Improving cardiovascular disease prevention: from risk assessment to novel therapy
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Target values for lipids, apolipoproteins and their ratios in patients receiving intensive statin therapy

Post-hoc analysis of the IDEAL study

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Submitted
ABSTRACT

Background – Recent evidence suggests that in patients receiving statin therapy, plasma levels of non-high-density lipoprotein (non-HDL) cholesterol, apolipoprotein B and the ratios of total to high-density lipoprotein (HDL) cholesterol (total/HDL cholesterol) as well as apolipoprotein B to A-I (apolipoprotein B/A-I) correlate more closely with the occurrence of cardiovascular disease (CVD) than low-density lipoprotein (LDL) cholesterol levels per se. These data, in conjunction with the ability to assess these non-LDL values under non-fasting conditions, have led to the suggestion that these parameters might also be considered as novel targets for statin treatment. However, clinical studies that have assessed actual target values are scarce. Our aim was to estimate such target values.

Methods and Results – In a post-hoc analysis of the ‘Incremental Decrease in End Points through Aggressive Lipid Lowering’ (IDEAL) study, we sought to determine those levels of non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I below which these parameters no longer correlated with cardiovascular events (CVE). These specific levels were than considered as estimates of target values for patients at high CVD risk receiving intensive statin therapy. The resulting values were 2.87 mmol/L for non-HDL cholesterol, 0.89 g/L for apolipoprotein B, 3.9 for total/HDL cholesterol and 0.67 for apolipoprotein B/A-I.

Conclusions – Our study has revealed specific levels of non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I below which a relationship with cardiovascular outcome is no longer present in patients receiving statin treatment. These levels may be considered as preliminary estimates of target values for intensive statin therapy as used in the IDEAL trial.

Abbreviations – apolipoprotein B/A-I, ratio of apolipoprotein B to A-I; CVD, cardiovascular disease; CVE, cardiovascular event; HDL, high-density lipoprotein; IDEAL, Incremental Decrease in End Points through Aggressive Lipid Lowering; LDL, low-density lipoprotein; non-HDL, non-high-density lipoprotein; total/HDL cholesterol, ratio of total to HDL cholesterol
INTRODUCTION

In current guidelines for cardiovascular disease (CVD) risk management, lipid lowering with HMG-CoA reductase inhibitors (statins) is recommended as first choice pharmacotherapy (1). The response to such therapy is generally evaluated by measuring plasma levels of low-density lipoprotein (LDL) cholesterol, in order to reach target values that are supported by a wealth of clinical trial evidence (2-4). Despite the well-documented benefit of this strategy (5), considerable residual CVD risk remains in patients who are on LDL cholesterol target (3). In order to further reduce this risk, research has mainly focused on the identification of novel treatment modalities, but better use of existing treatment strategies has also received considerable attention.

In view of the latter, definition of therapeutic goals only in terms of LDL cholesterol has become a matter of debate. This debate originates from studies that have repetitively shown that levels of non-high density lipoprotein (non-HDL) cholesterol and apolipoprotein B, as well as ratios of pro- to anti-atherogenic lipid fractions are more closely associated with the occurrence of CVD (6-9). For this reason, and given the fact that these parameters can all be reliably measured under non-fasting conditions, some expert panels have already recommended the use of non-HDL cholesterol or apolipoprotein B as alternative targets for statin therapy (1, 10). However, clinical use of these parameters is currently restricted to specific circumstances, in particular when plasma triglyceride levels are elevated (1). Recently, we could confirm the superiority of non-HDL cholesterol, apolipoprotein B and some ratios over LDL cholesterol alone as CVD risk determinants among patients receiving statin treatment (11). These data lend further support to implementation of such alternative lipoprotein measurements as target parameters for statin therapy. However, the current debate surrounding optimal target values for CVD precludes the wider implementation of these parameters in clinical practice.

The main objective of the present study was to estimate target values for statin therapy in terms of non-HDL cholesterol, apolipoprotein B and the ratios of total to HDL cholesterol (total/HDL cholesterol) and apolipoprotein B to A-I (apolipoprotein B/A-I). To accomplish this, we used existing data from a prospective study to determine cut-off levels for these parameters below which a statistical significant relationship with CVD occurrence disappeared. These specific levels were than considered as estimates of the target values. Patients were study participants in the ‘Incremental Decrease in End Points through Aggressive Lipid Lowering’ (IDEAL) clinical trial, which compared the efficacy of high-dose to usual-dose statin treatment for the secondary prevention of cardiovascular events (4). Analysis of residual risk and risk determinants among patients who were adequately treated according to the calculated target levels was included as a secondary study objective. Here, we present our results.


Chapter 6

METHODS

Study population
The IDEAL study has been published previously (4). In summary, IDEAL is a prospective, randomized, multicenter trial comparing the efficacy of high-dose to usual-dose statin treatment for the secondary prevention of cardiovascular events. A total number of 8,888 patients with a history of myocardial infarction were enrolled and randomized to either simvastatin 20 mg or atorvastatin 80 mg. Median follow-up was 4.8 years. Mean on-treatment levels of LDL cholesterol were 2.7 mmol/L in the simvastatin group, and 2.1 mmol/L in the atorvastatin group. The intensive treatment regime did not significantly reduce the occurrence of the primary outcome (major coronary event, MCE), but did reduce the risk of other composite secondary endpoints, such as ‘any cardiovascular event’ (CVE).

Outcome definition
The occurrence of CVE was selected as outcome measure for the current analysis. CVE included any of the following events: coronary death, hospitalization for nonfatal acute myocardial infarction, coronary revascularization procedure, hospitalization for unstable angina pectoris, resuscitation after cardiac arrest, congestive heart failure, stroke and peripheral artery disease.

Selection of study participants
In IDEAL, on-treatment lipid and apolipoproteins were measured at 3, 6 and 12 months after randomization. For the present analysis, we used means of the measurements at months 3 and 6. Given this approach, the current analysis was restricted to study participants with valid measurements at both these time points. Also, patients were only included when their CVE occurred after the 6 months measurement.

Laboratory measurements
Lipid and apolipoprotein measurements were performed on fasting blood samples. Levels of total cholesterol, HDL cholesterol and triglycerides were quantified using standard methodologies. LDL cholesterol was calculated using the Friedewald formula (12). Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL cholesterol. Plasma concentrations of apolipoprotein B and A-I were determined by immunonephelometry (Behring Nephelometer BNII, Marburg, Germany) with calibration traceable to the International Federation of Clinical Chemistry primary standards (13, 14).

Statistical analyses
Associations of the study parameters (LDL cholesterol, non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I) with CVE occurrence were assessed by the Cox proportional hazard model. The Cox model contained time to CVE as dependent variable, with
covariates for age, sex and smoking status recorded at baseline. First, relationships were determined using the complete study population. Then, the analysis was repeated on subgroups of patients who were below a certain cut-off value of each lipoprotein parameter. These cut-off values then were progressively lowered, until a value was found below which the relationship lost statistical significance (P<0.05). The analysis was performed on both treatment groups combined.

To further analyze residual risk, patients were included in a subsequent analysis when their on-treatment lipoprotein parameters were below the above calculated cut points. Residual CVE risk was expressed as percentage CVE's occurring in these subgroups. Stepwise backward Cox regression analysis was then performed to identify major CVE risk determinants in these subgroups. Candidate regression variables included age, sex, smoking, diabetes, hypertension, glucose and body mass index.

RESULTS

Study population
Following exclusion of patients with missing data and those with CVE before 6 months of treatment (n=1,114), data were analyzed from 7,774 IDEAL study subjects. This group represented 1,701 of 2,546 (66.8%) CVE's that occurred in the study. Baseline characteristics and on-treatment lipoprotein parameters of this study cohort are reported in table 1. Lipoprotein parameters are also specified for each treatment group separately. Mean age of the study participants was 61.7±9.4 years. The majority of them was male (80.9%) and non-smoking (78.8%). Use of statin therapy by all study participants led to decreased levels of LDL cholesterol (mean value of 2.4 mmol/L) and apolipoprotein B (mean value of 0.93 g/L). Triglyceride levels were in the normal range (mean value of 1.3 mmol/L). The different intensity of treatment regimes used in the IDEAL

TABLE 1. Baseline characteristics and on-treatment lipoprotein parameters of the IDEAL study participants included for the present post-hoc analysis

<table>
<thead>
<tr>
<th></th>
<th>Total population (n=7,774)</th>
<th>Simvastatin 20 mg (n=3,855)</th>
<th>Atorvastatin 80 mg (n=3,919)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.7 ± 9.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>80.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>21.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3 ± 3.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.2 ± 0.9</td>
<td>4.6 ± 0.7</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.4 ± 0.7</td>
<td>2.7 ± 0.6</td>
<td>2.0 ± 0.6</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 ± 0.5</td>
<td>1.5 ± 0.7</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>0.93 ± 0.27</td>
<td>1.06 ± 0.25</td>
<td>0.81 ± 0.23</td>
</tr>
<tr>
<td>Non-HDL cholesterol*, mmol/L</td>
<td>3.0 ± 0.8</td>
<td>3.4 ± 0.7</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>3.6 ± 2.0</td>
<td>3.9 ± 1.0</td>
<td>3.3 ± 0.9</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I</td>
<td>0.69 ± 0.22</td>
<td>0.76 ± 0.22</td>
<td>0.61 ± 0.19</td>
</tr>
</tbody>
</table>

Values are expressed as mean (± standard deviation), derived from visits at 3 and 6 months. * Calculated as total cholesterol minus HDL cholesterol.
study was represented by lower levels of all pro-atherogenic lipoprotein parameters among patients receiving atorvastatin.

**Estimation of target values**

In the complete IDEAL dataset used for the present analysis, all parameters evaluated (LDL cholesterol, non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I) revealed a significant relationship with CVE occurrence (P<0.0001 for all; table 2). When LDL cholesterol was adjusted downward, it became clear that the statistically significant relationship with CVE was present in patients with levels of 2.30 mmol/L or lower (P=0.01). However, statistical significance disappeared when patients were selected according to a one mg/dL unit lower LDL cholesterol cut-off level (≤2.28 mmol/L; P=0.08). For non-HDL cholesterol, a statistically significant association with CVE was present in patients with levels of 2.90 mmol/L or lower (P=0.03). This association was lost when the selection value was adjusted to 2.87 mmol/L (P=0.07). Similar analyses for apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I revealed that statistical significance was present in subgroups with values of ≤0.90 g/L (P=0.02), ≤4.0 (P=0.01) and ≤0.68 (P=0.04), respectively, but disappeared at the following cut-off levels: apolipoprotein B ≤0.89 (P=0.08), total/HDL cholesterol ≤3.9 (P=0.10) and apolipoprotein B/A-I: ≤0.67 (P=0.05).

**TABLE 2. Relationships between on-statin lipoprotein parameters and CVE occurrence in the IDEAL dataset and in subgroups following progressively lowering of cut-off levels of these parameters**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>P</th>
<th>Subgroup</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>No</td>
<td>Total/HDL cholesterol</td>
<td>No</td>
</tr>
<tr>
<td>≤2.30</td>
<td>&lt;0.0001</td>
<td>≤4.0</td>
<td>0.01</td>
</tr>
<tr>
<td>≤2.28</td>
<td>0.08</td>
<td>≤3.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Non-HDL cholesterol*, mmol/L</td>
<td>No</td>
<td>Apolipoprotein B/A-I</td>
<td>No</td>
</tr>
<tr>
<td>≤2.90</td>
<td>&lt;0.0001</td>
<td>≤0.68</td>
<td>0.04</td>
</tr>
<tr>
<td>≤2.87</td>
<td>0.07</td>
<td>≤0.67</td>
<td>0.05</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.90</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.89</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The relationships with CVE were calculated by a Cox proportional hazard model that included variables for study, age and sex. * Calculated as total cholesterol minus HDL cholesterol

**Analysis of residual CVE risk**

Residual risk in patients selected according to the above determined cut-off levels is given in table 3. Among patients with LDL cholesterol ≤2.28 mmol/L (n=3,819), a total number of 756 events occurred, resulting in an observed residual risk of 19.8%. In the subgroups with non-HDL cholesterol ≤2.87 mmol/L or apolipoprotein B ≤0.89 g/L, CVE risk numbers were 19.7% and 19.5%, respectively. Evaluating patients having reached the cut-off level for total/HDL cholesterol (≤3.9),
CVE risk turned out to be 20.2%. When patients were selected according to the apolipoprotein B/A-I cut-off value (≤0.67), CVE occurrence was 19.6%.

We then performed backward stepwise regression analysis to identify the most important, non-lipoprotein CVE risk factor in patients having reached the above calculated cut-off levels. Among the regression variables that were included: sex, body mass index and glucose were not significant risk factors. Evidently, age was highly significantly associated with CVE occurrence (P<0.001). However, among modifiable risk factors, smoking status turned out to be the most important CVE risk determinant (P<0.001) in all subgroups, such that smokers exhibited an approximately 50% higher CVE risk than non-smokers.

**TABLE 3.** Residual CVE risk in patients having reached the lipoprotein cut-off values below which no relationship with CVE was observed

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Number of CVE</th>
<th>CVE risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol ≤2.28 mmol/L</td>
<td>3,819</td>
<td>756</td>
<td>19.8</td>
</tr>
<tr>
<td>Non-HDL cholesterol* ≤2.87 mmol/L</td>
<td>3,783</td>
<td>747</td>
<td>19.7</td>
</tr>
<tr>
<td>Apolipoprotein B ≤0.89 g/L</td>
<td>3,574</td>
<td>697</td>
<td>19.5</td>
</tr>
<tr>
<td>Total/HDL cholesterol ≤3.9</td>
<td>5,207</td>
<td>1,054</td>
<td>20.2</td>
</tr>
<tr>
<td>Apolipoprotein B/A-I ≤0.67</td>
<td>4,189</td>
<td>822</td>
<td>19.6</td>
</tr>
</tbody>
</table>

* Calculated as total cholesterol minus HDL cholesterol

**DISCUSSION**

In the present study, we have attempted to estimate target values for non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I in patients at high CVD risk receiving intensive statin therapy. This was accomplished by calculating the values below which the relation between on-treatment levels of these parameters and the occurrence of cardiovascular events was lost in the IDEAL study population. This analysis resulted in estimates of 2.87 mmol/L for non-HDL cholesterol, 0.89 g/L for apolipoprotein B, 3.9 for total/HDL cholesterol and 0.67 for apolipoprotein B/A-I. If patients had reached these values, smoking status was the most important modifiable determinant of residual CVE risk.

**Treatment targets for non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I**

Whereas several studies have focused on the predictive value of on-treatment levels of lipoprotein parameters other than LDL cholesterol for CVD occurrence (8, 9, 11), none have actually assessed target values for these parameters. In fact, the target values proposed in literature have mostly been deduced indirectly from existing LDL cholesterol targets and the known relationship between LDL cholesterol and the parameter of interest. In 2004, the Expert Panel on Detection, Evaluation and Treatment of high blood Cholesterol in Adults (NCEP ATPIII) incorporated non-HDL cholesterol in their novel guidelines as secondary treatment target for patients with high
triglycerides (1). This panel recognized the difference of 30 mg/dL (0.78 mmol/L) between plasma levels of LDL cholesterol and non-HDL cholesterol, and concluded that non-HDL cholesterol target values were to be 0.78 mmol/L higher than those for LDL cholesterol. This led to the definition of 130 mg/dL (3.36 mmol/L) as non-HDL cholesterol treatment target for the highest risk group. For apolipoprotein B, target values were proposed by the Canadian Cardiovascular Society in their guidelines for cardiovascular risk management (10), as well as in an update on the NCEP ATP III guidelines (15). Based on the current LDL cholesterol target values and the relationship between LDL cholesterol and apolipoprotein B, an optimal therapeutic goal for patients at high cardiovascular disease risk was set at 0.90 g/L. When it comes to total/HDL cholesterol and apolipoprotein B/A-I, target values are more hypothetical. In the guidelines of the Canadian Cardiovascular Society, a level of 4.0 was recommended for total/HDL cholesterol as optimal value for patients at high cardiovascular disease risk (10). Of note, this value was arbitrarily chosen. For apolipoprotein B/A-I, 0.9 was initially proposed as target value (16), but more recent reports have suggested to adjust this value downward for the highest risk population (17). The current analysis reports cut-off levels for non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I below which no relationship exists with the occurrence of cardiovascular events in the IDEAL study population. These levels were considered as estimates of therapeutic goals in this cohort, comprising patients at high CVD risk who were already being treated with intensive statin therapy. For such high risk individuals, our results provide further evidence to support target values previously recommended for apolipoprotein B and total/HDL cholesterol (0.89 g/L and 3.9, respectively). With respect to non-HDL cholesterol, the present data suggest a lower level than currently advised, since previously this value would be set at 3.05 mmol/L (0.78 mmol/L above the calculated LDL cholesterol target in our study cohort). When it comes to apolipoprotein B/A-I, our results clearly support further lowering of the therapeutic goal, i.e. to 0.67.

We recognize that the currently proposed target values may be influenced by the characteristics of the IDEAL study cohort. Particularly, the mean on-treatment LDL cholesterol value in the study, i.e. 2.4 mmol/L, illustrates that patients with very low LDL cholesterol values were scarce, thereby limiting the power to detect statistical significant relationships among such patients. In line with studies reporting a statistical significant relationship between plasma LDL cholesterol and CVD risk even at very low LDL cholesterol levels (18, 19), we cannot exclude that the presence of a more intensive treatment regime in IDEAL would have led to even lower cut-off values. As a result of this limitation, additional post-hoc analyses in other large scale trials are required to define target values for these and other patient categories, such as those without a history of CVD requiring less intensive statin therapy.

Analysis of residual CVE risk
In the subgroups of patients classified as adequately treated according to the calculated cut-off levels, a substantial level of CVE risk was still present, ranging from 19.5% to 20.2%. A detailed
analysis to determine the origin of the observed residual cardiovascular disease risk revealed smoking status as the most important modifiable risk factor in all subgroups. In fact, smokers were at about 50% higher CVE risk than non-smokers. These data reemphasize the clinical significance of smoking, even under conditions of intensive lipid lowering therapy.

The analysis of residual risk further demonstrated that the differences in risk between the subgroups were small and definitely not statistically significant. This finding is somewhat unexpected, since the superiority of non-HDL cholesterol, apolipoprotein B and in particular apolipoprotein B/A-I as on-treatment risk predictors (11) can be hypothesized to result in lower residual risk once these parameters are used as target variables instead of LDL cholesterol. To further address this issue, we also analyzed residual risk among patients who were deviant with respect to their on-treatment plasma levels of LDL cholesterol and apolipoprotein B/A-I. Once patients had reached the apolipoprotein B/A-I target value, residual risk among those below the LDL cholesterol cut-off value (≤2.28 mmol/L) was 1.5% lower as compared to those with LDL cholesterol above this value. Alternatively, once the LDL cholesterol criterion had been reached, a higher difference in absolute risk was observed following dichotomization according to the apolipoprotein B/A-I cut-off value (i.e. 2.9%). Whereas this may reflect superiority of apolipoprotein B/A-I as CVD risk indicator on statin treatment, additional studies are required to precisely quantify the consequences of using these novel lipid parameters as a guide for the intensity of lipid lowering therapy in CVD risk management.

**Limitations**

In addition to the issues raised above, the present study has several limitations which merit further discussion. First, we do recognize that definition of optimal therapeutic goals needs a prospective trial format, evaluating two or more different treatment modalities in a randomized comparison. However, given the considerable investment in time and funds for such a study, it is virtually impossible to realize. Second, the outcome variable used for the titration analysis was a composite endpoint, including any cardiovascular event. The broad character of this endpoint was preferred since maximum statistical power was needed to reliably estimate the optimal target values. Nevertheless, despite this approach, we cannot exclude the possibility that the presence of more endpoints would have led to lower cut-off values. We, however, do not have access to more data to substantiate this.

**Final conclusions and clinical implications**

In the present study, target values were estimated for non-HDL cholesterol, apolipoprotein B, total/HDL cholesterol and apolipoprotein B/A-I in patients who are at the highest level of cardiovascular disease risk and received intensive statin therapy. These values turned out to be 2.87 mmol/L for non-HDL cholesterol, 0.89 g/L for apolipoprotein B, 3.9 for total/HDL cholesterol and 0.67 for apolipoprotein B/A-I. Our analysis might represent a next step in the debate
surrounding the clinical use of alternative lipoprotein parameters, and might assist expert panels in their considerations surrounding this issue.

REFERENCES