Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study


Summary

Background High plasma HDL cholesterol is associated with reduced risk of myocardial infarction, but whether this association is causal is unclear. Explaining the fact that genotypes are randomly assigned at meiosis, are independent of non-genetic confounding, and are unmodified by disease processes, mendelian randomisation can be used to test the hypothesis that the association of a plasma biomarker with disease is causal.

Methods We performed two mendelian randomisation analyses. First, we used as an instrument a single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG) Asn396Ser) and tested this SNP in 20 studies (20913 myocardial infarction cases, 95407 controls). Second, we used as an instrument a genetic score consisting of 14 common SNPs that exclusively associate with HDL cholesterol and tested this score in up to 12482 cases of myocardial infarction and 41331 controls. As a positive control, we also tested a genetic score of 13 common SNPs exclusively associated with LDL cholesterol.

Findings Carriers of the LIPG 396Ser allele (2.6% frequency) had higher HDL cholesterol (0.14 mmol/L higher, p=8x10-13) but similar levels of other lipid and non-lipid risk factors for myocardial infarction compared with non-carriers. This difference in HDL cholesterol is expected to decrease risk of myocardial infarction by 13% (odds ratio [OR] 0.87, 95% CI 0.84–0.91). However, we noted that the 396Ser allele was not associated with risk of myocardial infarction (OR 0.99, 95% CI 0.88–1.11, p=0.85). From observational epidemiology, an increase of 1 SD in HDL cholesterol was associated with reduced risk of myocardial infarction (OR 0.62, 95% CI 0.58–0.66). However, a 1 SD increase in HDL cholesterol due to genetic score was not associated with risk of myocardial infarction (OR 0.63, 95% CI 0.58–0.66, p=0.03). For LDL cholesterol, the estimate from observational epidemiology (a 1 SD increase in LDL cholesterol associated with OR 1.54, 95% CI 1.45–1.63) was concordant with that from genetic score (OR 2.13, 95% CI 0.68–1.26, p=0.63). For LDL cholesterol, the estimate from observational epidemiology (a 1 SD increase in LDL cholesterol associated with OR 1.54, 95% CI 1.45–1.63) was concordant with that from genetic score (OR 2.13, 95% CI 0.68–1.26, p=0.63). However, we noted that the 396Ser allele was not associated with risk of myocardial infarction (OR 0.93, 95% CI 0.91–0.95, p=0.18).

Interpretation Some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction. These data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions in risk of myocardial infarction.


Introduction Cholesterol fractions such as LDL and HDL cholesterol are among the most commonly measured biomarkers in clinical medicine. Observational studies have shown that LDL and HDL cholesterol have opposing associations with risk of myocardial infarction, with LDL cholesterol being positively associated and HDL cholesterol being inversely associated. However, observational studies cannot distinguish between a causal role in the pathological process and a marker of the underlying
pathophysiology. These two possibilities can be distinguished in human beings by changes of the cholesterol fractions in large-scale randomised trials or by studies of inherited DNA variation. For LDL cholesterol, the results of both randomised trials of LDL-cholesterol-lowering treatments and from human mendelian diseases are concordant and suggest that plasma LDL cholesterol is causally related to risk of myocardial infarction. However, the available evidence for the causal relevance of HDL cholesterol from randomised trials or mendelian diseases is scarce and inconsistent.

If a particular plasma biomarker is directly involved in an underlying pathological process, then inherited variation changing plasma concentrations of this biomarker should affect risk of disease in the direction and magnitude predicted by the plasma concentrations. Referred to as mendelian randomisation, this analytical approach has been previously applied to plasma HDL cholesterol, albeit with restricted sample sizes, a small number of single nucleotide polymorphisms (SNPs) at a few genes, and with SNPs that affect multiple lipid fractions. Hence, these studies have not been able to resolve fully the possible causal relevance of HDL cholesterol concentrations for risk of myocardial infarction.

Recently, we have used the genome-wide association approach to identify SNPs that affect blood lipid concentrations. Additionally, through resequencing, we identified a loss-of-function coding SNP at the endothelial lipase gene (LIPG Asn396Ser) that affects plasma HDL cholesterol in isolation. Here, we use these SNPs in case-control studies and prospective cohort studies to test the hypothesis that genetically raised plasma HDL cholesterol might be protective for myocardial infarction.

Methods

Study design

The study design consisted of two components. First, using a case-control design, we tested lipid-associated SNPs individually for association with risk of myocardial infarction. Second, using a mendelian randomisation design, we tested two instruments: (1) a single SNP that related exclusively to plasma HDL cholesterol (a loss-of-function coding polymorphism at the endothelial lipase gene, LIPG Asn396Ser, rs61755018); and (2) a genetic score consisting of 14 common SNPs that exclusively associate with HDL cholesterol.

Study participants

Characteristics of cases of myocardial infarction and controls are shown in appendix p 19. Data for up to 19139 cases of myocardial infarction and 50812 myocardial-infarction-free controls were available from 30 studies. Characteristics of the participants in six prospective cohort studies are shown in the appendix p 20. 50763 participants from six cohort studies were studied and, of these, 4228 developed an incident fatal or non-fatal myocardial infarction. All participants were of self-reported European or South Asian ancestry.

Statistical analysis

In myocardial infarction cases and controls, we tested each of 25 SNPs for association with myocardial infarction in up to 30 studies. These 25 SNPs represented the initial polymorphisms mapped for plasma HDL or LDL cholesterol concentrations with a genome-wide association approach. Each selected SNP has been associated with either HDL or LDL cholesterol at p≤5x10⁻⁸. Genotyping details are provided in the appendix p 2. We undertook logistic regression with the outcome variable of myocardial infarction status, predictor variable of individual SNP genotype, and covariates of age, sex, and principal components of ancestry. We assumed a log-additive genetic model. Overall association for each SNP was evaluated with a fixed-effects inverse-variance-weighted meta-analysis.

Fatal or non-fatal myocardial infarction outcomes were ascertained in each of six prospective cohort studies as described in the appendix p 10. We constructed logistic regression models to examine the association of LIPG Asn396Ser genotype with myocardial infarction status, excluding participants who had had a previous myocardial infarction or ischaemic stroke. The predictor variable of LIPG Asn396Ser genotype was modelled in an additive model (ie, 0, 1, 2 copies of the 396Ser allele). Covariates in the model included age and sex. Overall association for each SNP was evaluated across the six studies with fixed-effects inverse-variance-weighted meta-analysis.

We estimated a predicted risk for LIPG Asn396Ser on the basis of the association of this SNP with plasma HDL cholesterol (appendix p 21) and the association of plasma HDL cholesterol with myocardial infarction (appendix p 22) in the population. Details are provided in the appendix p 2.

We undertook instrumental variable analysis using LIPG Asn396Ser in six prospective cohort studies as listed in the appendix p 23. We additionally did an instrumental variable analysis using multiple genetic variants as instruments. Details of the instrumental variable analysis methods are provided in the appendix p 4. We regarded a two-tailed p<0·05 as nominally significant. Heterogeneity statistics were calculated as described. SAS version 9.1, the R package, STATA, or PLINK software were used for all statistical analyses.

Role of the funding source

The sponsors had no role in the conduct or interpretation of the study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

To validate the statistical framework and clinical samples, we first tested SNPs related to plasma LDL cholesterol in...
In case-control studies (table 1), for nine of ten SNPs associated with LDL cholesterol, the allele correlated with increased LDL cholesterol was also associated with increased risk of myocardial infarction (p<0.05; table 1). Having established that SNPs related to plasma LDL cholesterol consistently affected risk of myocardial infarction, we applied the same methodological framework in the same samples to test the hypothesis that genetic modulation of HDL cholesterol would affect risk of myocardial infarction. Of 15 loci related to plasma HDL cholesterol, at six loci (LPL, TRIB1, APOA1-APOC3, APOA4-APOA5 cluster, CETP, ANGPTL4, and GALNT2)
the allele correlated with raised HDL cholesterol was also associated with decreased risk of myocardial infarction (p=0·05; table 2). Of note, at the HNF4A locus, the HDL-cholesterol-raising allele was spuriously associated with increased risk of myocardial infarction (p=0·0009).

All six SNPs associated with both HDL cholesterol and myocardial infarction had additional effects on plasma LDL cholesterol or triglycerides, or both (p<5x10⁻⁸ for the pleiotropic effects of such SNPs undermine the ability to define a causal role for HDL cholesterol, independent of effects on LDL cholesterol or triglycerides.

To evaluate plasma HDL cholesterol specifically, we undertook mendelian randomisation, a form of instrumental variable analysis.22 We identified a variant that affected only plasma HDL cholesterol without changing other lipid or non-lipid cardiovascular risk factors. In the LIPG gene, roughly 2·6% of individuals carry a serine substitution at aminoacid 396 (substituted for wild-type asparagine). Carrier status for 396Ser was associated with significant increases in HDL cholesterol in each of four prospective cohort studies, with the effect size ranging from 0·08 mmol/L to 0·28 mmol/L per copy of the Ser allele (figure 1, appendix p 21; p=0·002 in FHS, p=0·02 in CCHS, p=5x10⁻⁶ in MDC, and p=7x10⁻⁷ in ARIC).

In a meta-analysis including all four studies, carrier status for 396Ser was associated with an increase of roughly 0·29 SD units in HDL cholesterol (p=8x10⁻¹³). There was no evidence of heterogeneity across the four studies (I²=0·58; Cochran’s heterogeneity p=0·07). LIPG Asn396Ser was not significantly associated with other risk factors for myocardial infarction including plasma LDL cholesterol, triglycerides, systolic blood pressure, body-mass index, risk of type 2 diabetes, fasting glucose, plasma C-reactive protein, waist-to-hip ratio, fibrinogen, and small LDL particle concentration (p>0·05 for each; appendix pp 24–26). Therefore, LIPG Asn396Ser satisfied the three main criteria for mendelian randomisation analysis—ie, that the genotype should be associated with an intermediate biomarker (figure 1), should not be associated with confounding factors (appendix pp 24–46), and should exert its effect on the clinical outcome only through the specific intermediate biomarker (appendix p 22).

Under the model that plasma HDL cholesterol causally relates to risk of myocardial infarction, individuals with an inherited increase in HDL cholesterol (eg, those carrying the LIPG 396Ser allele) are expected to have reduced risk of myocardial infarction. On the basis of the associations between SNPs and HDL cholesterol, and HDL cholesterol and myocardial infarction, we estimated that carriage of LIPG 396Ser should decrease risk of myocardial infarction by 13% (odds ratio [OR] 0·87, 95% CI 0·84–0·91).

To establish whether LIPG 396Ser carriers are indeed protected from risk of myocardial infarction, we studied the association of LIPG Asn396Ser with incident myocardial infarction in 50763 participants from six prospective cohort studies, the gold standard with respect to epidemiological study design. Of these participants, 4228 developed a first myocardial infarction event. LIPG Asn396Ser was not associated with myocardial infarction in any of the six studies (figure 2). Combining these
studies in a meta-analysis, *LIPG* Asn396Ser allele was not associated with myocardial infarction (OR 1·10, 95% CI 0·89–1·37, p=0·37; figure 2). There was no evidence for heterogeneity across the six cohorts (I²=0·17; Cochran’s heterogeneity p=0·31).

We also studied *LIPG* Asn396Ser in case-control studies involving an additional 16 685 cases of myocardial infarction and 48 872 controls and noted that this SNP was not associated with myocardial infarction (OR 0·94, 95% CI 0·82–1·09, p=0·41; table 2, figure 2), with no evidence of heterogeneity across the 14 case-control studies (P=0·34; Cochran’s heterogeneity p=0·11). Finally, we used meta-analysis to combine the evidence from both the prospective studies and case-control studies (116 320 participants; 20 913 cases and 95 407 controls). In all available samples, *LIPG* Asn396Ser remained not associated with risk of myocardial infarction (OR 0·99, 95% CI 0·88–1·11, p=0·85; figure 2). There was no evidence for heterogeneity across all 20 studies (I²=0·30; Cochran’s heterogeneity p=0·10).

We formally estimated the magnitude of an association of genetically raised HDL cholesterol with myocardial infarction, using *LIPG* Asn396Ser as the instrument. The mendelian randomisation estimate was computed from the ratio of the coefficient of the association between genotype and plasma HDL cholesterol to that of the association between genotype and disease to that of the association between genotype and plasma HDL cholesterol; this instrumental variable estimate reflects the potential causal effect of plasma HDL cholesterol on the risk of myocardial infarction.

Table 3 presents the instrumental variable estimate for the association of plasma HDL cholesterol with risk of myocardial infarction in each of six prospective cohort studies. In each study, genetically raised plasma HDL cholesterol was not associated with risk of myocardial infarction. In meta-analysis, genetically raised plasma HDL cholesterol was also not associated with risk of myocardial infarction (OR 1·02 per 0·03 mmol/L [1 mg/dL] increase in HDL cholesterol, 95% CI 0·95–1·09, p=0·64; OR 1·28 per 0·39 mmol/L [15 mg/dL] increase in HDL cholesterol, 95% CI 0·46–3·61, p=0·64).

Statistical power for instrumental variable analysis could be increased if multiple genetic variants in combination are used as instruments, according to a recent proposal.26 From our genome-wide association study of plasma lipid traits involving more than 100000 individuals,27 we noted that 13 common SNPs had statistical evidence at genome-wide levels of significance (p<5×10⁻⁸) for plasma LDL cholesterol and no evidence for association with triglycerides (p>0·01) or HDL cholesterol (p>0·01). We constructed a genetic score for LDL cholesterol combining the LDL-cholesterol-raising alleles at each of these 13 SNPs (appendix p 27).25 We also noted that 14 common SNPs had statistical evidence at genome-wide levels of significance (p<5×10⁻⁸) for plasma HDL cholesterol and no evidence for association with triglycerides (p>0·01) or LDL cholesterol (p>0·01). We constructed a genetic score for HDL cholesterol combining the HDL-cholesterol-raising alleles at each of these 14 SNPs (appendix p 28). Each SNP was given a weight based on the degree of change in LDL or HDL cholesterol as estimated in roughly 100 000 individuals.7

We tested the association of genetic scores for LDL and HDL cholesterol separately for association with myocardial infarction in up to 53 146 cases and controls from the CARDIoGRAM study.26 From observational epidemiology, an increase of 1 SD in usual LDL cholesterol was associated with raised risk of myocardial infarction (OR 1·54, 95% CI 1·45–1·63; appendix p 22). In a mendelian randomisation analysis, a 1 SD increase in LDL cholesterol due to genetic score was also associated with risk of myocardial infarction (OR 2·13, 95% CI 1·69–2·69, p=2×10⁻¹⁰; table 4). From observational epidemiology, a 1 SD rise in usual HDL cholesterol was associated with lowered risk of myocardial infarction (OR 0·62, 95% CI 0·58–0·66; appendix p 22). However, in mendelian randomisation analysis, a 1 SD increase in

<table>
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<tr>
<th>Cohort</th>
<th>Observational epidemiology</th>
<th>Genetically raised</th>
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<tr>
<td></td>
<td>Odds ratio (95% CI) per 0·03 mmol/L (1 mg/dL) increase in plasma HDL cholesterol</td>
<td>Odds ratio (95% CI) per 0·03 mmol/L (1 mg/dL) increase in plasma HDL cholesterol</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Atherosclerosis Risk in Communities Study</td>
<td>0·97 (0·96–0·98) 7×10⁻¹⁸</td>
<td>0·96 (0·86–1·07) 0·44</td>
</tr>
<tr>
<td>Copenhagen City Heart Study</td>
<td>0·98 (0·98–0·99) 6×10⁻¹⁵</td>
<td>1·09 (0·95–1·26) 0·21</td>
</tr>
<tr>
<td>Malmo Diet and Cancer Study, Cardiovascular Cohort</td>
<td>0·97 (0·96–0·98) 1×10⁻⁶</td>
<td>0·82 (0·66–1·01) 0·06</td>
</tr>
<tr>
<td>Framingham Heart Study</td>
<td>0·96 (0·94–0·98) 4×10⁻⁴</td>
<td>1·17 (1·00–1·37) 0·06</td>
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<tr>
<td>Health Professionals Follow-up Study</td>
<td></td>
<td>1·84 (0·39–8·62) 0·36</td>
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<tr>
<td>Danish Diet, Cancer, and Health Study</td>
<td></td>
<td>1·05 (0·79–1·41) 0·71</td>
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Table 3: Instrumental variable analysis estimate of the association of genetically raised HDL cholesterol and risk of myocardial infarction using *LIPG* Asn396Ser as an instrument
HDL cholesterol due to genetic score was not associated with risk of myocardial infarction (OR 0·93, 95% CI 0·68–1·26, p=0·63; table 4).

Discussion
For a biomarker directly involved in disease pathogenesis, we expect a genetic variant that modulates the biomarker to likewise confer risk of disease. We tested this hypothesis for two plasma biomarkers: LDL and HDL cholesterol. SNPs affecting LDL cholesterol were consistently related to risk of myocardial infarction. However, we unexpectedly found that LIPG Asn396Ser, a genetic variant that specifically and substantially increases plasma HDL cholesterol, did not reduce risk of myocardial infarction. A genetic score combining 14 variants exclusively related to HDL cholesterol also showed no association with risk of myocardial infarction (panel).

These results challenge several established views about plasma HDL cholesterol. First, these data question the concept that raising of plasma HDL cholesterol should uniformly translate into reductions in risk of myocardial infarction. We raise the strong possibility that a specific means of raising of HDL cholesterol in human beings—namely, inhibition of endothelial lipase—will not reduce risk of myocardial infarction. In animal models, inhibition or deletion of the endothelial lipase gene increases HDL cholesterol17 in a manner similar to pharmacological inhibitors of CETP.33 As such, whether the protection afforded by the CETP variant is due to the change in HDL or LDL cholesterol is difficult to distinguish.

Second, these findings emphasise the potential limitation of plasma HDL cholesterol as a surrogate measure for risk of myocardial infarction in intervention trials. The data presented here using mendelian randomisation are consistent with results from completed randomised controlled trials focused on raising plasma HDL cholesterol. Hormone replacement therapy raised plasma HDL cholesterol but did not lower risk of myocardial infarction.30 In the Atherosclerosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial,31 the addition of long-acting niacin to background simvastatin increased HDL cholesterol and lowered triglycerides but did not lower risk of cardiovascular events.

Of note, at the cholesterol ester transfer protein (CETP) gene, we did find that common genetic variation reduces risk of myocardial infarction by 4%, a result in line with an earlier meta-analysis.32 However, the CETP variant both increases HDL cholesterol and lowers LDL cholesterol32 in a manner similar to pharmacological inhibitors of CETP.33 As such, whether the protection afforded by the CETP variant is due to the change in HDL or LDL cholesterol is difficult to distinguish.

Third, biomarkers that assay HDL function might overcome some limitations of standard HDL cholesterol assays. However, a challenge will remain—namely, to prove that new functional HDL biomarkers reflect a causal association with myocardial infarction rather than an indirect one, as seems to be the case with plasma HDL cholesterol. For example, using a new in-vitro measure involving mouse macrophages and human serum, Khera and colleagues34 showed an inverse correlation between a specific functional property of HDL, cholesterol efflux capacity, and coronary artery disease status. The present study suggests that a fruitful approach to the causal evaluation of such functional measures in human beings might be large-scale study of relevant inherited DNA variation of HDL function.

There are inherent limitations to the mendelian randomisation study design. Naturally occurring genetic

### Table 4: Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology</th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†</th>
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<tr>
<td>LDL cholesterol</td>
<td>1·54 (1·45–1·63)</td>
<td>2·13 (1·69–2·69), p=2×10⁻¹⁰</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0·62 (0·58–0·66)</td>
<td>0·93 (0·68–1·26), p=0·63</td>
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</table>

*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Panel: Research in context

**Systematic review**

Electronic searches of Medline and PubMed, supplemented by hand searches of reference lists of other review articles, identified reports from three large mendelian randomisation studies for plasma HDL cholesterol28,30 In each of these previous reports, genetically increased plasma HDL cholesterol was not associated with risk of ischaemic heart disease.

**Interpretation**

The present study tested a naturally occurring loss-of-function variant in the endothelial lipase gene and, with this new instrument, we confirm that genetically raised plasma HDL cholesterol is not associated with risk of myocardial infarction. The study further extends previous work by testing an instrument consisting of 14 common variants exclusively associated with plasma HDL cholesterol. A genetic score consisting of these 14 variants was not associated with risk of myocardial infarction. These results show that some ways of raising HDL cholesterol might not reduce risk of myocardial infarction in human beings. Therefore, if an intervention such as a drug raises HDL cholesterol, we cannot automatically assume that risk of myocardial infarction will be reduced.
variation could be a useful instrument to assess causality provided that several requirements have been satisfied.\textsuperscript{35,36} First, one needs suitable genetic variants for the study of the modifiable exposure of interest (in our case, plasma HDL cholesterol). Although many loci are associated with plasma HDL cholesterol, we found \textit{LIPG} Asn396Ser to be particularly informative because it is specifically associated with substantial increases in HDL cholesterol. Additionally, we evaluated a set of 14 common genetic variants that also exclusively affected HDL cholesterol. Both instruments, \textit{LIPG} Asn396Ser and the genetic score, produced similar results.

Second, reliable genotype-to-intermediate-phenotype and intermediate-phenotype-to-disease effect estimates are needed. To obtain as precise estimates as possible, we derived SNP-to-lipid effect estimates from analysis of a large sample involving more than 24 000 participants. Estimates of plasma lipid to myocardial infarction were derived from meta-analysis of four large cohort studies involving more than 25 000 participants.

Third, there must not be pleiotropic effects of the genetic variants of interest. We cannot exclude all potential pleiotropic effects of the \textit{LIPG} Asn396Ser SNP; however, we have assessed but did not detect pleiotropic effects on other cardiovascular risk factors including LDL cholesterol, small LDL particle concentration, triglycerides, body-mass index, systolic blood pressure, plasma C-reactive protein, and type 2 diabetes status.

Finally, the absence of association of individual SNPs with myocardial infarction could be due to low statistical power. However, for the crucial SNP in the mendelian randomisation study for plasma HDL cholesterol, we had sufficient power. In this study, \textit{LIPG} Asn396Ser has been tested in 20 913 myocardial infarction cases and 95 407 myocardial-infarction-free participants. We had 90% power to detect the expected 13% reduction in risk of myocardial infarction for the \textit{LIPG} Asn396Ser variant (at a two-sided \( \alpha \) of 0.05).

In summary, our results showed that polymorphisms related to plasma LDL cholesterol were consistently associated with risk of myocardial infarction, whereas this was not the case for variants related to plasma HDL cholesterol. A polymorphism in the endothelial lipase gene and a genetic score of 14 common SNPs that associated with substantial increases in HDL cholesterol. Hence, interventions (lifestyle or pharmacological) that raise plasma HDL cholesterol cannot be assumed ipso facto to lead to a corresponding benefit with respect to risk of myocardial infarction.

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