Discriminative Ability of LDL-Cholesterol to Identify Patients With Familial Hypercholesterolemia
A Cross-Sectional Study in 26 406 Individuals Tested for Genetic FH

Roeland Huijgen, MD; Barbara A. Hutten, PhD; Iris Kindt, MD; Maud N. Vissers, PhD; John J.P. Kastelein, MD, PhD

Background—Screening for familial hypercholesterolemia (FH) within affected families is often based on cutoff values for low-density lipoprotein cholesterol (LDL-C). However, the diagnostic accuracy of LDL-C levels is influenced by the magnitude of the LDL-C overlap between FH patients and unaffected relatives. The purpose of the current study was to assess to what extent this overlap is influenced by the severity of specific FH mutations.

Methods and Results—Individuals were eligible if they underwent family screening for FH between 2003 and 2010. The entire cohort was then compared with those who were investigated for the presence of the most severe mutations (class 1). The area under the receiver operating characteristics curve and the sensitivity of the 90th percentile of LDL-C was calculated for both cohorts. We included 26 406 individuals, of whom 9169 (35%) carried an FH-causing mutation. In the entire cohort at baseline, mean LDL-C was 4.63±1.44 mmol/L for FH carriers (n=5372) and 2.96±0.96 mmol/L for unaffected relatives (n=15 148); P<0.001. The corresponding operating characteristics curve (95% CI) was 86.6% (85.9%–87.2%), and the cutoff level of LDL-C above the 90th percentile showed a sensitivity of 68.5%. The operating characteristics curve and sensitivity significantly improved when the 5933 individuals tested for class 1 mutations were assessed separately; 96.2% (95.3%–97.1%) and 91.3%, respectively.

Conclusions—In summary, the overlap in terms of LDL-C levels between those with molecularly proven FH and unaffected relatives is to a large extent because of the high prevalence of modestly severe LDL-receptor mutations in the Netherlands.

Key Words: familial hypercholesterolemia genotyping LDL-C LDL-receptor cascade testing

Familial hypercholesterolemia (FH) is a prevalent and inherited disorder of lipoprotein metabolism, characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and, if left untreated, premature coronary artery disease (CAD).1 Cholesterol-lowering treatment has been shown to dramatically reduce CAD risk in patients with FH and, as a consequence, early identification of FH patients followed by effective treatment is important.2,3 Therefore, current guidelines stipulate screening of relatives of patients with FH for the presence of that condition.4,5

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Screening for individuals with elevated LDL-C levels may occur at the general population level (ie, population screening strategy), or may be targeted to relatives of previously identified carriers, sometimes in conjunction with molecular analysis. The latter strategy is known as genetic cascade screening. In the Netherlands, a nationwide genetic cascade screening for FH has been ongoing since 1994. For this purpose, DNA samples from clinically suspected FH patients are analyzed for the presence of an LDLR or APOB mutation.6 A patient is considered a proband for family screening when a pathogenic mutation has been identified. Subsequently, first-degree relatives of the identified probands are offered DNA analysis for the presence of the specific FH-causing mutation. Cascade screening is extended to identify distant relatives of the probands by using the inheritance pattern across the pedigree.7 Hitherto, more than 20 000 FH heterozygotes have been identified with this strategy.

An alternative strategy to perform cascade screening for FH is based on LDL-C cutoff values.8,9 A potential limitation of this strategy is the overlap of these levels between carriers of an FH mutation and unaffected relatives.9 The extent of overlap between carriers and noncarriers may differ from family to family. For example, within our cohort, approximately 15% of the untreated subjects with molecularly
proven FH do not exhibit severely elevated LDL-C levels at diagnosis.\textsuperscript{7,10} In contrast, the overlap in cholesterol levels between carriers and noncarriers in a Japanese study was minimal.\textsuperscript{11} This difference in overlap may determine the sensitivity of LDL-C cutoff levels in the diagnosis of FH between different countries and may be related to severity of the LDL-receptor gene mutations in those regions.

The purpose of the current study was to assess to what extent the overlap in cholesterol levels between carriers and unaffected relatives is related to the severity of the mutation. We evaluated the discriminative ability of LDL-C to diagnose genetic FH in 5 subsequent selection steps toward severe mutations. Here, we present our results.

Methods

Study Population

The source population for this study was derived from the genetic cascade screening program for FH in the Netherlands.\textsuperscript{7} Individuals were potentially eligible if they were screened for FH between August 2003 and January 2010. Subjects that had fasted for less than 3 hours, probands, and homozygous FH patients were excluded. In addition, those without a complete lipid profile were excluded, including those with triglyceride levels above 4.5 mmol/L, for whom LDL-C could therefore not be calculated. The cascade program itself was approved and financed by the Dutch government. All subjects gave written informed consent for genetic screening for FH.

Selection of Subgroup Populations in 5 Steps

We selected in 5 subsequent steps, 5 subgroup populations from the pool of 26,406 participants to evaluate the discriminative ability of LDL-C to diagnose genetic FH. Selection was based on the assumed severity of the mutation for which subjects were tested. The first 4 steps were based on mutation characteristics for untreated individuals only, whereas the last step included data from individuals treated with lipid-lowering medication as well. Step 1 was the selection of all untreated individuals (ie, carriers and unaffected relatives that did not use cholesterol-lowering medication at screening). Step 2 was the selection of untreated individuals tested for mutations, which were prevalent and confirmed to be pathogenic.\textsuperscript{12,13} Thus, carriers and unaffected relatives tested for confirmed nonpathogenic sequence variants were excluded, as were those who were tested for assumed pathogenic mutations with a low prevalence.\textsuperscript{12,13} Step 3 was the selection of untreated individuals tested for a LDLR mutation only. Consequently, subjects tested for the pathogenic p.R3527Q mutation in APOB were excluded.\textsuperscript{14} Step 4 was the selection of untreated individuals tested for a class 1 mutation (ie, those LDLR mutations where no protein can be synthesized from the affected allele).\textsuperscript{1} Step 5 was the selection of carriers and unaffected relatives, both untreated and treated, tested for a pathogenic class 1 LDLR mutation. To estimate the pretreatment LDL-C level, we multiplied the on-treatment LDL-C level by a correction factor based on the potency of their treatment regimen as described in detail before.\textsuperscript{10} In short, we determined the estimated LDL-C lowering potency of a specific lipid-lowering drug and dose. We multiplied the on-treatment LDL-C level with that treatment potency, yielding an estimated pretreatment LDL-C level.

Lipid Profile and Mutation Analysis

Experienced genetic field workers gathered the demographic and clinical data of the subjects and drew blood samples for lipid analysis and DNA extraction after a fast of at least 3 hours. The lipid profile was routinely measured with the LDX analyzer from August 2003 onward.\textsuperscript{15} LDL-C levels were estimated based on the Friedewald formula, only if triglycerides were below 4.5 mmol/L.\textsuperscript{16} DNA of the tested individuals was isolated from 10 mL of freshly collected blood containing EDTA as anticoagulant. The method of mutation analysis of the LDLR and APOB has been described previously.\textsuperscript{17,18} Mutations were described according to the nomenclature as proposed by den Dunnen and Antonarakis.\textsuperscript{19}

Statistical Analysis

Differences in demographic and clinical characteristics between carriers and noncarriers were evaluated using linear or logistic regression analysis. Multiple linear regression models were used to assess differences in LDL-C between carriers and noncarriers during the subsequent selection steps, adjusted for age and sex. All analyses were performed using the generalized estimating equations method to account for correlations within families. The exchangeable correlation structure was used for these models.

LDL-C levels of untreated individuals without genetic FH were used as reference levels. All these individuals were categorized based on age and sex. Subsequently, the \( z \) score of the LDL-C of each individual (LDL-C\textsubscript{individual}), both carriers and noncarriers, in our study cohort was determined, as a standardized deviation from the mean of the group from the same sex and age category (LDL-C\textsubscript{group}). The \( z \) score was calculated as the difference of LDL-C\textsubscript{individual} and LDL-C\textsubscript{group} divided by the SD of the group. This \( z \) score was used to calculate the age- and sex-specific percentile LDL-C for each individual based on the LDX measurements.

The percentiles for LDL-C were used to plot receiver operating characteristics curves\textsuperscript{20} and to calculate the area under the curve (AUC), also referred to as \( c \)-statistic, to assess the discriminative ability of LDL-C to distinguish carriers from unaffected relatives after the subsequent selection steps. The AUC and its corresponding 95\% CI, were calculated using the nonparametric method. AUCs range from 1.0, corresponding to perfect discrimination, to 0.5, indicating no discrimination. A probability value <0.05 was considered statistically significant. Data were analyzed with SPSS for Windows 16.0.2.

Results

Study Population

Between August 2003 and January 2010, 26,406 individuals underwent family screening for genetic FH, including a complete lipid assessment. In another 402 individuals, a lipid profile was determined, but LDL-cholesterol could not be calculated due to triglyceride levels above 4.5 mmol/L. The characteristics of this excluded subpopulation are described in the Supplement Data, http://stroke.ahajournals.org. Of the 26,406 participants screened, 9169 (35\%) had a mutation that was assumed to cause FH at the time of screening (Table 1). More specifically, 7686 (84\%) subjects carried such a mutation in the LDLR gene, and 1483 in the APOB gene. Patients
with molecular FH were younger than those in the noncarrier group. At screening, 3797 (41%) carriers and 2068 (12%) of the noncarriers were treated with cholesterol-lowering medication. Statins were the most frequently (99%) prescribed lipid-lowering agents.

The untreated subjects with FH exhibited on average higher LDL-C and total cholesterol levels than unaffected relatives (shown as adjusted only for family ties in Table 1). In addition, mean HDL-cholesterol and median triglyceride levels were slightly lower in carriers. Figure 1 represents the frequency plot of LDL-C levels in both untreated carriers and noncarriers. The age- and sex-specific mean LDL-C levels of untreated individuals without FH are shown in Supplemental Table S1.

**Selected Subgroup Populations**

Table 2 describes the main characteristics of the subsequently selected subpopulations. In addition, values of the area under the receiver operating characteristics curve (c-statistic [95% CI]) and the sensitivity of the 90th percentile of LDL-C are listed.

In the total untreated study population (step 1), LDL-C levels were normally distributed in the group of carriers and noncarriers (Figure 1). There was overlap in LDL-C levels between the groups, particularly in the range of 2 to 5 mmol/L. The 90th percentile of LDL-C was associated with a sensitivity of 68.5% and a specificity of 90. The AUC (95% CI) was 86.6% (85.9%–87.2%; Table 2). The mean LDL-C level (SD) adjusted for age and sex was 4.63±1.44 mmol/L for carriers and 2.96±0.96 for the noncarriers, respectively (P<0.001; Table 2).

The 3 subsequent selection steps, (ie, steps 2–4), induced several changes (Table 2). First, the study population of untreated carriers was reduced from 5372 to 833 subjects. Second, the median age (IQR) of all untreated carriers was reduced from 27 (15–41) in step 1 (Table 1) to 19 (10–33) in Step 4. In addition, mean LDL-C levels (SD) of the untreated carriers rose from 4.63±1.44 to 5.66±1.49. Last, the diagnostic value of LDL-C improved: the sensitivity of the 90th percentile increased from 68.5% in Step 1 to 91.3% in Step 4 (Table 2), whereas specificity remained generally unchanged (approximately 90%, data not shown). Consequently, the AUC increased from 86.6% to 96.2% (Table 2). Figure 2 illustrates the receiver operating characteristics curves of the first 4 selection steps, which correspond to the c-statistic values in Table 2.
Steps 2–4 led to the situation where only 833 individuals identified with class 1 LDLR mutation (44%) were untreated at screening. To apply LDL-C cutoffs for the entire group of 5933 individuals tested for those class 1 LDLR mutations, the treated individuals were included as well (Step 5). For each treated subject separately, the on-treatment LDL-C level was adjusted for treatment potency to estimate their pretreatment level. Consequently, the mean LDL-C levels (untreated or estimated pretreatment levels) for both carriers (6.42 ± 2.15 mmol/L) and noncarriers (3.00 ± 1.04 mmol/L) were higher than levels observed in previous selections of mean untreated levels (Table 2). The predictive value of the LDL-C from step 5, with a sensitivity of the 90th percentile of 92.5%, and an AUC of 96.5%, were comparable to that in Step 4.

Discussion

In the current study, we assessed the discriminative ability of LDL-C to identify patients with FH in a large cohort of 26,406 individuals tested for assumed pathogenic LDLR or APOB variants. Our findings indicate that the overlap of LDL-C levels between FH causing mutation carriers and noncarriers is to a large extent determined by the severity of the mutation. Selection of subjects tested for class 1 mutations in the LDLR did result in a marked separation of LDL-C levels between carriers and noncarriers. In fact, the high AUC of class 1 mutations (ie, 96.2% [95% CI, 0.953–0.971]) implicates that genetic cascade screening for FH can efficiently identify persons with extreme hypercholesterolemia, and is therefore crucial in the prevention of CAD in these families.

Table 2. Characteristics and the Discriminative Ability of LDL-C to Distinguish Carriers From Unaffected Relatives for Each of the Five Selected Subgroup Populations

<table>
<thead>
<tr>
<th></th>
<th>Carriers</th>
<th></th>
<th>Non-Carriers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Untreated</td>
<td>LDL-C</td>
<td>All</td>
</tr>
<tr>
<td>Step 1</td>
<td>N</td>
<td>N (% of All)</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td>All untreated</td>
<td>9169</td>
<td>5372 (59)</td>
<td>4.63 ± 1.44</td>
<td>17 237</td>
</tr>
<tr>
<td>Step 2</td>
<td>Confirmed pathogenic</td>
<td>6994</td>
<td>3894 (56)</td>
<td>4.90 ± 1.36</td>
</tr>
<tr>
<td>Step 3</td>
<td>LDLR mutation only</td>
<td>5664</td>
<td>3026 (53)</td>
<td>5.03 ± 1.40</td>
</tr>
<tr>
<td>Step 4</td>
<td>Class 1 mutation only</td>
<td>1906</td>
<td>833 (44)</td>
<td>5.66 ± 1.49</td>
</tr>
<tr>
<td>Step 5*</td>
<td>Class 1 mutation only and correction treatment</td>
<td>1906</td>
<td>Not applicable</td>
<td>6.42 ± 2.15</td>
</tr>
</tbody>
</table>

LDL-C, low-density lipoprotein–cholesterol; Sens P90, sensitivity at LDL-C cut-off level of 90th percentile; LDLR, LDL-receptor.

LDL-cholesterol, c-statistic, and sensitivity are based on untreated subjects only, except for Step 5 (*), which is based on the data of untreated and treated individuals combined, with estimated pre-treatment levels of LDL-cholesterol.

The selection steps 1 to 5 are described in more detail in the method section in the text.

LDL-C levels were corrected for age, sex and family ties.

Steps 2–4 led to the situation where only 833 individuals identified with class 1 LDLR mutation (44%) were untreated at screening. To apply LDL-C cutoffs for the entire group of 5933 individuals tested for those class 1 LDLR mutations, the treated individuals were included as well (Step 5). For each treated subject separately, the on-treatment LDL-C level was adjusted for treatment potency to estimate their pretreatment level. Consequently, the mean LDL-C levels (untreated or estimated pretreatment levels) for both carriers (6.42 ± 2.15 mmol/L) and noncarriers (3.00 ± 1.04 mmol/L) were higher than levels observed in previous selections of mean untreated levels (Table 2). The predictive value of the LDL-C from step 5, with a sensitivity of the 90th percentile of 92.5%, and an AUC of 96.5%, were comparable to that in Step 4.

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In the current study, we assessed the discriminative ability of LDL-C to identify patients with FH in a large cohort of 26,406 individuals tested for assumed pathogenic LDLR or APOB variants. Our findings indicate that the overlap of LDL-C levels between FH causing mutation carriers and noncarriers is to a large extent determined by the severity of the mutation. Selection of subjects tested for class 1 mutations in the LDLR did result in a marked separation of LDL-C levels between carriers and noncarriers. In fact, the high AUC of class 1 mutations (ie, 96.2% [95% CI, 0.953–0.971]) implicates that genetic cascade screening for FH can efficiently identify persons with extreme hypercholesterolemia, and is therefore crucial in the prevention of CAD in these families.

Figure 2. Receiver operating characteristics curve for selection steps. The curves numbered 1–4 represent receiver operating characteristics curves based on 4 subsequent selection steps. Step 1: untreated individuals, tested for LDLR or APOB mutations (N=20,520). Step 2: untreated individuals, tested for LDLR and APOB mutations that were validated to be pathogenic (N=15,901). Step 3: untreated individuals, tested for pathogenic LDLR mutations only (N=13,067). Step 4: untreated individuals, tested for pathogenic class 1 LDLR mutations (N=4,436).
However, among the more than 500 FH-causing-mutations identified in the Netherlands, only a minority are in fact class 1 mutations.\textsuperscript{17,21} Moreover, some of the 10 most prevalent mutations result in a relatively mild phenotype, such as the p.R3527Q in APOB and the p.N564H/2393del9bp and the p.G343S mutations in LDLR.\textsuperscript{12,22} As a consequence, the overlap in LDL-C levels between carriers and noncarriers is considerable in our country. If cascade screening for FH would be based on, for example, the 90th percentile for LDL-C 10% of patients, by definition, would test false-positive and more than a quarter of patients with molecular FH would be labeled as not having FH. The discriminative ability of LDL-C to identify FH can be slightly improved when mutations of established pathogenicity were selected.\textsuperscript{12,13} Nevertheless, cascade screening using LDL-C-specific cutoff values would be associated with an unacceptable low sensitivity.

Region-specific LDL-C cutoffs, on the other hand, could work well for FH screening in other countries where primarily 1 or 2 severe mutations are present, such as Finland or South Africa.\textsuperscript{23,24} For most countries, however, no large-scale genetic testing of clinically identified FH patients or their relatives is performed. Without extensive knowledge on the genetic basis of the FH patient cohort in a specific region, it is difficult to determine to what extent LDL-C levels will overlap between molecularly proven FH patients and nonaffected relatives. Therefore, the applicability of specific LDL-C cutoff will be unknown for most countries and has to be assessed before a decision can be made what strategy is most efficient.

As for the Netherlands, with a high prevalence of mild FH mutations, an important dilemma is the medical management of the individuals with molecular FH but without severe hypercholesterolemia. To address this dilemma, we recently performed a study with carotid intima-media thickness assessment in 421 individuals that were screened for genetic FH. We observed that these individuals generally do not exhibit the extent of atherosclerosis as observed in FH patients with severe hypercholesterolemia and their mean intima-media thickness differed not significantly from the mean intima-media thickness in unaffected relatives.\textsuperscript{25} As such, that study provides the cautious suggestion that pharmacological intervention in individuals with an FH genotype who do not express hypercholesterolemia does not need to be as aggressive as is the standard in FH per se. Thus, the extent of hypercholesterolemia should in our opinion contribute to the decision to intensify lipid-lowering therapy in FH patients, also of course taking into account other cardiovascular risk factors.

Several limitations merit discussion. First, we used calculated LDL-C levels. Possible, the applicability of lipid cutoffs could be enhanced with using direct LDL-C or APOB measurements. One advantage could be that accuracy would improve. However, the correlation between calculated LDL-C levels and APOB levels was remarkable in a subpopulation of our study population (data not shown). An additional advantage of direct LDL-C or APOB measurements would be that the problem introduced by high triglyceride levels is avoided. Total cholesterol cutoff levels are still of value to discriminate carriers from noncarriers in this group with hypertriglyceridemia, but the accuracy was somewhat less than in the included study population (Supplemental Data). However, the inability to calculate LDL-C levels because of triglyceride levels above 4.5 mmol/L occurred in 1.3%, thus the effect of excluding those subjects is therefore likely to be modest.

In summary, the extensive overlap in LDL-C levels between those with genetic FH and unaffected relatives can be attributed to a large extent to the high prevalence of modestly severe LDL-receptor mutations in the Netherlands. Consequently, LDL-C specific cutoffs are of less clinical utility in those countries that have a high prevalence of mild mutations as the molecular basis of FH.

**Acknowledgments**

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Patients with familial hypercholesterolemia (FH) generally are at severely increased risk of coronary artery disease. Consequently, screening for FH within families is ongoing within several countries. Such screening is often based on cutoff values for low-density lipoprotein cholesterol. A potential limitation of this strategy is the overlap of these levels between carriers of an FH mutation and unaffected relatives. We studied the effect of selecting for severe mutations in a large Dutch cohort of 26 406 individuals, who underwent family screening for genetic FH. Our findings demonstrate that the separation of LDL-C levels between carriers and noncarriers was only modest for the entire cohort, as shown by an area under the curve (AUC) of 86.6% (95% CI, 85.9–87.2). The 90th percentile for LDL-C, for example, would label more than a quarter of patients with molecular FH as not having FH. In contrast, selection of subjects tested for the severe class 1 mutations in the *LDLR* did result in a marked separation of LDL-C levels between carriers and noncarriers, with a high AUC of 96.2% (95% CI, 95.3–97.1). Thus, region-specific LDL-C cutoffs could work well for FH screening in other countries where primarily severe FH mutations are present. However, LDL-C specific cutoffs are of less clinical utility in our country, because of the high prevalence of LDL-receptor mutations of modest severity in the Netherlands.
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http://circgenetics.ahajournals.org//subscriptions/
### Supplemental table 1: Mean LDL-cholesterol in untreated subjects without a FH mutation categorized for age and gender

<table>
<thead>
<tr>
<th>Age category, years</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>LDL-C, mmol/L</td>
</tr>
<tr>
<td>1-10</td>
<td>393</td>
<td>2.32 ± 0.66</td>
</tr>
<tr>
<td>10-15</td>
<td>430</td>
<td>2.23 ± 0.66</td>
</tr>
<tr>
<td>15-20</td>
<td>383</td>
<td>2.46 ± 0.79</td>
</tr>
<tr>
<td>20-25</td>
<td>419</td>
<td>2.57 ± 0.72</td>
</tr>
<tr>
<td>25-30</td>
<td>440</td>
<td>2.62 ± 0.83</td>
</tr>
<tr>
<td>30-35</td>
<td>551</td>
<td>2.73 ± 0.83</td>
</tr>
<tr>
<td>35-40</td>
<td>711</td>
<td>2.85 ± 0.84</td>
</tr>
<tr>
<td>40-45</td>
<td>811</td>
<td>2.90 ± 0.86</td>
</tr>
<tr>
<td>45-50</td>
<td>830</td>
<td>3.12 ± 0.85</td>
</tr>
<tr>
<td>50-55</td>
<td>814</td>
<td>3.40 ± 0.92</td>
</tr>
<tr>
<td>55-60</td>
<td>751</td>
<td>3.58 ± 0.97</td>
</tr>
<tr>
<td>60-65</td>
<td>574</td>
<td>3.55 ± 0.88</td>
</tr>
<tr>
<td>65-70</td>
<td>433</td>
<td>3.51 ± 0.91</td>
</tr>
<tr>
<td>70-75</td>
<td>303</td>
<td>3.42 ± 0.98</td>
</tr>
<tr>
<td>75-80</td>
<td>190</td>
<td>3.43 ± 0.87</td>
</tr>
<tr>
<td>80-110</td>
<td>173</td>
<td>3.20 ± 0.91</td>
</tr>
<tr>
<td>Total</td>
<td>8,206</td>
<td>3.02 ± 0.96</td>
</tr>
</tbody>
</table>

LDL-C: LDL-cholesterol; N: number
Supplemental data file 1: Excluded subjects with high triglycerides.

Supplemental table 2: Demographic and clinical characteristics of carriers and non-carriers with triglycerides above 4.5 mmol/L

<table>
<thead>
<tr>
<th></th>
<th>Carriers (N=107)</th>
<th>Non-carriers (N=295)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>79 (74%)</td>
<td>204 (69%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Age years, median (IQR)</td>
<td>48 (36-58)</td>
<td>51 (41-59)</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>27 ± 4.1</td>
<td>28 ± 4.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Untreated lipid profile available, n (%)</td>
<td>48 (45%)</td>
<td>185 (63%)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol mmol/L</td>
<td>7.7 ± 1.9</td>
<td>6.3 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentile total cholesterol (IQR)</td>
<td>96 (90-98)</td>
<td>84 (52-95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides mmol/L, median (IQR)</td>
<td>5.5 (4.8-6.4)</td>
<td>5.3 (4.8-6.6)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation (SD) unless otherwise indicated. IQR: outer borders of interquartile range; N: number.

Supplemental figure 2: Receiver operating characteristics curve with total cholesterol levels for untreated subjects with triglycerides above 4.5 mmol/L

The AUC (95% confidence interval) for total cholesterol levels for untreated carriers and non-carriers was 0.764 (0.685-0.844).