it worth the trouble? Arch Intern Med 2012; 172:1710–1712.

8. Nordestgaard BG, Hilsted L, Stender S. Plasmalipider hos ikkefastende patienter og signalværdier på laboratoriesvar. Ugeskr Laeger 2009; 171:1093.

9. Langsted A. Nordestgaard BG. Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58 434 individuals from the Copenhagen General Population Study. Clin Chim Acta 2011; 37:482–489.

10. NICE clinical guideline CG181. Lipid modification: cardiovascular risk assessment and management. Circulation 2008; 118:1001–1007.

11. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Ginsberg H. Anewer M, Boren J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Watts GF. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2012; 6:653–666.

12. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63:2899–2934.

13. Pennathur S. Triglycerides and cardiovascular disease: a scientific statement from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2013; 34:3521–3537.

14. Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, Filardi PP, Masana L, Reiner Z, Taskinen MR, Tokgozoglu L, Tybjaerg-Hansen A. Lipoprotein(a) and increased risk of myocardial infarction. J Am Coll Cardiol 2011; 57:363–365.

15. Jones SR. Comparison of a novel method vs the Friedewald equation for estimating high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011; 32:1345–1361.

16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of preparative ultracentrifugation. Clin Chem 1972; 18:499–502.

17. Tanno K, Okamura T, Ohsawa M, Onoda T, Ikai S, Kakata K, Nakamura M, Oiga T, Kawamura K, Okayama A. Comparison of low-density lipoprotein cholesterol concentrations measured by a direct homogeneous assay and by the Friedewald formula in a large community population. Clin Chim Acta 2010; 411:1774–1780.

18. Mora S, Rifi N, Buring JE, Ridker PM. Comparison of LDL cholesterol concentrations by Friedewald calculation and direct measurement in relation to cardiovascular events in 27 331 women. Clin Chem 2009; 55:888–894.

19. Varbo A, Benn M, Tybjerg-Hansen A, Jorgensen AB, Frikile-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013; 61:427–436.

20. Varbo A, Benn M, Tybjerg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Gastroenterology 2013; 145:1208–1209.

21. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2013; 384:626–635.

22. Kamstrup PR, Tybjerg-Hansen A, Steffen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009; 301:2331–2339.

23. Khera AV, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. Clin Chim Acta 2011; 412:1783–1787.

24. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuvienenhofen JA, Averna M, Boren J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Watts GF, Wiklund O. The nongenetic nature of hypertriglyceridaemia: implications for defin-
37. Doran B, Guo Y, Xu J, Weintraub H, Mora S, Maron DJ, Bangalore S. Prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol levels on long-term mortality: insight from the National Health and Nutrition Examination Survey III (NHANES-III). *Circulation* 2014;130:546–553.

38. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008;300:2142–2152.

39. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007;298:309–316.

40. White KT, Moorthy MV, Akinkuolie AO, Demler O, Ridker PM, Cook NR, Mora S. Identifying an optimal cutoff point for the diagnosis of hypertriglyceridemia in the nonfasting state. *Clin Chem* 2015;61:1116–1125.

41. Langsted A, Nordestgaard BG. Nonfasting lipid profiles: the way of the future. *Clin Chem* 2015;61:1123–1125.

42. Kolovou GD, Mikhailidis DP, Kovar J, Laino D, Nordestgaard BG, Ooi TC, Perez-Martinez P, Biliounou H, Aragnostroupolou K, Panopoulou G. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement. *Curr Vasc Pharmacol* 2011;9:258–270.

43. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masa L, Descamps OS, Wiklund O, Hegele RA, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Averna M, Pajukanta P, Ray K, Stalenhoef AF, Stroes ES, Taskinen MR, Tybjaerg-Hansen A. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478–3490.

44. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray K, Stalenhoef AF, Stroes ES, Taskinen MR, Wiklund O. Familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;35:2146–2157.

45. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Boren J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Ray K, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Wiklund O. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;36:2425–2437.

46. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechivanis S, Budoff MJ, Harris TB, Malhotra R, O’Brien KD, Kamstrup PR, Nordestgaard BG, Tybjaerg-Hansen A, Averna M, Aspelund T, Cnqui MH, Heckbert SR, Hwang SJ, Liu Y, Spogran M, van der Pals J, Kalsch H, Muhleisen TW, Nothen MM, Copples LA, Caslake M, Di AE, Danesh J, Rotter JI, Sigurdsson S, Wong Q, Erbel R, Kathiresan S, Melander O, Gudnason V, O’Donnell CJ, Post WS. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;368:503–512.

47. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;63:470–477.

48. Jessen RH, Dass CJ, Eckfeldt JH. Do enzymatic analyses of serum triglycerides really need blanking for free glycerol? *Clin Chem* 1990;36:1372–1375.