Effect on cardiovascular risk of the high density lipoprotein targeted drug therapies niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117 411 patients

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EDITORIAL by Kritharides

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STUDY QUESTION

Do treatments to increase the level of high density lipoprotein (HDL) deliver the cardiovascular event reduction that might be expected from the strong relation seen in observational studies?

SUMMARY ANSWER

In randomised controlled trials neither niacin, fibrates, nor cholesteryl ester transfer protein (CETP) inhibitors were found to reduce all cause mortality, coronary heart disease mortality, myocardial infarction, or stroke in people treated with statins, despite HDL levels being significantly increased. In people not receiving statins, niacin was found to significantly reduce the risk of stroke and non-fatal myocardial infarction, whereas fibrates reduced the risk of non-fatal myocardial infarction.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In observational studies, higher levels of HDL are associated with better cardiovascular outcomes. Three available classes of agent aim to increase HDL levels: niacin, fibrates, and the CETP inhibitors. In trials where patients were receiving statin treatment, none of the three classes of agent has so far been found to improve cardiovascular outcomes.

Selection criteria for studies

We identified randomised controlled trials that compared niacin, fibrates, and CETP inhibitors agents with control in primary or secondary prevention. We searched Medline, the Cochrane Central Register of Randomised Controlled Trials, and the WHO International Clinical Trials Registry Platform search portal. We separated the trials into those in which participants had no statin treatment and those in which some or all of the participants received statins.

Primary outcome

The primary outcome was all cause mortality.

Main results and role of chance

117 411 patients were randomised in a total of 39 trials. All interventions increased the levels of HDL cholesterol. No significant effect was seen on all cause mortality for niacin (odds ratio 1.03, 95% confidence interval 0.92 to 1.15, P=0.59), fibrates (0.98, 0.89 to 1.08, P=0.66), or CETP inhibitors (1.16, 0.93 to 1.44, P=0.19); on coronary heart disease mortality for niacin (0.93, 0.76 to 1.12, P=0.44), fibrates (0.92, 0.81 to 1.04, P=0.19), or CETP inhibitors (1.00, 0.80 to 1.24, P=0.99); or on stroke outcomes for niacin (0.96, 0.75 to 1.22, P=0.72), fibrates (1.01, 0.90 to 1.13, P=0.84), or CETP inhibitors (1.14, 0.90 to 1.45, P=0.29). In studies with patients not receiving statins, niacin was associated with a significant reduction in non-fatal myocardial infarction (0.69, 0.56 to 0.85, P=0.0004). However, in patients receiving statins, niacin showed no significant effect (0.96, 0.85 to 1.09, P=0.52). A significant difference was seen between these subgroups (P=0.007). A similar trend relating to non-fatal myocardial infarction was seen with fibrates: without statin treatment (0.78, 0.71 to 0.86, P<0.001) and with all or some patients taking statins (0.83, 0.69 to 1.01, P=0.07).

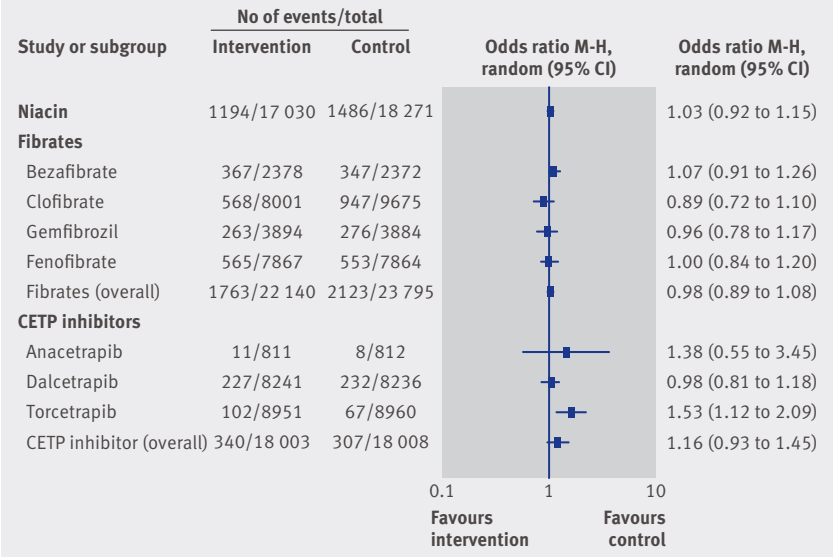
Bias, confounding, and other reasons for caution

The hypothesis that any treatment which increases the levels of HDL should decrease cardiovascular mortality, seems to be incorrect. For patients unable to take statins, the earlier (statin free) trials indicated benefits on some cardiovascular endpoints. Whether those benefits were mediated by an increase in HDL levels remains unknown.

Study funding/potential competing interests

DPF receives funding from the British Heart Foundation; this study is an unrelated independent academic activity. We have no competing interests.

Forest plot showing effect of agents to increase levels of high density lipoprotein on all cause mortality



thebmj.com
- Research: Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies (*BMJ* 2013;346:e8539)
- Clinical Review: Translating genomics into improved healthcare (*BMJ* 2010;341:c5945)
- Research: Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis (*BMJ* 2009;338:b92)

Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality

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STUDY QUESTION

What is the effect on mortality of pooled human albumin as part of fluid volume expansion and resuscitation in intensive care patients with sepsis compared with control fluid?

SUMMARY ANSWER

Albumin did not reduce mortality, but it seems to be safe as no signal towards harm was detected.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Pooled human albumin is recommended as part of fluid volume expansion and resuscitation. This study evaluated new information from EARRS and ALBIOS trials and found that use of pooled human albumin solutions as part of fluid volume expansion and resuscitation did not reduce all-cause mortality in adults with sepsis in critical or intensive care.

Selection criteria for studies

Data sources were PubMed, PubMed Central, Web of Science (includes Medline, Conference Proceedings Citation Index, Data Citation Index, Chinese Science Citation Database, CAB abstracts, Derwent Innovations Index), OvidSP (includes Embase, Ovid Medline, HMIC, PsycINFO, Maternity and Infant Care, Transport Database), Cochrane Library, clinicaltrials.gov, controlled-trials.com, online material, relevant conference proceedings, hand searching of reference lists, and contact with authors as necessary.

Eligibility criteria. We included prospective randomised clinical trials of adults with sepsis of any severity (with or without baseline hypoalbuminaemia) in critical or intensive care who received pooled human albumin solutions as part of fluid volume expansion and resuscitation (with or without improvement of hypoalbuminaemia) compared with those who received control fluids (crystalloid or colloid), if all-cause mortality outcome data were available. No restriction of language, date, publication status, or primary study endpoint was applied.

Primary outcome(s)

All-cause mortality at final follow-up.

Main results and role of chance

We included 18 articles reporting on 16 primary clinical trials that randomised 4190 adults in critical or intensive care with sepsis, severe sepsis, or septic shock. Overall, a median of 70.0 g daily of pooled human albumin was received over a median of three days by adults with a median age of 60.8 years as part of fluid volume expansion and resuscitation (with or without correction of hypoalbuminaemia). The relative risk of death in the albumin groups was similar to that in the control fluid groups (relative risk 0.94; 95% CI 0.87 to 1.01; P=0.11; I^2=0%). Trial sequential analysis corrected the 95% confidence interval for random error (0.85 to 1.02; D^2=0%). We achieved 88% of the required information size (meta-analysis sample size) of 4894 patients, and the cumulative effect size measure (z score) crossed the boundary of futility, supporting the notion of no relative benefit of albumin (GRADE quality of evidence was moderate). Evidence of no difference was also found when albumin was compared with crystalloid fluids (relative risk 0.93; 0.86 to 1.01; P=0.07; I^2=0%) in 3878 patients (GRADE quality of evidence high; 79.9% of required information size) or colloid fluids in 299 patients (relative risk 1.04; 0.79 to 1.38; P=0.76; I^2=0%) (GRADE quality of evidence very low; 5.8% of required information size).

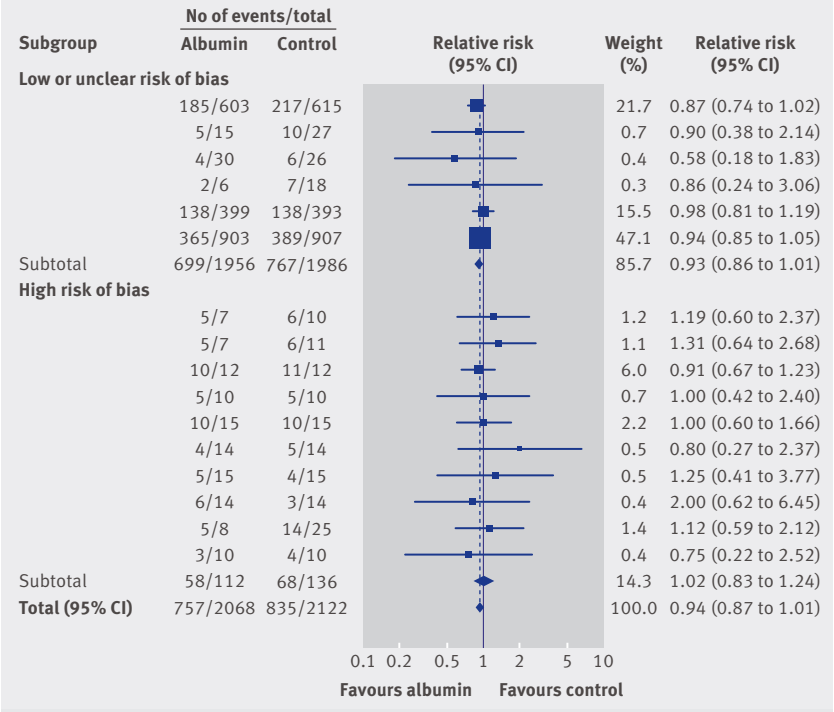
Bias, confounding, and other reasons for caution

When studies at high risk of bias were excluded in a predefined subgroup analysis, the finding of no mortality benefit remained, and the cumulative z score was just outside the boundary of futility. Overall, the meta-analysis was robust to sensitivity, subgroup, meta-regression, and trial sequential analyses.

Study funding/potential competing interests

No specific funding or competing interests.

Relative risk of all-cause mortality in patients exposed to human albumin solutions compared with control fluids



Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications

The DISCO study group

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- Editorial: Subgroup analyses (*BMJ* 2012;344:e2022)
- Research: The influence of study characteristics on reporting of subgroup analyses in randomised controlled trials: systematic review (*BMJ* 2011;342:d1569)
- Research Methods & Reporting: Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses (*BMJ* 2010;340:c117)
- Practice: Subgroup analyses: how to avoid being misled (*BMJ* 2007;335:96)

STUDY QUESTION

How good is the agreement between the planning and reporting of subgroup analyses in randomised controlled trials, and how trustworthy are statements about subgroup prespecifications in journal publications?

SUMMARY ANSWER

Large discrepancies exist between the planning and reporting of subgroup analyses in randomised controlled trials. Published statements about subgroup prespecification are not trustworthy, because more than a third could not be verified.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Although it is well accepted that prespecification of subgroup analyses is an important criterion to assess the credibility of subgroup effects in randomised controlled trials, we found large discrepancies between the planning of subgroup analyses in protocols and the reporting of those analyses in the publications of the randomised controlled trials. When judging the credibility of a subgroup effect, readers should not rely only on what was reported in a single publication, but should also look for similar studies and consider whether subgroup findings are consistent.

Participants and setting

We included protocols of randomised controlled trials including patients and approved between 2000 and 2003 by six research ethics committees in Switzerland, Germany, and Canada. We identified subsequent full journal publications of these trials by electronic literature searches.

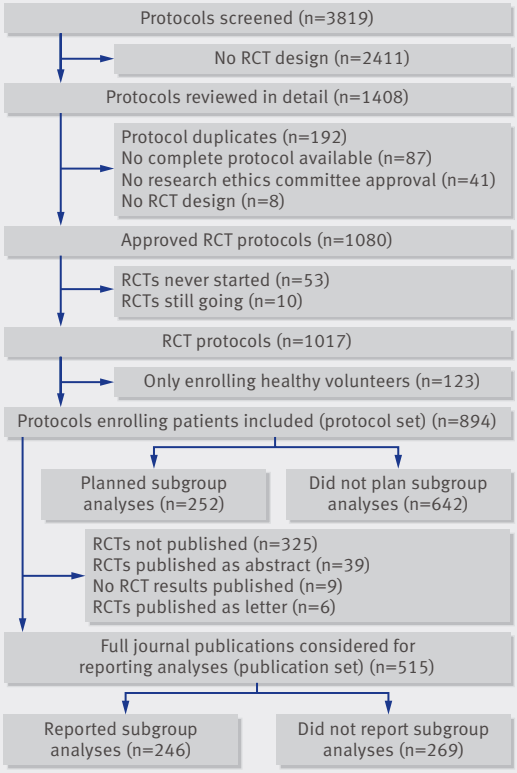
Design, size, and duration

This is a retrospective cohort study based on 894 protocols of randomised controlled trials and 515 corresponding full journal publications. Based on this cohort, we extracted information about subgroup planning in the protocols and their reporting in the subsequent publication. We compared each protocol-publication pair for agreement between subgroup planning and reporting. The median follow-up duration for included trials (time from approval to the latest literature search for the publication) was 11.6 years (range 8.8-12.6 years).

Main results and the role of chance

Of 894 protocols of randomised controlled trials, 252 (28.2%) included one or more planned subgroup analyses. Of those, 17 (6.7%) provided a clear hypothesis for at least one subgroup analysis, 10 (4.0%) anticipated the direction of a subgroup effect, and 87 (34.5%) planned a statistical test for interaction. Industry sponsored trials more often planned subgroup analyses compared with investigator sponsored trials (195/551 (35.4%) *v* 57/343 (16.6%), P<0.001). Of 515 identified journal publications, 246 (47.8%) reported at least one subgroup analysis. In 81 (32.9%) of the 246 publications reporting subgroup analyses, authors stated that subgroup analyses were prespecified but this was not supported by 28 (34.6%) corresponding protocols. In 86 publications, authors claimed a subgroup effect, but only 36 (41.9%) corresponding protocols reported a planned subgroup analysis.

Study flow of protocols of randomised controlled trials (RCTs) and publications



Bias, confounding, and other reasons for caution

Our sample was restricted to six research ethics committees and the protocols of the included randomised controlled trials were approved over 10 years ago. The planning of such trials and reporting practice may therefore have improved over time.

Generalisability to other populations

Our question was specific to randomised controlled trials. Whether our findings about the planning and reporting of subgroup analyses also apply to other study designs (for example, cohort studies) cannot be answered by our study.

Study funding/potential competing interests

This study was funded by the Swiss National Science Foundation and the German Research Organization. We have no competing interests.

Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother

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Visit the online version of this paper to watch a video of the authors discussing their findings

STUDY QUESTION

What is the association between adverse birth outcomes and the time interval between pregnancies, after complete accounting for persistent maternal risk factors?

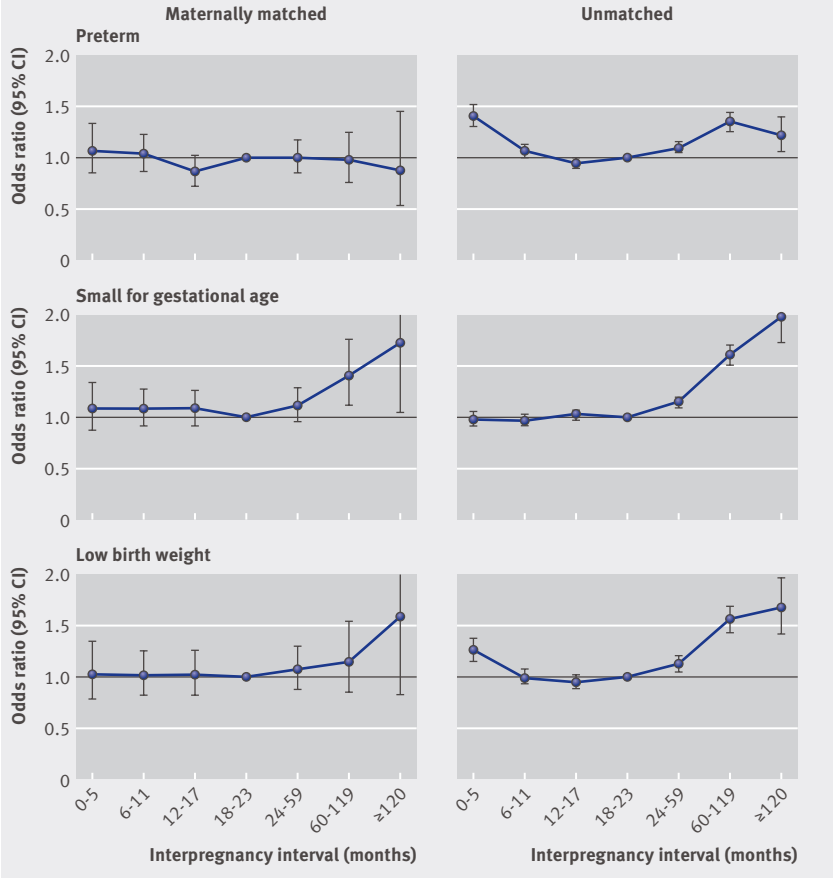
SUMMARY ANSWER

After control for each mother's overall risk of adverse birth outcomes, short intervals between pregnancies had very little effect on the odds of preterm birth, small for gestational age birth, and low birth weight, and long intervals had little effect on the odds of preterm birth.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Mothers with short and long interpregnancy intervals typically have higher incidences of adverse birth outcomes, but previous studies have relied on between mother comparisons that may inadequately account for maternal risk factors. This study, by applying a method that completely adjusts for all persistent maternal factors, questions the causal effect of short interpregnancy intervals on adverse birth outcomes and of long intervals on the risk of preterm birth.

Relation between interpregnancy interval and odds ratios (reference 18-23 months) for adverse birth outcomes



Participants and setting

We analysed the second and third births of mothers who had their first three births as liveborn singletons while resident in Perth, Western Australia.

Design, size, and duration

This was a retrospective cohort study of the birth records of 40 441 women over the period 1980 to 2010. We applied a maternally matched design, which effectively treats each mother as her own control for factors that predispose her children to adverse birth outcomes. We additionally controlled for maternal age, parity, birth year, and socioeconomic status as factors that can vary between pregnancies. For comparison with previous studies, we also generated results by using an unmatched design, controlling for maternal age, parity, birth year, socioeconomic status, ethnicity, and the outcome of the previous birth.

Main results and the role of chance

The maternally matched model indicated much weaker effects of short interpregnancy intervals (<18 months between birth and subsequent conception) on the odds of preterm birth and low birth weight compared with estimates we generated using a traditional unmatched model. Short interpregnancy intervals were estimated to have a weak effect on the odds of small for gestational age birth regardless of model type. The matched model indicated weak effects of long interpregnancy intervals (>23 months) on the odds of preterm birth compared with the unmatched model. However, long interpregnancy intervals had high odds of small for gestational age birth and low birth weight regardless of model type.

Bias, confounding, and other reasons for caution

To facilitate the matched design, we excluded mothers of only two children and the fourth and subsequent births to any mothers with four or more children. We cannot dismiss the possibility that an effect of interpregnancy interval applies to these excluded births. Furthermore, interpregnancy interval may affect other health outcomes not considered in this study.

Generalisability to other populations

Our results may be context dependent. For example, whereas our study was conducted in a developed country, women in developing regions may have slower recovery between pregnancies owing to poor access to nutrient rich foods.

Study funding/potential competing interests

This study was funded by the Australian National Health and Medical Research Council.