Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling

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Scientific summary

Monitoring lipid levels in patients with CVD

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Scientific summary

Introduction

There is good evidence of the predictive nature of lipid measures on cardiovascular disease (CVD) events; however, uncertainty remains regarding which lipid measure (or combination) is the most useful for prognosis and monitoring. There is also a growing body of evidence suggesting that, in the absence of treatment or lifestyle changes, most observed differences in lipid measures within a 3-year period are likely to be due to biological variability or measurement error (noise).

Combined with their safety profile, the efficacy of statins in reducing lipids [specifically low-density lipoprotein (LDL) cholesterol], and consequently the risk of CVD events, has meant that their use has gradually extended to greater numbers of the population. Their use has even been suggested as part of universally treating individuals aged > 55 years.

Guidelines for the management of individuals at risk of a new (primary prevention) or subsequent (secondary prevention) CVD event vary regarding choice of lipid measure, CVD risk score, threshold for action (typically a change in treatment regime), and frequency of visits required for adequate management. This is probably due to the paucity of evidence for many of these issues, further accentuated by the numerous strategies potentially available. We therefore combined data from multiple sources to test several of these strategies in order to make recommendations about the optimal choice of lipid measure and the appropriate interval of lipid measurement, as well as their impact on both treatment choices and CVD events/mortality.

Objectives

We aimed to determine the clinical value and cost-effectiveness of different lipid measures and monitoring intervals for managing primary and secondary CVD prevention.

Our specific objectives were to:

1. identify the relative ability of different lipid measures (single or combination) to detect important changes in lipid status
2. estimate the incremental gains and costs of different strategies (lipid measurements and intervals) for risk assessment and monitoring of lipid levels in patients at risk of or with CVD
3. develop and populate an economic model of lipid monitoring
4. explore how the choice of lipid measure impacts on risk assessment of CVD compared with original risk scores
5. disseminate the impact of our findings on CVD risk assessment.

Methods

We carried out a systematic review of prognostic studies to estimate predictive associations, summarised as adjusted hazard ratios (HRs) per one standard deviation (SD), for lipid markers and ratios, with three outcomes: CVD events, CVD mortality and all-cause mortality. Study inclusion was restricted to cohorts that had at least 12 months of follow-up and a minimum of 1000 participants. Results were stratified by populations taking statins versus not and without (primary prevention) compared with (secondary prevention) previous CVD. Random-effects summary estimates were obtained for each lipid (or combination) and each outcome for which at least three studies reported data. Sensitivity analyses examined the impact of definition of outcome, study quality and the type of summary data available.

To estimate the dose-related effectiveness of atorvastatin in reducing lipid measures, and hence inform subsequent economic modelling, we carried out a meta-analysis of randomised controlled trials (RCTs) of atorvastatin against other statins or placebo. We used trials identified in a recent systematic review and we included trials with at least 1000 participants and 12 months of follow-up. Two reviewers carried out an assessment of the risk of bias per included study. Data were extracted for lipid measures at baseline and 12 months (or closest available follow-up). The summary measure of effect calculated was the difference in mean values between trial arms. Dose-specific estimates were obtained and compared with previously reported estimates.

Analyses of data from the Clinical Practice Research Datalink (CPRD), an anonymised database of routinely collected UK medical records, and an independent international cohort (St Luke's, Japan) were used to estimate parameters of progression and variability for lipid measures currently used in clinical practice: total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, LDL cholesterol and their composites including non-HDL cholesterol and ratios. These parameters include the rate of change in lipid measure over time (at population and individual level) and the short-term variation (regarded as the *noise* in the measurement). We use the signal–noise (SN) ratio to summarise the ability of each lipid measure to distinguish individuals with true change from those with apparent change due to noise.

We carried out analyses stratified by primary prevention populations (not taking and taking statins) and secondary populations taking statins, and by gender. Age thresholds for inclusion were 40 years for men, for consistency with the earliest age at which lipid monitoring starts in programmes such as the UK NHS Health Check, and 55 years for women, to reduce extra variability associated with the transition from premenopause to perimenopause to post menopause. Linear random-effects models for each lipid measure were used to obtain estimates.

Using these parameter estimates, simulation modelling was used to quantify the impact of monitoring strategies on the proportion of individuals incorrectly identified as above the lipid or risk threshold, who in reality would be below threshold, and were therefore being unnecessarily identified for treatment, and the proportion incorrectly identified as below the lipid or risk threshold and therefore potentially undertreated. Additional analyses explored the impact that different threshold levels, risk scores and lipid measures would have on these proportions.

The simulation models were extended to an economic model of lipid monitoring in order to obtain estimates of relative cost-effectiveness of lipid-monitoring strategies. We assumed that lipid monitoring would lead to initiation or dose increase of atorvastatin: in primary prevention, when 10-year CVD risk calculated from risk factors including lipid exceeds a threshold, and in secondary prevention, when lipid exceeds monitoring threshold. Thresholds were based on UK guidelines and sensitivity analyses considered alternative thresholds. Information from the systematic review provided estimates of effectiveness of atorvastatin. The model was populated with a cohort of simulated individuals with baseline characteristics based on those observed in the CPRD, and lipid values over time based on the statistical models described above. CVD and mortality rates were estimated from the CPRD, from the QRisk2 risk equation, and from life tables. The main outcome measure for the economic model was the cost per quality-adjusted life-year (QALY), with QALY values for relevant health states drawn from previous literature and comparisons reported as the incremental cost per QALY gained between monitoring strategies. The perspective of the economic evaluation was that of the health-care provider.

We held a dissemination meeting to present early results and obtain feedback on our findings from clinicians, opinion leaders and stakeholders.

Results

Our systematic review of the association between lipid measures and CVD events found most evidence for populations not taking statins (90 publications reporting 110 cohorts, compared with 25 publications reporting 28 cohorts in populations taking statin therapy). For CVD events in populations not taking statins, the summary adjusted HR with 95% confidence interval (CI) per SD of non-HDL cholesterol was 1.27 (95% CI 1.14 to 1.41), apolipoprotein B (Apo B) 1.26 (95% CI 1.15 to 1.38) and for the ratios TC/HDL cholesterol 1.25 (95% CI 1.17 to 1.33), LDL/HDL cholesterol 1.28 (95% CI 1.24 to 1.32) and Apo B/apolipoprotein A-I (Apo A-I) 1.35 (95% CI 1.22 to 1.50). Associations for other lipid measures were smaller. Fewer studies gave data for mortality outcomes. In populations not taking statins, TC (HR 1.17, 95% CI 1.10 to 1.24), triglycerides (TGs) (HR 1.17, 95% CI 1.04 to 1.31), HDL cholesterol (HR 1.18, 95% CI 0.08 to 1.28) and TC/HDL cholesterol ratio (HR 1.14, 95% CI 1.02 to 1.38) were significantly associated with CVD mortality; LDL and non-HDL cholesterol were not ($p > 0.05$), and there were insufficient data for other lipid and ratio measures. For populations taking statins, the adjusted HRs for CVD events were: TC 1.28 (95% CI 1.04 to 1.58); LDL cholesterol 1.31 (95% CI 0.94 to 1.83); and HDL cholesterol 0.62 (95% CI 0.46 to 0.84). There were not sufficient data for other lipid measures or for mortality outcomes in populations taking statins.

We identified 10 large RCTs of atorvastatin with at least 12 months' follow-up, across four RCTs.

Although only 10 studies meeting inclusion criteria were identified, estimates confirmed the effect of atorvastatin relative to placebo or usual care at low doses [10 and 20 mg/day: in four studies, TC reduction ranged from 0.92 mmol/l (95% CI 0.86 to 0.98 mmol/l) to 2.07 mmol/l (95% CI 1.99 to 2.15 mmol/l) and LDL cholesterol reduction ranged from 0.88 mmol/l (95% CI 0.83 to 0.93 mmol/l) to 1.86 mmol/l (95% CI 1.80 to 1.92 mmol/l)]. Estimates for the effect of atorvastatin 40 mg were based on a single study assessed as having high risk of bias and with results inconsistent with findings from the lower and higher doses [TC reduction 0.49 mmol/l (95% CI 0.40 to 0.58 mmol/l), LDL cholesterol reduction 0.38 mmol/l (95% CI 0.32 to 0.44 mmol/l)]. At 80 mg, in the only eligible study, TC reduction was 1.58 mmol/l (95% CI 1.54 to 1.62 mmol/l) and LDL cholesterol reduction 1.44 mmol/l (95% CI 1.40 to 1.48 mmol/l). Reductions in TGs were also seen at all doses of atorvastatin, but no clinically important effect on HDL was observed at any dose.

In statistical models of data from the CPRD and from St Luke's Hospital, Japan, the SN ratio over 1 year was < 1 for all lipid measures considered. In the CPRD, in men and women not taking statins, the SN ratio over 5 years was < 1 for all lipid measures considered; in men and women taking statins the SN ratio over 4 years was < 1 for all lipid measures considered.

For primary prevention, we estimate that annual monitoring (compared with 3-yearly monitoring) using a QRisk2 threshold of 20%, would unnecessarily identify 9 per 1000 more men (28 vs. 19 per 1000) and 5 per 1000 more women (17 vs. 12 per 1000) for treatment over a 3-year period. However, annual monitoring under this scenario would also undertreat 9 per 1000 fewer men (7 vs. 16 per 1000) and 4 per 1000 fewer women (7 vs. 11 per 1000). For secondary prevention, we estimate that annual monitoring (compared with 3-yearly monitoring) using a TC threshold of 4 mmol/l unnecessarily identifies 66 per 1000 more men (224 vs. 157 per 1000) and 31 per 1000 more women (136 vs. 105 per 1000) for increased treatment over a 3-year period, with a decrease in those undertreated of 29 per 1000 men (6 vs. 36 per 1000) and 28 per 1000 men (5 vs. 33 per 1000).

We estimate that the use of non-HDL cholesterol instead of TC/HDL cholesterol ratio in CVD risk estimation would have found potential for about 1 person in 10 to be classified differently. In contrast, averaging repeated measures instead of single measures made negligible difference to risk estimation.

In primary prevention populations, annual monitoring using a 20% CVD risk threshold appeared less costly and more effective than less frequent levels of monitoring. In exploratory sensitivity analyses we found that any harms of statins not currently included in the model would need an estimated QALY decrement of

0.11 for women and 0.08 for men for biennial monitoring to be more cost-effective than annual monitoring. For secondary prevention, annual monitoring using a TC threshold of 4 mmol/l or a LDL cholesterol threshold of 2 mmol/l appeared less costly and more effective than less frequent monitoring, and additional statin-related QALY decrements of 0.06 and 0.04 for women and men, respectively, would be required for biennial monitoring to be more cost-effective than annual monitoring.

Discussion

This work extends a body of knowledge which has identified that many observed changes in lipid measurements, in the absence of a lipid-lowering treatment change, are due to short-term variability rather than true change. We have reviewed the literature on predictive power of lipids and effects of atorvastatin, estimated variability of lipids, and modelled the consequences, including costs and health effects, of a variety of lipid-monitoring strategies.

Most of the results in this work are based on mathematical models and simulation; nevertheless, we have used established methods based on summaries from the published literature and routinely collected data in the UK (CPRD), which are likely to give an approximate representation of current practice.

Conclusions

We consistently found that a lipid-monitoring strategy that places more individuals under treatment is likely to be cost-effective compared with one that treats fewer. In all comparisons considered in this report, annual lipid monitoring was cost-saving and effective compared with less frequent monitoring. The implications of universal treatment without monitoring require further investigation: until then, regular lipid monitoring in those with and without CVD is likely to be beneficial to patients and to the health service.

Research priorities

Individual patient data from worldwide collaborations should be used to estimate associations for ratios and other lipid measures, in particular for Apo B and Apo A-I, and report on their relative association for the different relevant groups (age/condition).

Trials that provide a better quantification of both the benefits and harms of atorvastatin at doses of 40 and 80 mg.

Large-scale surveillance studies are needed to determine the safety profile of statins among long-term users, as well as to obtain estimates of long-term adherence.

Qualitative and quantitative studies to identify and estimate the role that monitoring plays on adherence to drug regimes and, in particular, statins.

Study registration

This study is registered as PROSPERO CRD42013003727.

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