Author's response to reviews

Title: Prevalence of Lipid Abnormalities Before and After Introduction of Lipid Modifying Therapy among Swedish Patients with Dyslipidemia (PRIMULA)

Authors:

Billie Pettersson (billie_pettersson@merck.com)
Baishali Ambegaonkar (baishali_ambegaonkar@merck.com)
Vasilisa Sazonov (vasilisa.sazonov@merck.com)
Mats Martinell (mats.martinell@lul.se)
Jan Stålhammar (jan.stalhammar@lul.se)
Per Wändell (per.wandell@ki.se)

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Author's response to reviews: see over
Dear Editors,

We send you the revised version of the manuscript, with all points of the reviewers considered, including a review of the language. We find that the manuscript has improved, and are grateful for the valuable comments!

With best regards,

Billie Pettersson, MSc
Baishali Ambegaonkar, PhD
Vasilisa Sazonov, PhD
Mats Martinell, MD
Jan Ståhammar, MD PhD
Per Wändell, MD, PhD, Ass Professor

Corresponding author:
Billie Pettersson
Pontongränd 13
183 68 TÄBY
Sweden
Billie_pettersson@merck.com
Tel: +46 768 850010
Fax: +46 8 626 14 22
In general the paper is well-written and it represents a real world practice I have no major comments except two minors:

1] It would be worth presenting cholesterol/triglycerides levels in both units, i.e. mmol/L and mg/dl. We choose to add the conversion formulas in the table legend, due to limited space in the table:
   To convert the values for cholesterol to mg/dL, multiply by 1/0.02586. To convert the values for triglycerides to mg/dL, multiply by 1/0.01129.

2] Table 1: the numbers in brackets, I presume, that express the SD. If so please clarify. Yes, this is SD. Clarification is done in table title.
Reviewer #2

This study presents the prevalence of lipid abnormalities before and after introduction of lipid modifying therapy among Swedish people with dyslipidemia. The paper is poorly written and its novelty is questionable.

To our knowledge there are no studies on treatment of lipids in all three lipid parameters in Swedish patients. The closest study was published in 2005 (Lindgren et al) and was only concerned with total cholesterol and LDL-cholesterol, reflecting old treatment guidelines.

Furthermore, there are some major concerns:

Of all patients only 40% were classified as high-risk, with 60% having low to moderate risk. Are the treatment goals the same for high and non-high risk patients in Sweden? This is not the case elsewhere in the world.

Different goals apply to different risk groups. In this study this is not addressed and the 60% of moderate to low risk groups are given the same targets. This represents misclassification at baseline and at follow-up and therefore the findings might not be valid.

Treatment guidelines in Sweden also advocate different goals for patients at risk vs non-risk patients. This has been taken into consideration when assessing dyslipidemia and goal attainment for different patients according to the following:

Normal and goal lipid levels were defined according to Swedish guidelines: Total Cholesterol (TOT–C) < 4.5 mmol/l for patients at risk (< 5 mmol/l for non-risk patients), LDL-C >2.5mmol/l (<3.0 mmol/l for non-risk patients), TG <1.7 mmol/l and HDL-C >1.0 and >1.3 mmol/l for men and women, respectively.

Also you included data from 1994 to 2007. The guidelines have substantially been changed during this period elsewhere in the world. Was that the case also in Sweden? In that case it is tricky to use the same target for the whole period of time as the guidelines at each time might reflect different practices.

That is correct and we discussed how this should be handled in the analysis. We thought it could be handled by carrying out an analysis based on old guidelines to be able to compare between old and new treatment goals and goal attainment. Please see below from the manuscript:

In an earlier study [23], where goal attainment was defined as having a TOT-C below 5.0 mmol/l and LDL-C level below 3.0 mmol/l (as recommended by the Swedish Medical Products Agency at that time) 31% reached goal levels, compared to 43% in this study, which could indicate improved treatment of TOT-C or LDL-C disorders.

We think this is a plausible methodology of handling this issue.
More information on the database should be provided. Is it a GP database? What is the catchment area? Does it include the whole population or a representative sample? What type of information is available in this database? Which age-groups does the database include? 5,424 patients does not seem to be a large number for a period of 13 years. What is the denominator?

We agree the method part should be more detailed, the manuscript has been revised accordingly.

In short:
The primary care data in which patients were identified included records of care-giver contacts, laboratory measurements, drug prescriptions, diagnoses and biometrics (blood pressure, height and weight) carried out within each centre. Records were available from the date of instalment of electronic charts (Profdoc system, Profdoc AB, Uppsala, Sweden) which took place during 1993–1994 at the majority of study centres.

Data was collected retrospectively from electronic patient protocols using a search engine (The Pygargus Customized eXtraction Program (CXP) to scan patient protocols in 26 out of 30 public primary healthcare centers in the county of Uppsala, Sweden, covering about 77% of total population (322 000 apr in 2007).

Three CXP mediated extractions was made in order to identify patient protocols for patients with ICD-10 (-9) codes for dyslipidemia, ATC code for lipid modifying therapy (LMT) and existing laboratory results of TC, TG, LDL and HDL measurement.

In methods, it is mentioned that the baseline period is 15 months prior to lipid modifying therapy (LMT). What is the reason for choosing 15 months as the baseline period and not, for example, 12 months, similar to the follow-up?

The baseline period was defined as the period 15 months prior to the initiation of lipid modifying therapy (LMT) (denoted as the Index Date). In clinical primary health care practice in Sweden, patients with chronic illnesses in stable state usually only visit their GP once every 12 months. By using a 15 months prescription free interval before index date one could assume that the included individuals were naive users of LMT.

Why did you use 35 years as the age cut-off and not, for example, 40 years which is the age for screening as some guidelines suggest?

We didn't think that any major guidelines mention about this particular age 40. We choose 35 based on the fact that prior to 35 people are not likely to initiate lipid modifying therapy. In fact only 35 persons were excluded due to non fulfilment of age criteria. We think this is a good indicator for well specified age criteria.

High-risk groups were identified using the ICD diagnostic codes? Are these validated in the Swedish population?

Yes. We use this coding system in Sweden. We agree that this should be clarified in the manuscript, we added some paragraphs on that:
Patients with T2DM and those with CHD were identified from the International Classification of Disease (ICD) diagnostic codes of T2DM. (ICD-10 codes E11-E14; ICD-9 code 250) diagnoses. Further selections was done to ensure inclusion of T2DM patients only, these patients were required to be 35 years or older and not being prescribed insulin the first year after diagnosis.

There is no mention on missing data, except something vague at the very end of the discussion. Does this mean that there were no missing data? This would be very surprising in a clinical database. If you only used data from patients without missing data this could have introduced a selection bias. If only patients with complete data were included what is the number of the potentially eligible patients (with dyslipidemia) but without complete data? If there are missing data, the percentage should be mentioned as well as the method that was used to handle them.

We agree this should be explored in the manuscript and we added the following paragraphs to clarify on how we handled missing data:

Total patients that met all predefined inclusion and exclusion criteria and were included in the analysis were 5424, about 58% of total study population (n=5424/9384). The inclusion criteria of complete lipid profiles caused an exclusion of about 21% (n=1933/9384), which may result in selection bias, since patients with high CVD risk should have better documentation and a greater probability of selection in the cohort and this could be a limitation of generalizability. The problem of missing complete lipid profiles was reported by other researchers and the analytical solution used in this study was adapted from their prior work (Phatak et al). In short, they compared baseline lipid values for those patients with complete lipid profiles compared to the included patients. If baseline lipid profiles were similar they concluded that those patients with complete profiles were representative for the entire cohort. Using the same methodology in this study no major differences in baseline lipid values were found between excluded and included cases. Nonetheless, one should use caution when extrapolating these data to the general population of patients using LMT.

In Table 1 there is a line about baseline diastolic blood pressure but there are no data presented for this parameter.

It's inserted now.

Were the lipid values measured in a fasting blood sample (at baseline and follow-up)? This is not mentioned. If a fasting sample was not used the results about triglyceride levels might not be valid. If it is a fasting sample, is it in all participants? On the other hand, if all participants were fasting it is strange how it was managed to have all the patients fasting in a clinical database, except if only patients with fasting profiles were included in your analyses, which again might have introduced a bias. Please clarify.

In this study fasting or non-fasting lipid values were captured from the database. If a non-fasting sample was used the results about triglyceride levels might not be valid. To address that issue in this study LDL-C measurements were considered invalid if the triglyceride value was >4.5 mmol/L.
A paragraph on that was inserted in the manuscript.

Page 7, second paragraph it is mentioned that certain variables were included in the final model and refers to Table 3. However, this information is not provided in this table.

That is right, the reference was misplaced. We moved the reference to next paragraph.

Although you have included time on statin in your models we do not know what is the percentage of patients who discontinued their statin treatment? It is possible that a high percentage had discontinued treatment at the 12-month follow-up, which could explain in part the high percentage of treatment failure. As per protocol, treatment gaps are not allowed only in the first 6 weeks post index date. Another possibility is that low doses of statins were used and therefore, the treatment goals were not reached. However, no information about dosage (and dosage titration) is provided and this is a major issue.

One of the inclusion criteria was that patients should have refilled their prescriptions. This was checked against the data on iteration on the prescription, if these iteration were enough for use in 12 month, we assumed patients were compliant to the treatment. But then of course we don’t really know if the medication was used and we agree that this is a limitation, which is now is added in the discussion.

When it comes to dosage we agree this is interesting information and we added the following paragraph:

Almost 94% of all patients were treated with statins and mostly simvastatin, which of 43% were treated with 10 mg/day, 52% on 20 mg/day and 4.9% on 40 mg/day and only 0.1% (2) persons were treated with 80 mg/day. The calculated weighted average dose per day on simvastatin was 16.74 mg, which is a fairly low dose according to recommendation and could partly explain the findings that duration of treatment with statin was negatively associated to goal attainment.

In the models for TG and HDL you still used time on statin. Is that appropriate?

We thought it is still interesting to keep this variable since it is not in fact expected to have impact on TG and HDL, however many patients (94%) are only treated with statins. This variable is viewed as an important explanatory variable to keep in the model, since it should further underline that it's not appropriate to target these lipid abnormalities with statins.

Page 7, last line the upper CI is 0.87 which is lower than the OR (0.93). Is that a typo? OR should be within the range of the 95% CI.

Yes, that was a typo, now corrected.

The discussion is poorly written and insufficient.
We agree that the discussion could be more extensive, we have revised the discussion section. Please see draft manuscript.
Reviewer # 3

This is an interesting study on the attainment of lipid goals with lipid-lowering treatment (mostly with statins) in the general population.

Major Compulsory Revisions

1. It would be more useful for the reader if the authors could report the rates of attainment of lipid targets as defined by the latest NCEP/ATP guidelines instead of the Swedish guidelines.

We carried out the analysis both according to NCEP and Swedish guidelines. It was deemed that Swedish guidelines should be presented in the manuscript because this more reflect the treatment practice in Sweden. However the results don't differ much, whether the analysis uses NCEP guidelines or Swedish guidelines.

We added this into the discussion. Please see draft.

2. The prevalence of the metabolic syndrome has not been studied in this report and therefore the paragraph on this syndrome should be removed from the discussion.

That's correct, we added this phrase to clarify, since we still find this interesting to keep in the manuscript.

At present guidelines focus on LDL-C levels [15] and statins are the gold standard for lowering LDL-C. However, type 2 diabetes mellitus (T2DM) and cardiovascular disease are associated with increased risk of metabolic syndrome, which includes dyslipidemia, [16] and the dyslipidemia in the metabolic syndrome is characterized by hypertriglyceridemia and low levels of HDL -C [17-18].

3. The authors should add a brief comment on recent studies which cast doubt on the benefit of combination treatment in diabetic patients (ACCORD trial) as well as on the predictive role of HDL-C levels in patients who are treated with high-dose statin treatment (Ridker et al, JACC, JUPITER trial).

We agree. We added this to the discussion:

In the ACCORD study, combination treatment of simvastatin and fenofibrate in patients with type 2 diabetes was not found to reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone.

The authors conclude that the results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. However since the patients in the ACCORD study were of special high risk for CVD, the findings can not be generalizable for all patients.

When it comes to the Jupiter study, we couldn't find any reference for HDL-C as predictor. In Jupiter the aim was to assess the increased levels of the inflammatory biomarker high-sensitivity C-reactive protein for predicting cardiovascular events.
Reviewer's report (4)
Title: Prevalence of Lipid Abnormalities Before and After Introduction of Lipid Modifying Therapy among Swedish Patients with Dyslipidemia (PRIMULA) Version: 1 Date: 29 August 2010 Reviewer: Peter J Lansberg Reviewer's report:

Major compulsory revisions: NONE

Minor essential revisions:

Page 4 Methods: for me it is not clear what kind of records you scanned. where these electronic patient files? if so I belief it would be better to rephrase that sentence.

Yes, it was electronic patient files. In addition the methods section has been revised. It now gives more detailed information. Please see under methods section and answer to reviewer nr 2.

Definitions: normal and goal lipids should read <4.5 mmol/l and <5 mmol/l etc. on pages 7 That's right. It's now corrected.

figures 3 and 4 should be figures 1 and 2

That's right. It's now corrected.

discretionary revisions
do you have any data on the specific lipid lowering medication and dosage used due to the impact that diabetes has on lipid levels it would be interesting to see the impact on the lipid levels of well controlled diabetes versus poor controlled diabetes was (page 7 patients with T2DM had lower odds of attaining lipid goals)

This is an interesting question, but out of scope of this study. However this could be subject for another article.

if data on apo lipoproteins are available an analysis of how may patients that reached an LDL-C target reaching were also reaching an apo B target would be interesting particular in diabetics and patients with MD

We don't have data on apo-lipoproteins as these are not regularly measured in Swedish primary health care. We agree this could have been interesting.