Non-HDL or LDL cholesterol in heterozygous familial hypercholesterolaemia: findings of the Simon Broome Register

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Abstract

Purpose of review: The role of non-high-density lipoprotein cholesterol (non-HDL-C) in the identification and management of lipid disorders is not clearly defined, although UK guidelines recommend its wider use in assessing the need for lipid-lowering therapy and as a treatment target.

Recent findings: We examined the implications of the use of non-HDL-C as opposed to LDL-C in 253 people with hypercholesterolaemia before treatment and 573 after treatment in whom fasting total serum cholesterol, HDL-C and LDL-C had been recorded and the diagnosis of heterozygous familial hypercholesterolemia (heFH) was investigated by genetic testing. The difference and the limits of agreement between non-HDL-C and LDL-C calculated using the Friedewald formula were assessed in those with and without heFH-causing mutations.

Summary: There were 147 mutation positive and 106 mutation-negative pre-treatment participants and 395 mutation positive and 178 mutation-negative patients receiving treatment. The difference between non-HDL-C and LDL-C pre-treatment in mutation-positive people (mean LDL-C 7.73mmol/l) was 0.67 mmol/L (95% CI 0.62–0.73) and post-treatment (mean LDL-C 4.71mmol/l) was 0.62 mmol/l (95% CI 0.59–0.65) with wide limits of agreement of -0.02–1.37 mmol/L and 0.07–1.18 mmol/L respectively. Among patients with heterozygous familial hypercholesterolaemia, use of estimated LDL-C derived from non-HDL-C in place of calculated LDL-C may result in diagnostic misclassification and difficulty in assessing the true reduction in LDL-C with treatment, because of the wide inter-individual limits of agreement around the mean difference between non-HDL-C and LDL-C.

Key words: heterozygous familial hypercholesterolemia, diagnosis, non-HDL-cholesterol, LDL-cholesterol

Key points

- NICE and the Joint British Societies recommended replacement of LDL-C with non-HDL-C, including in the identification and treatment of heterozygous familial hypercholesterolaemia (heFH), whereas other bodies in Europe and North America continued to advise the use of LDL-C in heFH
- Non-HDL-C was introduced to monitor treatment in hypertriglyceridaemia too severe to permit LDL-C measurement in routine clinical laboratories. Even for this purpose it has recently received criticism, evidence favouring the use of apolipoproteinB in these circumstances.
- We compare LDL-C and non-HDL-C before and after treatment in a large series of genetically identified heFH patients.
- Non-HDL offered no advantage over LDL-C and could contribute to misdiagnosis and undertreatment.

Introduction

The use of non-high-density lipoprotein cholesterol (non-HDL-C) in treatment decision-making is recognised in the current American College of Cardiology/ American Heart Association guidelines to be a critical question that should be addressed in future [1]. The earlier Adult Treatment Panel III guidelines [2] had recommended non-HDL-C as a treatment target when triglyceride concentrations concentrations exceed 4.5mmol/l, when they are too high for LDL cholesterol to be estimated using the Friedewald formula [3]. The Joint British Societies' guidelines (JBS3) [4] and the United Kingdom National Institute for Health and Clinical Excellence (NICE) [5] go further and both employ non-HDL-C both for identification of dyslipidaemia and monitoring of treatment. The rationale for this was that the Friedewald estimation of LDL cholesterol requires a fasting blood samples. More

recently it has become evident that the small increment, if any, in triglycerides in non-fasting samples in the general population does not invalidate the results of LDL-C estimated from Friedewald [6]. In any case ,NICE and JBS3 recommended a fasting sample to include triglyceride as well as total serum cholesterol and HDL-C when high non-HDL-c is encountered on initial screening [4,5].

The use of non-HDL-C therapeutic targets in clinical practice has recently been criticised for use in dyslipidaemia in general, but ironically in particular in hypertriglyceridaemia for which it was introduced, because the relative proportions of LDL-C and VLDL-C which comprise non- HDL-C is highly variable depending on the triglyceride concentrations [7]. Apolipoprotein B is increasingly recognised as a better target, especially in hypertriglyceridaemia [8-10]. In the case of heterozygous FH (HeFH) triglyceride concentrations are not, however, elevated. Indeed, raised triglyceride values reduce the likelihood that hypercholesterolaemia is due to HeFH [11]. The use of non-HDL-C as a screening test to select people suitable for specialist investigation of possible HeFH may thus have some merit despite as yet lacking any evidence base. However, the only evidence that non-HDL cholesterol can replace LDL cholesterol in monitoring treatment was a meta-analysis of summary results of randomised controlled statin trials in which non-HDL cholesterol values were obtained by multiplying the reported LDL cholesterol concentrations by 1.24, which was the average ratio between non-HDL-C and LDL-C in the trials included [12]. The typical LDL-C concentration in clinical end-point statin trials is lower than in HeFH and thus the ratio cannot extend to HeFH.

The British recommendations could thus have unforeseen implications, if applied to the identification and management of individuals with a possible diagnosis of HeFH,

which is the commonest autosomal dominant condition with a gene frequency of between 1:250 and 1:500 [13-14]. It is characterised by elevated concentrations of LDL-C and results in a substantially increased risk of early coronary disease [15,16] that can be reduced with cholesterol-lowering drug therapy [17,18] As LDL-C concentration is a crucial component of the diagnostic criteria, it is important to determine whether using a derived estimate of LDL-C from a reported non-HDL-C concentration is valid. To derive non-HDL-C thresholds and targets from their LDL-C equivalents, the US Adult Treatment Panel III (ATPIII) specified the addition of 0.78 mmol/L provided the triglyceride concentration was less than 1.7 mmol/l [2]

Our aims were (i) to report the results of non-HDL-C and LDL-C routinely available from clinical laboratories in patients with genetically diagnosed HeFH; (ii) to compare these with values specified in published guidelines, and (iii) to determine whether the limits of agreement of the observed difference between non-HDL-C and LDL-C are sufficiently close to allow conversion of non-HDL-C to LDL-C to be used to identify individuals with a possible diagnosis of heFH and to assess the effect of treatment.

Methods

Participants

We studied 697 people who had been tested for monogenic heFH-causing mutations (*LDLR*, *APOB* or *PCSK9*). All were white Caucasian and all had either been referred to the clinic by their primary care physician with a presumptive diagnosis of possible heFH based on an elevated total or LDL-C concentration or had been identified as having a clinical diagnosis of heFH by screening families already attending a clinic (Table 1). They were aged 18 or over. There were 295 who at the time of referral were not receiving treatment and 579 on treatment with complete data to allow

calculation of both LDL-C and non-HDL-C. Local Ethical Committee approval was obtained by the participating clinics. The recruitment methods and detailed clinical characteristics for the two groups of patients have been described previously [19,20]. Of the participants 409 with xanthomatous heFH were attending one of six hospital specialist outpatient lipid clinics in England [19]. They had agreed to participate in the Simon Broome British Heart Foundations Study (SBBHF). An additional 288 attended the Lipid Clinic in Oxford, UK (OXFH) [20]. They were categorised into 3 groups according to the following clinical criteria [14]. Definite heFH (total cholesterol concentration >7.5 mmol/L and/or an LDL-C >4.9 mmol/L (using the highest treated or untreated concentration), together with the presence of tendon xanthomas either in the patient or in a parent, child, grandparent, sibling, uncle or aunt), possible (in the absence of tendon xanthomata, a family history of myocardial infarction below the age of 50 in a 2nd degree relative, or below the age of 60 in a 1st degree relative or, alternatively, a family history of raised cholesterol concentrations >7.5 mmol/L in an adult 1st or 2nd degree relative or >6.7 mmol/L in child or sibling under 16) and unclassified (patients who had been referred to the clinic by their primary care physician with a presumptive diagnosis of possible heFH based on an elevated total or LDL-C). Of the total 697 participants 473 met the criteria for definite heFH,150 for possible heFH and 74 for unclassified hypercholesterolemia. They were reclassified into mutation-positive and mutation-negative when the results of DNA testing were known.

Biochemical and molecular genetic analyses

Blood samples were obtained fasting by venepuncture. Measurement of pre-treatment lipids and lipoproteins for the SBBHF group was undertaken by the routine

National Health Service hospital biochemistry laboratory used by the participating patient's general practice. Post-treatment concentrations were measured by a central laboratory (details published previously) [19]. Pre- and post-treatment blood samples for lipid and lipoprotein concentrations for the OXFH participants were taken in primary care and measured by the Oxford John Radcliffe Hospital biochemistry laboratory. All laboratories participated in the same national quality control scheme. LDL-C concentrations were calculated using the Friedewald equation (LDL-C = total serum cholesterol – (HDL-C + triglyceride/2.19) [3,21]. Triglyceride divided by 2.19 is the VLDL-C. The Friedewald factor is 2.19 (equivalent to a value of 5 when units are mg/dl as in the original publication [3]). For each patient receiving treatment the most recent LDL-C and non-HDL-C value was analysed.

Molecular genetic analyses were undertaken for both groups of patients by the same laboratory and a detailed description of the methods has been published previously [19].

Statistical analyses

The distribution of age, sex and mutation status was calculated for each of the two patient groups. Subsequent analyses, after combining the two patient groups, were conducted after stratifying patients by the presence or absence of a mutation. Non-HDL-C concentrations were calculated by subtracting HDL-C from the total cholesterol concentration. We calculated the mean difference with 95% confidence intervals between non-HDL-C and LDL-C for the mutation positive and negative groups before and after treatment. We excluded from the analyses eight mutation negative and 11 mutation positive patients with triglyceride concentrations >3.5

mmol/L since secondary causes of hypertriglyceridaemia could not be excluded and the Friedewald formula is invalid for concentrations exceeding 4.5 mmol/L [21] and two pre-treatment and five post-treatment outliers (defined as differences in non-HDL-C minus LDL-C that were more than +4SD from the mean). The statistical significance of differences between the pre- and post-treatment mean differences were tested using a paired t-test, between mutation groups using a two sample t-test, and were compared to the published conversion values using a one-sample test.

We examined the limits of agreement of the difference between non-HDL-C and LDL-C in mutation positive subjects using Bland-Altman plots [22]. The mean LDL-C was calculated for each subject using (i) the value derived from the Friedewald formula and (ii) from the mean difference between non-HDL-C and LDL-C obtained from the study (pre-treatment 0.67 mmol/L (95% CI 0.62–0.73) and post-treatment 0.62 mmol/l (95% CI 0.59–0.65). See results.). This was plotted on the x-axis against non-HDL-C minus LDL-C (calculated using the Friedewald formula) on the y-axis. Analyses were undertaken separately using conversion factors for the derivation of non-HDL-C of 0.78 added to LDL-C (additive model) and of LDL-C multiplied by 1.24 (multiplicative model). For the multiplicative model, data were logarithmically transformed (Ln x) before the analysis.

The limits of agreement were shown graphically as $\pm$2SDs of the mean difference between non-HDL-C minus LDL-C. For comparison, the two published values for converting non-HDL-C to LDL-C using additive and multiplicative models were also shown on the respective Bland-Altman plots. Differences in variance across the range of LDL-C were assessed by Pitman's Test. A linear regression analysis was

conducted to examine the relationship between the triglyceride concentration and the pre-treatment difference in non-HDL-C minus LDL-C. The statistical analyses were conducted using Stata Version 13 (StatCorp, Texas).

Results

The age and sex distribution among the 697 patients in the two groups is shown in Table 1. All subjects in the SBBHF group had clinically defined definite heFH compared with only 22% of the OXFH group and the proportion of mutations identified was therefore higher in the SBBHF than OXFH group (81.7% vs 35.4%). Overall 62.6% were mutation-positive and 92.8% of the identified mutations were in *LDLR*, with 5.5% in *APOB* and 1.6% in *PCSK9.*Pre-treatment and post-treatment LDL-C and non-HDL-C results were available for 253 and 573 participants respectively (Table 2). The higher number receiving treatment is because of referrals already on a statin.

Table 2 shows the pre- and post-treatment lipid and lipoprotein concentrations for mutation positive and negative groups, and demonstrates with treatment the expected decrease of more than 30% in both LDL-C and non-HDL-C. Overall, the pre-treatment difference between non-HDL-C and LDL-C was significantly higher at 0.75 mmol/L than the post-treatment difference of 0.65 mmol/L ($p=4x10^{-5}$). The pre- and post-treatment differences for the mutation-positive subjects of 0.67 mmol/L and 0.62 mmol/L respectively were significantly smaller than those of the mutation-negative subjects (0.87 mmol/L [p=0.0003] and 0.71 mmol/L [p=0.0007]). There was a positive correlation (r=0.80) between the individual differences in non-HDL-C

minus LDL-C and the corresponding triglyceride concentrations (slope 0.454 (0.028) and intercept 1.35 (SE 1.67)).

The Bland-Altman plots for mutation-positive subjects show wide inter-individual limits of agreement for the mean difference between non-HDL-C and LDL-C pre- and post-treatment. The mean difference pre-treatment was 0.67 mmol/L (8.7%) with limits of agreement of -0.02—1.37 mmol/L (figure 1) and the variance changed significantly over the range of observations of LDL-C (r=0.235, p=0.04). The figure also shows that the observed difference was significantly smaller (0.11 mmol/l, 95% CI 0.05-0.16, p=0005) than the ATPIII subtraction value of 0.78.

Figure 2 shows the mean difference to be less post-treatment at 0.62 mmol/L, with the limits of agreement remaining wide at 0.07—1.18 mmol/L and with the variance changing significantly (r=0.165, p=0.001) across the range of values. The observed difference was significantly smaller (0.16 mmol/L, 95% CI 0.13—0.19, p=0005) than the ATPIII value of 0.78

Data plots for the multiplicative analyses are shown as supplementary figures 3 and 4. The differences pre- and post-treatment were similar to the additive model, with non-HDL-C being 8.5% (95% CI 8.0-9.6) and 13.9% (13.2—14.6) higher respectively than LDL-C. The mean difference pre-treatment (log n) was 0.085 (95% CI 0.077—0.092) and post-treatment 0.130 (0.124—0.136). Compared with the additive model, log-transformation did not consistently improve changes in the variance with increasing LDL-C concentrations (pre-treatment r = -0.148, n = 147, p = 0.081; and post-treatment r = -0.382, n = 395, p = 3.4×10^{-15}).

Discussion

Among pre-treatment patients with a genetically confirmed diagnosis of heFH, using an additive analysis we found a mean difference between non-HDL-C and LDL-C of 0.67 mmol/L, but the wide inter-individual limits of agreement indicate that for any particular patient the accuracy with which their LDL-C can be estimated using non-HDL-C is poor. This partly reflects some random analytical variability, but principally inter-individual biological variability in very low-density lipoprotein (VLDL-C) concentration. The additive conversion factor (VLDL-C) of 0.78 in theory can only be correct when the triglyceride concentration is 1.7mmol/l (VLDL-C is then 1.7/divided by the Friedewald factor of 2.19). At lower triglyceride concentrations VLDL-C is <0.78mmol/l and when triglycerides exceed 1.7mmol/l VLDL-C will be >0.78mmol/l. This is consistent with our finding of a strong correlation (r=0.80) between triglyceride concentrations and differences in non-HDL-C and LDL-C. The wide limits of agreement would result in diagnostic misclassification if either our observed subtraction value, or the ATPIII value, are used to estimate LDL-C concentration in clinical practice. With statin treatment the difference between non-HDL-C and LDL-C was smaller reflecting a likely reduction in VLDL-C, but the decrease in the conversion value with treatment, and the wide inter-individual variability, would complicate the use of non-HDL-C in assessing the true reduction in LDL-C with statins or other cholesterol-lowering treatment.

Theoretically multiplying LDL-C by 1.24 to obtain the equivalent non-HDL-C will be correct only when LDL-C is exactly 3.25mmol/l and triglycerides are exactly 1.7mmol/l (3.25 X 1.24 = 4.03 = 3.25 + 0.78). It is thus affected by *both* LDL-C and

triglyceride concentrations. For example, if LDL-C on treatment is 2mmol/l, non-HDL is theoretically 2.48, but for this to be correct triglycerides must be exactly 1.05mmol/l. At a higher LDL-C value, say 6mmol/l, the non-HDL-C would be expected to be 7.44mmol/l (6 X 1.24 = 7.44), but only if the triglyceride value is exactly 3.15mmol/l (1.44 x 2.19 = 3.15). Our results confirm that the multiplicative factor of 1.24 used in the JBS3 guidelines [4] can only exceptionally estimate LDL-C concentrations correctly.

The study was based on 698 well characterised individuals of whom nearly two thirds had a genetically confirmed diagnosis of heFH, the majority of which were due to causative mutations in the *LDLR* gene. There are, however, a number of limitations. A full fasting lipid profile was only available pre-treatment for 147 patients with an identified mutation, often because they had been started on therapy before attending a specialist clinic or, in some instances, previous records were unavailable. The lipid and lipoprotein measurements were undertaken by several different hospital biochemistry laboratories, but all participated in UK external quality assurance schemes, which assess their accuracy in relation to a consensus mean of the method used. Most laboratories track close to the consensus mean for the various schemes and will achieve accuracy well within the recommended three per cent for the method [23]. Perhaps most important was that our study was of guidelines for clinical practice and these thus should rightly be evaluated using routinely available lipid results.

It should be appreciated that our samples were obtained fasting. Strictly speaking non-fasting samples as well as VLDL-C also contain any circulating remnant

cholesterol present. Except in the absence of delayed clearance, usually indicated by high triglyceride concentrations, the remnant contribution to VLDL cholesterol is usually negligible, except shortly after a very fatty meal. This is the reason that LDL-C concentrations estimated by the Friedewald equation and measured directly in non-fasting samples have a high measure of agreement [6]. None the less, any greater inaccuracy of the Friedewald formula in non-fasting samples (which was the justification for introducing non-HDL generally into lipid practice), would lead to a larger difference between non-HDL-C and LDL-C with wider limits of agreement due to greater inter-individual variability. We were not able to estimate the extent to which Lp(a) contributed to either LDL-C or non-HDL-C which in some individuals may be a significant confounder since about 30% of Lp(a) mass is cholesterol [24]. Nevertheless, as the frequency distribution of Lp(a) is highly positively skewed, the mean percentage contribution to LDL-C and non-HDL-C concentrations would have been small and concentrations would only be appreciably overestimated in a few individuals with substantially elevated Lp(a) concentrations.

There do not appear to be any previously published studies that have assessed the inter-individual variability in difference between non-HDL-C and LDL-C in patients with heFH and examined the implications. There are, of course, a number of advantages in using non-HDL-C measurement in assessing cardiovascular risk. In particular, non-fasting sampling is more convenient, and calculated LDL-C may be inaccurate in patients who have triglycerides >4.5 mmol/L, or have low LDL-C concentrations [21]. However, any potential advantages of using non-HDL-C are offset by the wide inter-individual variability in the difference between non-HDL-C and LDL-C concentrations, which is sufficiently large to result in diagnostic

misclassification among patients with heFH. This is evident when examining the implications of the UK NICE recommendation, that individuals with a non-HDL-C >7.5 mmol/L should receive specialist assessment to exclude heFH [5]. Using our observed conversion value, this equates to an LDL-C threshold of 6.8 mmol/L with limits of agreement ranging widely from 6.1 to 7.5 mmol/L. There would be an approximately normal frequency distribution around the true value, but an individual with an LDL-C of 6.8 mmol/L would, nevertheless have a 50% chance of their estimated LDL-C being below this threshold. To put this into context, a third of the sequentially recruited Oxford clinic participants with a genetically confirmed diagnosis of heFH (49/147) would have been excluded by this threshold. With regard to the monitoring of treatment, evidence suggests that among statin-treated patients, neither LDL-C nor non-HDL-C concentrations are associated with future major cardiovascular events as closely as concentrations of apolipoprotein B [25]. There is a cogent need to evaluate this further in heFH rather than shift from LDL-C to non-HDL-C.

Most of the 1 in 250-500 people with heFH go undiagnosed [26] despite increasing recognition that, even whilst asymptomatic, it should be regarded as an ASCVD risk equivalent [27]. Without the diagnosis being suspected by the non-lipid specialist clinician making the initial contact, this situation is likely to persist. We now know that almost 1 in 10 of younger patients admitted to coronary care units have heFH [28-30]. The introduction of unfamiliar indices with no clear benefit, such as non-HDL-C, is only likely to confuse the situation further and to foster continuing inactivity. LDL-C or, failing that total serum cholesterol, afford people with heFH the best opportunity of gaining access to specialist services [31]. The recent revision of the NICE recommendations specifically relating to FH recognise this [32] and it is relevant

that, based on published evidence, the NICE clinical indications for PCSK9 inhibition rely on LDL-C not non-HDL-C [33].

In summary, the principal clinical implications of our study are that using a using a non-HDL-C derived estimate of LDL-C concentration in individuals with a possible diagnosis of heFH will result in diagnostic misclassification in a significant proportion and difficulty in assessing the true reduction in LDL-C with treatment. Consequently, if an individual's phenotypic features include an elevated total cholesterol concentration together with a family or personal history of premature coronary heart disease, or when no family history can be elicited, a fasting venous blood sample should be taken to calculate LDL-C using the Freidewald formula. If the LDL-C concentration is consistent with a clinical diagnosis of heFH, this should be confirmed by a DNA test, as recommended by NICE CG71, to increase the certainty of the diagnosis and to assist the identification of affected relatives [26,27].

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Conflicts of interest: none

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A clinical case-finding algorithm, the familial hypercholesterolaemia case ascertainment tool (FAMCAT) identifies familial hypercholesterolaemia in a primary care register with greater accuracy than currently recommended approaches.

32. **National Institute for Health and Clinical Excellence (NICE). Familial hypercholesterolaemia: identification and management 2019 https://www.guidelines.co.uk/genetic-conditions/nice-fh-guideline/453843.article

*Advice to search primary care records for people younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l **and** 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l as these are the people who are at highest risk of FH*

33. Carroll C, Tappenden P, Rafia R, et al. Evolocumab for Treating Primary Hypercholesterolaemia and Mixed Dyslipidaemia: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics*. 2017;35(5):537–547. doi:10.1007/s40273-017-0492-6

Table 1. Age, gender and mutation status of two study groups. SBHF, Simon Broome British Heart Foundations Study; OXFH, Oxford Lipid Clinic .

	SBBHF n=409	OXFH n=288
Age (years)	49.1 (13.6)	58.1 (14.0)
% male	51.3% (210)	49.8% (144)
Mutation % (n)		
None	18.3% (75)	64.6% (186)
LDLR	76.8% (314)	31.6% (91)
APOB	3.2% (13)	3.8% (11)
PCSK9	1.7% (7)	0 (0)

Table 2. Pre- and post-treatment mean (SD) non-HDL-C and LDL-C in mutation positive- and mutation-negative participants

		LDL-C mmol/l	Non-HDL-C mmol/l	Difference (95% CI)	% Difference
Mutation Positive	Pre-treatment (n=147)	7.73 (1.74)	8.40 (1.82)	0.67 (0.62 to 0.73)	8.7%
	Post-treatment (N=395)	4.71 (1.30)	5.33 (1.34)	0.62 (0.59 to 0.65)	13.2%
Mutation Negative	Pre-treatment (n=106)	6.43 (1.41)	7.29 (1.45)	0.87 (0.78 to 0.96)	13.5%
	Post-treatment (n=178)	3.72 (1.36)	4.43 (1.45)	0.71 (0.66 to 0.76)	19.1%
Overall	Pre-treatment (N=253)	7.19 (1.73)	7.94 (1.76)	0.75 (0.70 to 0.81)	10.5%
	Post-treatment (n=573)	4.40 (1.39)	5.05 (1.44)	0.65 (0.63 to 0.67)	14.7%

Figure captions:

Figure 1. Bland-Altman plot showing difference between non-HDL-C and LDL-C plotted against mean LDL-C concentration in 147 mutation positive heFH patients before receiving cholesterol-lowering treatment. Additive model to examine validity of non-HDL-C is equal to LDL-C plus 0.78mmol/l. All values are in mmol/l.

Figure 2. Bland-Altman plot showing difference between non-HDL-C and LDL-C against mean LDL-C concentration in 395 mutation positive heFH patients after receiving treatment. Additive model to examine validity of non-HDL-C is equal to LDL-C plus 0.78mmol/l. All values are in mmol/l.

Figure 3. Bland-Altman plots comparing non-HDL-C and LDL-C concentrations in 147 mutation positive heFH patients before receiving cholesterol-lowering treatment. Multiplicative model to examine validity of non-HDL-C equates to LDL-C multiplied by 1.24. All values are in mmol/l.

Figure 4. Bland-Altman plots comparing non-HDL-C and LDL-C concentrations in 395 mutation positive heFH patients after receiving treatment. Multiplicative model to examine validity of non-HDL-C equates to LDL-C multiplied by 1.24. All values are in mmol/l.

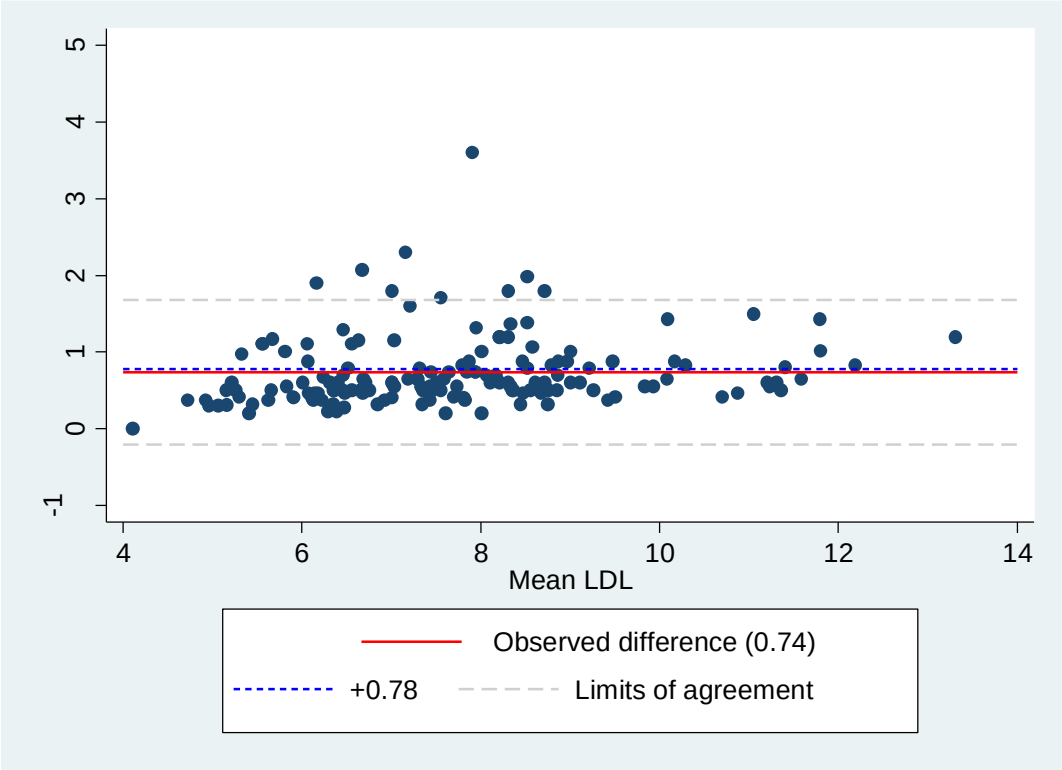

Figure 1.

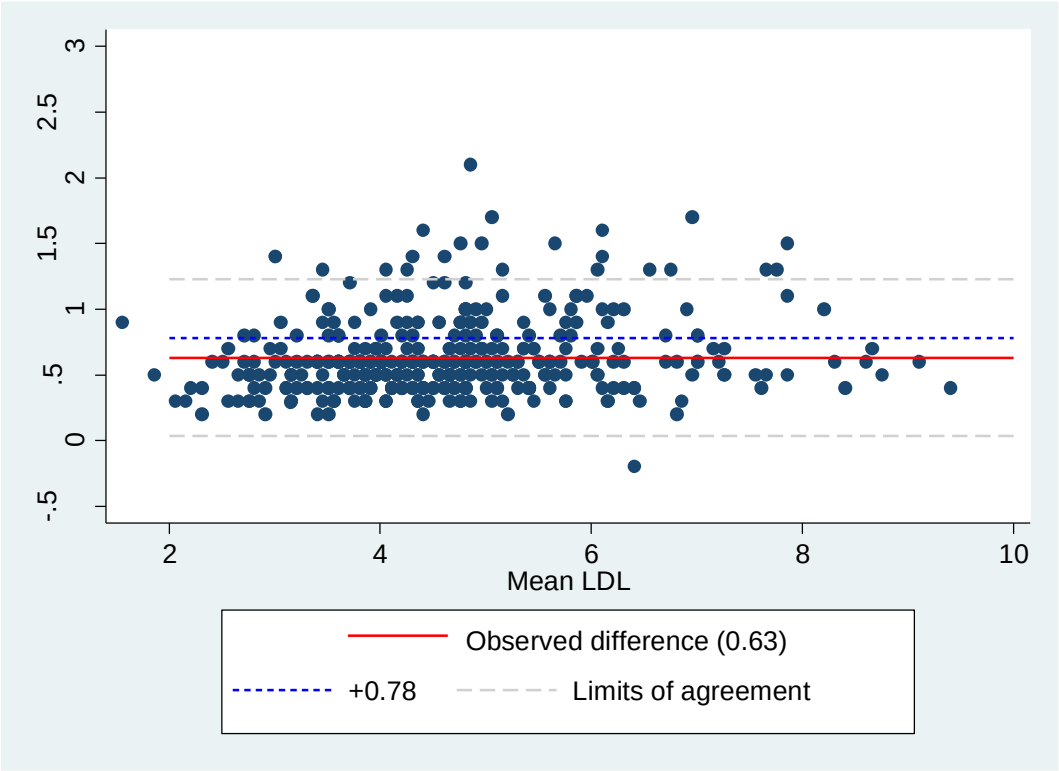

Figure 2.

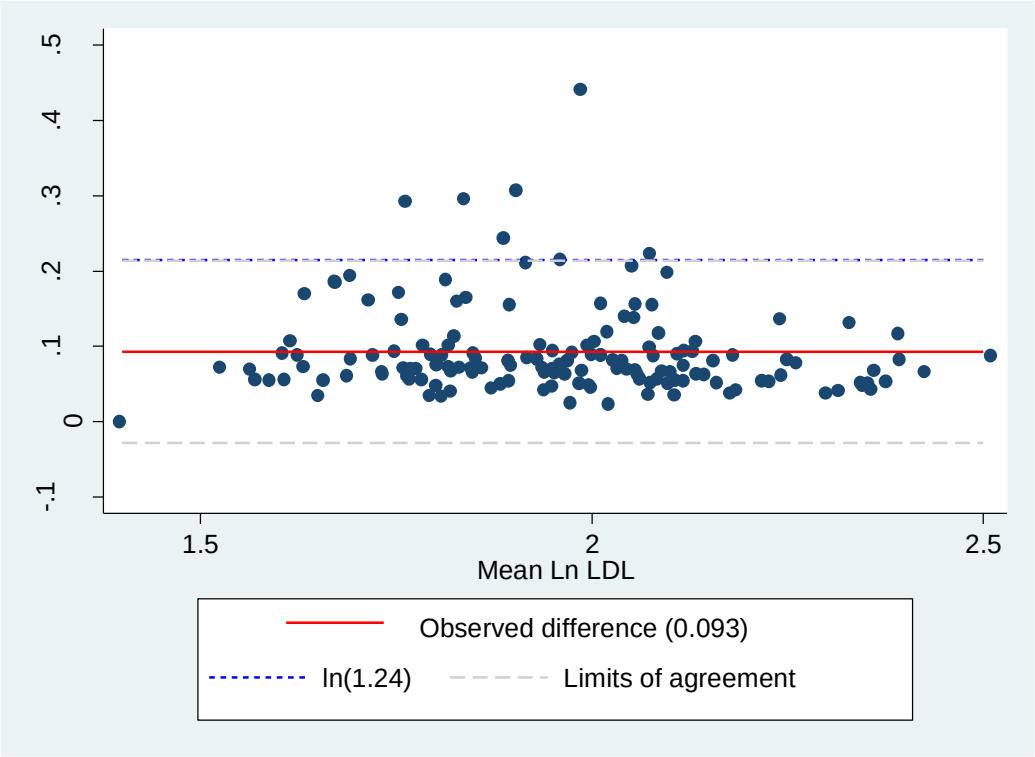

Figure 3

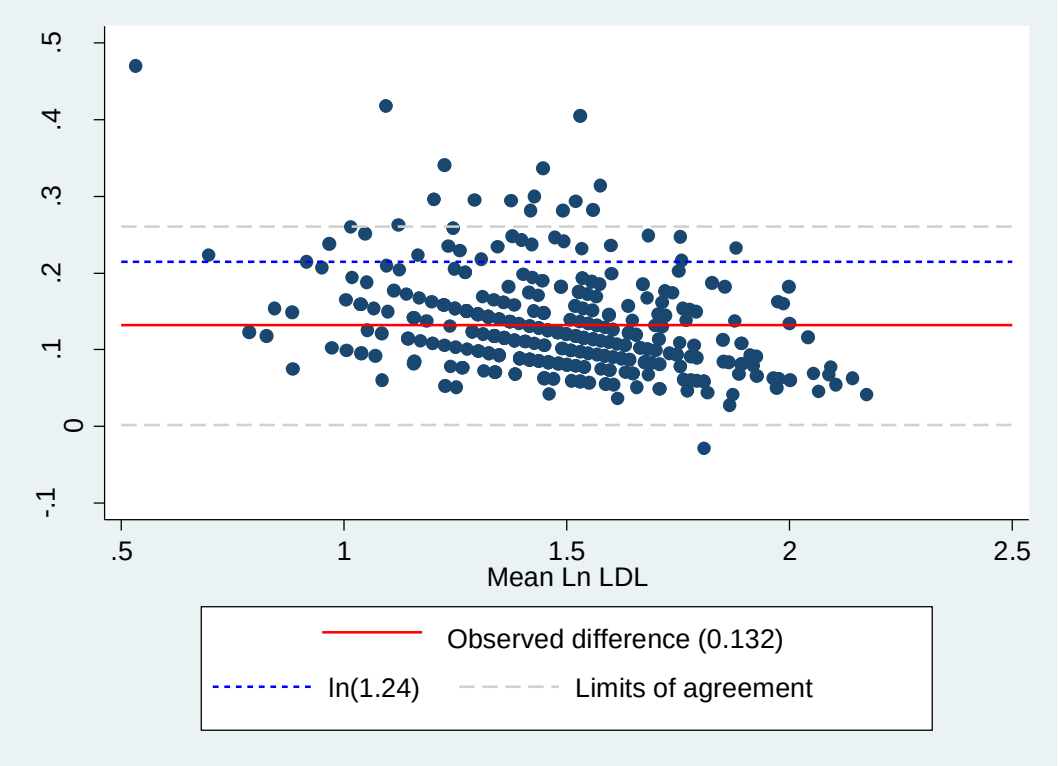
-.1
0
.1
.2
.3
.4
.5
.5
1
1.5
2
2.5
Mean Ln LDL
Observed difference (0.132)
ln(1.24)
Limits of agreement

Figure 4