Low density lipoprotein subfractions: systematic review of measurement methods and association with cardiovascular outcomes

Balk E, Ip S, Chung M, Lau J, Lichtenstein A H

CRD summary
This review concluded that there was insufficient evidence on the value of measuring low density lipoprotein (LDL) subfractions when assessing cardiovascular risk. The question of whether treating patients based on LDL subfractions would reduce their risk of cardiovascular disease (CVD) was not addressed. The review was generally well conducted and these cautious conclusions are likely to be reliable.

Authors' objectives
To assess the relationship between low-density lipoprotein (LDL) subfractions and cardiovascular outcomes. A number of sub-questions relating to prognostic and diagnostic value and therapeutic reduction were addressed, of which the following are within the scope of this abstract: the relative test performance of different methods of measuring LDL subfractions; the nature and strength of the relationship between LDL subfractions and outcome measures related to cardiovascular disease (CVD); the incremental increase in diagnostic performance associated with using LDL subfraction tests in conjunction with other cardiovascular risk assessment technologies; and the efficacy and safety of therapies designed to alter LDL subfractions in terms of CVD outcomes.

Searching
The following databases were searched from 1950 to August 2007: MEDLINE, CAB Abstracts, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Search terms were reported. The FDA website was searched. In addition, references of included studies and relevant reviews were checked and experts were contacted. Only English language publications were eligible for inclusion.

Study selection
Inclusion criteria for prognostic review questions were studies of LDL subfractions from serum or plasma samples from adults aged at least 18 years. A range of additional criteria were applied to each subquestion (full details provided in the report). Inclusion criteria for the efficacy of therapeutic reduction question were randomised controlled trials (RCTs) or nested case control studies within an RCT, with at least 10 participants per treatment group, which assessed pharmaceutical or other interventions hypothesised to beneficially effect LDL subfractions. Acceptable comparators were alternative interventions for LDL subfractions, placebo, usual care or no treatment. In each case highly atypical populations were excluded on a case by case basis. Clinical or selected surrogate cardiovascular outcomes were considered (full details provided in the report). Selected studies were highly heterogeneous in the measurement methods employed, the populations assessed, and the study designs employed.

Studies were assessed for inclusion by three reviewers; it was not clear whether this was done independently.

Assessment of study quality
Validity was assessed by one reviewer and checked by a second. Studies were graded as good quality (low risk of bias), fair quality (moderate risk of bias) or poor quality (major risk of bias). The criteria used for these assessments were not fully described but included study design description of population and study methods, appropriateness of outcome measurement and of statistical analyses, and reporting of withdrawals and drop-outs. An assessment of applicability to the general population and particular subgroups was also conducted, with studies rated as 'high', 'moderate' or 'low'.

Data extraction
Separate data extraction forms were used for prognostic/diagnostic and effectiveness studies. Efficacy studies were categorised as showing a significantly positive, significantly negative or no association with CVD outcomes.

The data were extracted by one reviewer and checked by at least one other reviewer.
Methods of synthesis
The studies were combined in a narrative synthesis grouped by the review question addressed and study quality. Other differences between studies were discussed in the text and were further apparent from the accompanying evidence tables.

Results of the review
Test performance: Nine studies compared test performance, of which one was good, seven were fair and one was poor quality. Comparisons between different methods of assessing LDL subfractions were inconsistent. This included results for nuclear magnetic resonance (NMR), gel electrophoresis (GE) and for Lipoprint versus other GE assessed patterns. Differentials varied between subpopulations. Differences were also found between high pressure liquid chromatography (HPLC) and GE assessed LDL sizes.

Relationship of LDL subfractions with CVD outcomes: Three of six fair quality studies found an association between small LDL measured by Lipoprint GE and prevalent CVD or intermediate markers in adjusted analyses. The remaining three studies found no such association. There was a substantial degree of clinical heterogeneity between the studies. One study found a relationship between average LDL subfraction IVb percentage and rate of coronary artery stenosis over 4 years. Of the non-clinically available methods only LDL particle concentration measured by NMR was consistently associated with incident CVD in adjusted analyses (41 studies). Equal numbers of studies suggested that LDL subfraction was a stronger and a weaker predictor of CVD compared with more traditional risk factors (10 studies).

Impact of testing or treatment for LDL subfractions: No studies on the impact of clinically available LDL subfraction tests on existing diagnostic assessments were found. None of the seven studies of interventions assessed whether treatment based on LDL subfractions was associated with improvements in true CVD outcomes. Three studies weakly suggested that CVD risk associated with abnormal LDL subfractions may be mitigated by pravastatin (seven studies in total).

Authors’ conclusions
Clinically useful evidence on whether measurement of LDL subfractions is a helpful tool in evaluating cardiovascular risk, or altering treatment of such risk, was lacking. Limited evidence suggested that LDL subfraction analysis is not a consistently strong predictor of CVD compared to other known risk factors. The question of whether treating patients based on LDL subfractions would reduce their risk of CVD was not addressed.

CRD commentary
The review questions and inclusion criteria were clear. The authors searched a number of relevant databases and other sources, but the decision to restrict the review to published studies reported in English may have led to the introduction of publication or language bias, as well as the possible exclusion of relevant studies. It appears that rigorous methodology was employed at all stages of the review process, but the validity assessment was poorly described and it is not clear how appropriate the criteria employed were. The assessment was, however, used to inform the synthesis. The decision to adopt a narrative synthesis was clearly correct in view of the level of clinical heterogeneity between the studies. The authors’ cautious conclusions accurately reflected the evidence and, despite some concerns about the scope of the search and some concerns about reporting of the review process, are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that routine use of clinically available LDL subfraction tests to estimate CVD risk is premature.

Research: The authors made a number of recommendations for further research which included: the development of uniformly defined measures of LDL subfractions using available tests for CVD incidence or progression; further research on LDL subfraction relative and incremental value as a predictor of CVD both generally and in particular at-risk groups; and investigation of within-subject variability in LDL subfractions.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.