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# Does LDL-C determination method affect statin prescribing for primary prevention? A register-based study in Southern Denmark

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## Aims

Examine whether the low-density lipoprotein cholesterol (LDL-C) determination method influences the rate of statin initiation for primary prevention of cardiovascular disease.

## Methods and results

We conducted a register-based retrospective study in the Region of Southern Denmark. Two hospital-based laboratories in the region directly measure LDL-C whereas four laboratories calculate LDL-C using Friedewald's formula. Physicians do not choose which method is used. We included all statin-naïve patients  $\geq 40$  years with no history of cardiovascular disease, diabetes, or chronic kidney disease, who had their LDL-C determined during 2018–2019. There were 202 807 people who had LDL-C determined during the study period (median age 59 years, 44% women) of which 37% had a direct LDL-C measurement. The median reported LDL-C was 3.40 mmol/L [interquartile range (IQR) 2.90–4.00] for those with a direct measurement vs. 3.00 mmol/L (IQR 2.40–3.50) for those with calculated LDL-C. For those with direct measurement, re-calculated LDL-C (using Friedewald's formula) was 0.35 mmol/L lower than the reported direct LDL-C measurement. Among those with directly measured LDL-C, 3.6% initiated statins compared with 2.7% of those with a calculated LDL-C. Direct LDL-C measurement led to higher odds of having a statin initiated compared with calculated LDL-C (adjusted odds ratio 1.23, 95% CI 1.17–1.30); for those with triglycerides  $> 1.7$  mmol/L the adjusted odds ratio was 1.41 (95% CI 1.30–1.52).

## Conclusion

Differences in the reporting of LDL-C from laboratories using different methods have a substantial influence on physician's decisions to prescribe statins.

## Keywords

Statin • Primary prevention • Cardiovascular disease

## Introduction

Statins reduce the risk of developing cardiovascular disease (CVD).<sup>1</sup> The decision to initiate a statin for persons without a history of CVD (primary prevention) should depend on a person's cardiovascular risk score.<sup>1–3</sup> Plasma low-density lipoprotein cholesterol (LDL-C) level is one of several factors which contribute to overall risk.<sup>1,2</sup> Some laboratories use biochemical methods for directly measuring LDL-C, whereas most calculate LDL-C using Friedewald's formula.<sup>4</sup> Since results using Friedewald's formula may differ from those using newer calculation methods (e.g. the Sampson or Martin-Hopkins equations) or direct measurements,<sup>5</sup> the method of LDL-C determination could

have an influence of whether a clinician serviced by a particular laboratory considers prescribing a statin or not. While risk scores rather than LDL-C values alone should be used to inform decisions, it is possible that LDL-C values flagged as abnormal could influence prescribing. For example, in Denmark, the LDL-C result is flagged as abnormal if it is  $\geq 3$  mmol/L irrespective of other risk factors. As different laboratories in Southern Denmark use different methods for determining LDL-C, we leveraged natural experiment conditions to study whether the method of LDL-C determination (directly measured or calculated using Friedewald's formula) led to differences in statin initiation rates.

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## Methods

We did a register-based retrospective study in Southern Denmark using the Danish National Prescription Registry,<sup>6</sup> the Danish National Patient Registry,<sup>7</sup> Danish Population Registry,<sup>8</sup> Danish Registry of Laboratory Results,<sup>9,10</sup> and Danish Provider Registry. We included all residents in the region aged  $\geq 40$  years as of 1 January 2018. Within this group, we identified all who had their LDL-C determined between 1 January 2018 and 31 December 2019. To be eligible for cohort inclusion, people must have been statin naïve 5 years leading up to the first LDL-C determination (no filling of a statin prescription), and have no medical history of CVD, diabetes, or chronic kidney disease (CKD) as of the date of their first LDL-C in the time period. We only considered the first LDL-C result over the two years for each patient, and only included results between 1.0 and 7.0 mmol/L. We excluded people with triglycerides  $>4$  mmol/L since Friedewald's formula is inaccurate and not recommended at triglyceride concentrations greater than around 4 mmol/L.<sup>5</sup> Definitions are in [Supplementary material online, eTables 1–3](#).

We used data from the six hospital-based biochemical laboratories in Southern Denmark, of which two use direct LDL-C measurement (enzymatic methods from two suppliers, Roche and Abbott) and four calculate LDL-C. Physicians cannot choose which method will be used to determine LDL-C. We first examined the median (interquartile range, IQR) reported LDL-C values for each method of measurement, and calculated the difference in reported LDL-C. For persons with direct LDL-C measurement, we re-calculated their LDL-C using Friedewald's formula and compared the direct vs. calculated values. We further examined rates of statin initiation, both overall and based on the method of LDL-C determination. We considered a statin prescription to have been initiated in response to an LDL-C determination if a prescription was filled within the 30-day period following a reported LDL-C. We described the characteristics of all patients and of those in the two groups defined by the LDL-C determination method. We calculated the proportion who initiated statins overall and in the two groups defined by the LDL-C determination method. We also estimated the odds ratio (OR) of statin initiation for those with directly measured vs. calculated LDL-C using logistic regression and adjusting for age, sex, and LDL-C (LDL-C as a continuous variable; we used calculated LDL-C values only and converted direct LDL-C measurements to calculated values for this analysis). We did a supplementary data analysis using a 60-day statin prescription window following an LDL-C determination.

In post-hoc analyses, we examined the difference in direct vs. re-calculated LDL-C when LDL-C was calculated with the Sampson equation (5) and the Martin-Hopkins (5) equation instead of Friedewald's formula. We also performed analyses which examined the odds ratio of statin initiation when LDL-C was 2.0–2.9 mmol/L or 3.0–5.0 mmol/L. We applied these different cut-offs to examine differences at different LDL-C levels based on common guideline thresholds and because Danish laboratories flag LDL-C  $\geq 3$  mmol/L as abnormal. To determine if the type of assay for direct LDL-C had any impact on results, we examined the odds ratio of statin initiation excluding results from Esbjerg Hospital which uses a different direct LDL-C assay (Abbott) than Lillebælt Hospital (Roche). Finally, we examined results based on triglycerides. For those with direct LDL-C, we computed the difference between Friedewald-re-calculated LDL-C and direct LDL-C based on quartiles of triglyceride levels. We then examined the association between direct LDL-C measurement and statin initiation for those below the median triglyceride level and above the median triglyceride level. Finally, we examined the association between direct LDL-C measurement and statin initiation for people with triglycerides  $>1.7$  mmol/L (the upper reference limit in Denmark).

The study was approved by The Danish Health Data Authority and registered at the University of Southern Denmark's repository (record no. 11.249). Approval from the Ethics Committee was not required.

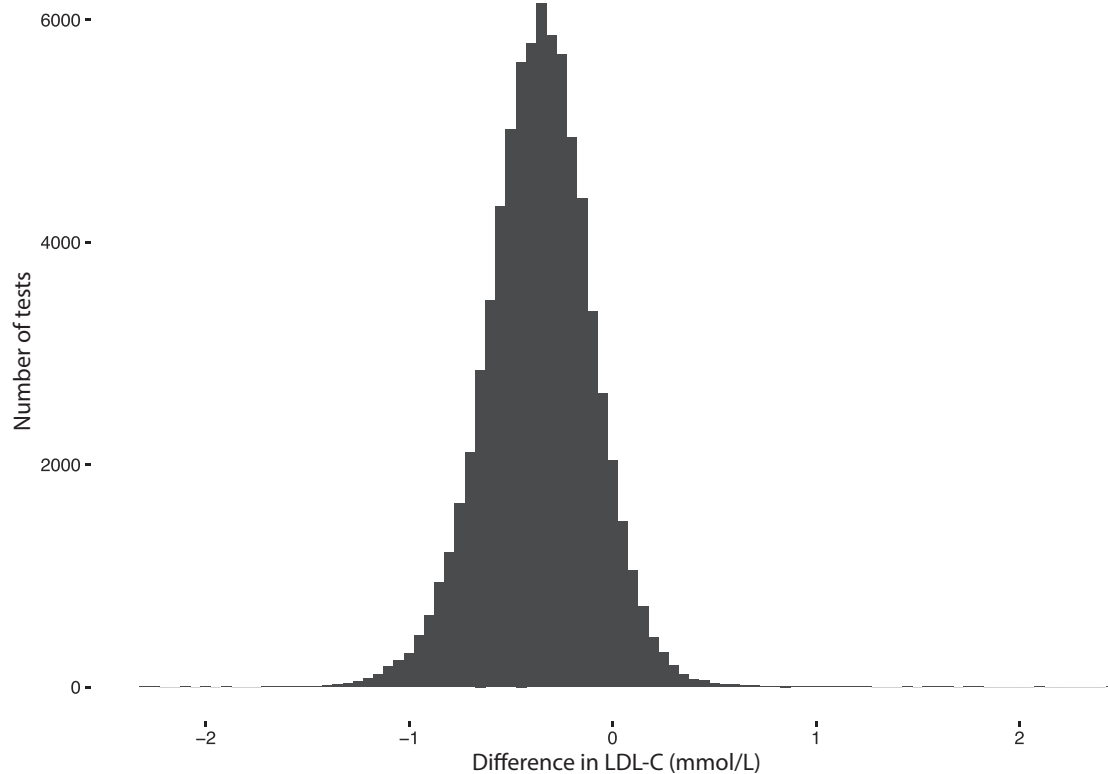
## Results

From 540 946 patients  $\geq 40$  years of age with an LDL-C measurement during 2018–2019, we included 202 807 persons who were statin naïve, had no previous reported CVD, diabetes, or CKD, and had a measured LDL-C between 1 and 7 mmol/L. The median age was 59 years and 44% were women. A total of 74 835 (37%) had a direct LDL-C measurement. For those with direct LDL-C measurement, the median LDL-C was 3.40 mmol/L (IQR 2.90–4.00). For those with calculated LDL-C, the median was 3.00 (IQR 2.40–3.50), which was statistically significantly different from the direct measurement group ( $P < 0.001$ ). The median re-calculated LDL-C for those with a direct measurement was 3.05 mmol/L (IQR 2.53–3.60). This was 0.35 mmol/L or about 10% lower than the directly measured values ([Figure 1](#)).

A total of 3.0% of people filled a prescription for a statin within 30 days after their LDL-C was determined. Among those who had their LDL-C directly measured, the proportion of statin initiators was 3.6% compared with 2.7% for those whose LDL-C was calculated. [Figure 2](#) shows the proportion of patients initiating statins according to the LDL-C determination method, plotted against their LDL-C levels (re-calculated using Friedewald's formula for those who had their LDL-C directly measured). People with a direct LDL-C measurement had significantly higher odds of having a statin initiated compared to those with calculated LDL-C (adjusted odds ratio [aOR] 1.23, 95% CI 1.17–1.30).

The Sampson equation produced calculated LDL-C measurements that were 0.29 mmol/L lower than directly measured values, while the Martin-Hopkins equation produced LDL-C measurements that were 0.31 mmol/L lower than directly measured values. Direct LDL-C determination led to higher odds of statin initiation compared with LDL-C calculation using the Sampson equation (aOR 1.23, 95% CI 1.17–1.30) or the Martin-Hopkins equation (aOR 1.23, 95% CI 1.17–1.30) ([Supplementary material online, eTable 4](#) and [eFigures 1](#) and [2](#)). Direct measurement of LDL-C was associated with an increased likelihood of statin initiation compared with calculated LDL-C when restricting LDL-C to 3.0–5.0 mmol/L (aOR 1.16, 95% CI 1.09–1.24) but not when LDL-C was restricted to 2.0–2.9 mmol/L (aOR 0.98, 95% CI 0.79–1.21) (see [Supplementary material online, eTable 4](#)). For Esbjerg Hospital (Abbott direct LDL-C assay), the Friedewald-calculated LDL-C was 0.22 mmol/L lower than directly determined LDL-C and for Lillebælt (Roche direct LDL-C assay) the difference was 0.43 mmol/L. When we excluded Esbjerg Hospital (Abbott direct LDL-C assay) and only examined the site using the Roche direct LDL-C assay, the adjusted odds ratio for statin initiation was 1.29 (95% CI 1.22–1.38). Using a 60-day follow up, the proportion of statin initiation was 4.3% for direct measurement and 3.2% for calculated, with similar associations between direct measurement and statin initiation as in the main analysis ([Supplementary material online, eTable 4](#)).

The difference between Friedewald-calculated LDL-C and direct LDL-C increased with each quartile of triglyceride levels, with the median calculated LDL-C 0.24 mmol/L lower than direct LDL-C in the lowest quartile and 0.54 mmol/L lower in the highest quartile ([Supplementary material online, eTable 5](#)). In those with triglycerides above the median value, direct LDL-C determination was associated with higher odds of statin initiation (aOR 1.36, 95% CI 1.27–1.45; [Supplementary material online, eTable 4](#)). There was no statistically significant association between statin initiation and the LDL-C determination method for people with triglycerides below the median (aOR 1.03, 95% CI 0.94–1.12). For people with triglycerides  $>1.7$  mmol/L, direct LDL-C determination was associated with higher odds of statin initiation compared with Friedewald-calculated LDL-C (aOR 1.41, 95% CI 1.30–1.52).



**Figure 1** Difference in LDL-C (in mmol/L) when calculated using Friedewald's formula compared with direct measurement. Based on sample of persons with direct LDL-C measurement, where LDL-C was re-calculated using Friedewald's formula.

## Discussion

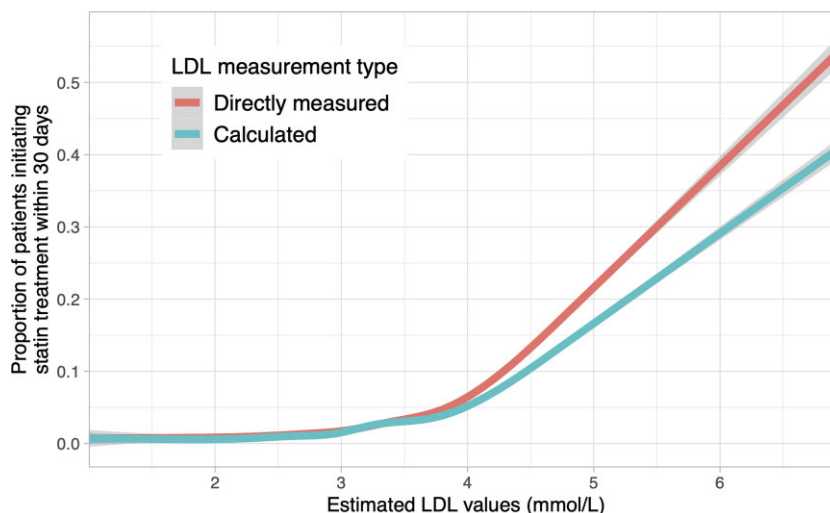
While we cannot say which LDL-C determination is more correct or what the most appropriate statin initiation rate is, our study documents that differences in LDL-C determination method led to differences in reported LDL-C values and that this difference was an independent predictor of physician statin prescribing for primary prevention.

Prescribers and health system stakeholders may be largely unaware of the potential clinical impact of LDL-C determination methods. Guideline LDL-C targets and risk scores have been based primarily on values calculated using Friedewald's formula. While LDL-C is only part of estimating overall cardiovascular risk, inaccuracy in its measurement may have important impacts. For example, in the US, underestimation in LDL-C calculated by Friedewald's formula has been shown to misclassify the cardiovascular risk category in around 15% of patients.<sup>11,12</sup> This could lead to undertreatment in regions where risk calculators include LDL-C. Even in regions where LDL-C is not integrated into risk scores,<sup>3</sup> if clinicians are reacting only to abnormal LDL-C values listed on a laboratory report (e.g. LDL-C > 3 mmol/L) vs. 10-year cardiovascular risk scores, inaccuracy in LDL-C could affect statin initiation decisions. Indeed, prescribing behaviour might be influenced by the perceived level of LDL-C elevation without regard to cardiovascular risk score or other factors (e.g. non-HDL-C, apoB).

Clinicians may wonder if other methods of calculating LDL-C address potential inaccuracies; however, we found that the use of alternatives to Friedewald's formula, such as the Sampson equation

or Martin-Hopkins equation, did not resolve differences between calculated and direct measurement. Although post-hoc, our analysis based on triglyceride level shows the association between direct LDL-C determination and statin initiation is more pronounced in those with higher triglycerides. This is consistent with previous data suggesting Friedewald-calculated LDL-C is particularly inaccurate with higher triglycerides.<sup>4</sup> Thus, our findings underscore the utility of direct LDL-C determination with higher triglycerides. We also found that differences between direct and calculated LDL-C were more pronounced when LDL-C is >3 mmol/L compared with LDL-C 2.0–2.9 mmol/L, suggesting differences between direct and calculated LDL-C are most important when LDL-C is >3 mmol/L. Future studies could investigate statin initiation for different LDL-C equations (Martin-Hopkins or Sampson) compared with direct LDL-C determination at various LDL-C cutpoints as the accuracy of Friedewald's formula has been questioned at low LDL-C (e.g. <1.8 mmol/L).<sup>4</sup> This may be particularly important with increasing focus on treating to lower LDL-C targets in contemporary guidelines,<sup>13,14</sup> both in primary and secondary prevention, as even a 0.3 mmol/L inaccuracy in LDL-C may affect decisions around treatment intensification. Indeed, discordance between different LDL-C equations has been shown to be particularly pronounced at low LDL-C levels (<1.8 mmol/L).<sup>15</sup>

While external quality assessment programs service accredited laboratories to overcome problems with inaccuracy, such programs often only compare performance of participating laboratories using the same method (e.g. direct measurement using assay from Roche, Friedewald-calculated using assay from Abbott etc.), thus not



**Figure 2** Rates of statin initiation for direct LDL-C compared to LDL-C calculated using Friedewald's formula.

addressing systematic bias between different methods and assays. One consideration is that the method of LDL-C determination could be included on the laboratory report, which may inform decision-making particularly when LDL-C is close to a threshold that might prompt initiation or intensification of lipid-lowering therapy.

Our study involved a large sample of people which is representative of Denmark. Groups were balanced in terms of age and sex (major drivers of atherosclerotic CVD risk). This was a natural experiment, and physicians do not choose which method is used. One possible limitation is that the different laboratories serve distinct parts of Southern Denmark, where regional differences in populations and practice patterns may exist and account for differences we observed. Another limitation is that there may be differences in accuracy between direct measurement assays, which could introduce bias into direct LDL-C values. We did not investigate the influence of more recent lipoprotein measurement approaches such as non-HDL-C or apoB on statin initiation. These are increasingly being included in practice guidelines<sup>14</sup> to overcome the limitations of calculated LDL-C. Future research could investigate use of these measurements and the influence on statin prescribing. A final limitation is that we did not evaluate the effect of LDL-C determination method on clinical outcomes such as cardiovascular events. Statins have been well-demonstrated to lower risk of cardiovascular events in primary prevention, and a systematic difference in their prescribing is likely clinically relevant itself. However, examination of the direct association between LDL-C determination method and downstream clinical outcomes would strengthen understanding of the importance of LDL-C determination method.

In conclusion, our study highlights that above levels where LDL-C is flagged as abnormal, LDL-C determination method influences statin initiation. This is particularly pronounced at elevated triglyceride levels, where calculated LDL-C is systematically lower than directly measured LDL-C. Our findings highlight the importance of individual laboratories (and health systems) carefully considering their method for measuring biochemical variables, particularly when reference intervals or action limits are identical. Further work could evaluate impact of LDL-C determination methods in secondary prevention and investigate downstream health consequences such as future cardiovascular events.

## Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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None.

**Conflict of interest:** None declared.

## Data availability

Data cannot be shared publicly nor by request to the corresponding author as data are only available with permission from Statistics Denmark.

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