Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps

Brian A. Ference

Purpose of review
Mendelian randomization studies have the potential to transform our understanding of cardiovascular medicine by generating naturally randomized data that can fill evidence gaps when a randomized trial would be either impossible or impractical to conduct. Here, we review recent Mendelian randomization studies evaluating the effect of low-density lipoprotein cholesterol (LDL-C) on the risk of coronary heart disease (CHD).

Recent findings
Mendelian randomization studies consistently demonstrate that LDL-C is causally associated with the risk of CHD. Furthermore, exposure to genetically mediated lower LDL-C appears to be associated with a much greater than expected reduction in CHD risk, thus suggesting that LDL-C has a cumulative effect on the risk of CHD. In addition, genetically mediated lower LDL-C is log-linearly associated with the risk of CHD and the effect of polymorphisms in multiple different genes on the risk of CHD is remarkably consistent when measured per unit lower LDL-C.

Summary
The naturally randomized genetic evidence suggests that LDL-C has a causal and cumulative effect on the risk of CHD, and that the clinical benefit of exposure to lower LDL-C is determined by the absolute magnitude of exposure to lower LDL-C independent of the mechanism by which LDL-C is lowered.

Keywords
coronary heart disease, low-density lipoprotein cholesterol, Mendelian randomization, statins

INTRODUCTION

It is well established that low-density lipoprotein cholesterol (LDL-C) is causally associated with the initiation and progression of atherosclerosis. Perhaps, the most compelling evidence supporting the causal role of LDL-C in the pathogenesis of atherosclerosis is the fact that in meta-analyses of randomized trials, lowering LDL-C with a statin reduces the risk of major atherosclerotic cardiovascular events by approximately 20% for each mmol/l reduction in LDL-C [1,2]. However, persons being treated with a statin continue to experience a high residual risk of events. The cause of this residual risk is unclear. The prevailing conventional wisdom is that perhaps there are other risk factors that are causally related to the risk of atherosclerotic cardiovascular disease and treating these other risk factors may reduce the residual risk. Unfortunately, with the exception of lowering blood pressure, several large randomized trials have failed to demonstrate that raising high-density lipoprotein cholesterol, lowering triglycerides, lowering serum glucose among persons with diabetes or reducing markers of inflammation further reduce the risk of coronary heart disease (CHD) when added to treatment with a statin [3–8].

An alternative, but complementary, hypothesis to explain residual risk is that we may initiate LDL-C lowering therapy too late in the atherosclerotic disease process to achieve the maximum potential clinical benefit of lowering LDL-C. It is well known from autopsy and other studies that atherosclerosis is a chronic progressive disease that begins early in

Division of Translational Research and Clinical Epidemiology, Division of Cardiovascular Medicine, Wayne State University School of Medicine, Detroit, Michigan, USA

Correspondence to Brian A. Ference, MD, MPhil, MSc, FACC, Division of Translational Research and Clinical Epidemiology (TRaCE) and the Division of Cardiovascular Medicine, Wayne State University School of Medicine, UHC 2E2, Detroit, MI 48202, USA. Tel: +1 313 745 2647; fax: +1 313 745 5565; e-mail: bference@med.wayne.edu

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KEY POINTS

- Mendelian randomization studies can provide naturally randomized evidence to fill evidence gaps when a randomized trial would be impossible or impractical to conduct.
- LDL-C has both a causal and cumulative effect on the risk of cardiovascular disease.
- The clinical benefit of exposure to lower LDL-C appears to be independent of the mechanism by which LDL-C is lowered.

life and progresses slowly over several decades before becoming clinically manifest [9]. This finding has led to the hypothesis that lowering LDL-C beginning earlier in life (and therefore earlier in the atherosclerotic disease process) may prevent or substantially slow the progression of atherosclerotic lesions and thereby substantially improve the clinical efficacy of therapies that lower LDL-C (and thus reduce the corresponding residual risk) [10].

Ideally, this hypothesis would be tested in a long-term randomized trial. However, the cost and logistical complexity of randomizing a very large number of young asymptomatic persons to an LDL-C lowering therapy or to placebo and then following them forward for several decades would likely be prohibitive. As a result, such a trial is unlikely to ever be conducted.

Genetic studies can potentially help to fill this evidence gap. In the absence of a long-term randomized trial, it may be possible to evaluate the effect of lifelong exposure to lower LDL-C on the risk of cardiovascular disease, and to address other unresolved issues in cardiovascular medicine and lipidology, by appealing to the principle of Mendelian randomization.

MENDELIAN RANDOMIZATION: NATURE'S RANDOMIZED TRIALS

Numerous polymorphisms in multiple different genes have been reported to be associated with small differences in circulating LDL-C levels at genome-wide level of significance [11,12▪]. Each of these polymorphisms is allocated approximately randomly at the time of conception in a process sometimes referred to as Mendelian randomization [13,14]. Therefore, inheriting an allele associated with lower LDL-C is analogous to being randomly allocated to an LDL-C lowering therapy at birth while inheriting the other allele is analogous to being randomly allocated to usual care. Comparing the rate of cardiovascular events among persons with and without such an LDL-C lowering polymorphism should, therefore, provide an unconfounded causal estimate of the effect of long-term exposure to lower LDL-C on the risk of CHD in a manner analogous to a long-term randomized trial.

Several Mendelian randomization studies have reported that polymorphisms that are associated with lower LDL-C are also associated with a correspondingly lower risk of CHD [15–17]. This finding provides strong confirmation that LDL-C is causally related to the risk of CHD. Furthermore, when the effect of polymorphisms associated with lower LDL-C, but not with other lipid or nonlipid pleiotropic effects, is plotted against their effect on CHD, there appears to be a log-linear association between the absolute magnitude of the exposure to lower LDL-C and the risk of CHD [17]. This log-linear relationship between genetically mediated LDL-C and the risk of CHD is very similar to the log-linear relationship observed between LDL-C levels and the risk of cardiovascular events in both observational epidemiologic studies and in randomized statin trials [1,18], and thus provides strong naturally randomized genetic evidence to support the notion that with regard to LDL-C 'lower is better' (Fig. 1).

If we think of Mendelian randomization studies evaluating polymorphisms in different genes, each of which presumably lowers LDL-C by a different mechanism or pathway, as distinct 'naturally randomized trials', we can extend the analogy to a portfolio of naturally randomized trials each evaluating a different method of lowering LDL-C. If we first adjust the observed effect of each polymorphism on the risk of CHD for a given unit change in LDL-C, we can then combine the results of these studies in a meta-analysis to produce a summary estimate of the effect of long-term exposure to each unit lower LDL-C on the risk of CHD [17]. Interestingly, this method is numerically and computationally equivalent to calculating a genetic LDL-C score using summary level data [19▪]. Importantly, this method is also exactly the same method used by the Cholesterol Treatment Trialists' Collaborators who first adjusted the effect of each statin trial per mmol/l lower LDL-C and then meta-analyzed the adjusted effect sizes to estimate the effect of each mmol/l lower LDL-C during treatment with a statin on the risk of CHD [1,2]. When the Mendelian randomization studies are meta-analyzed in this way, or equivalently the combined effect of these polymorphisms is evaluated as a genetic LDL-C score, we see that long-term exposure to each mmol/l lower LDL-C is associated with a substantial 50–60% reduction in the risk of CHD (with a robust P value of 10^{-45}) [17,20,21].

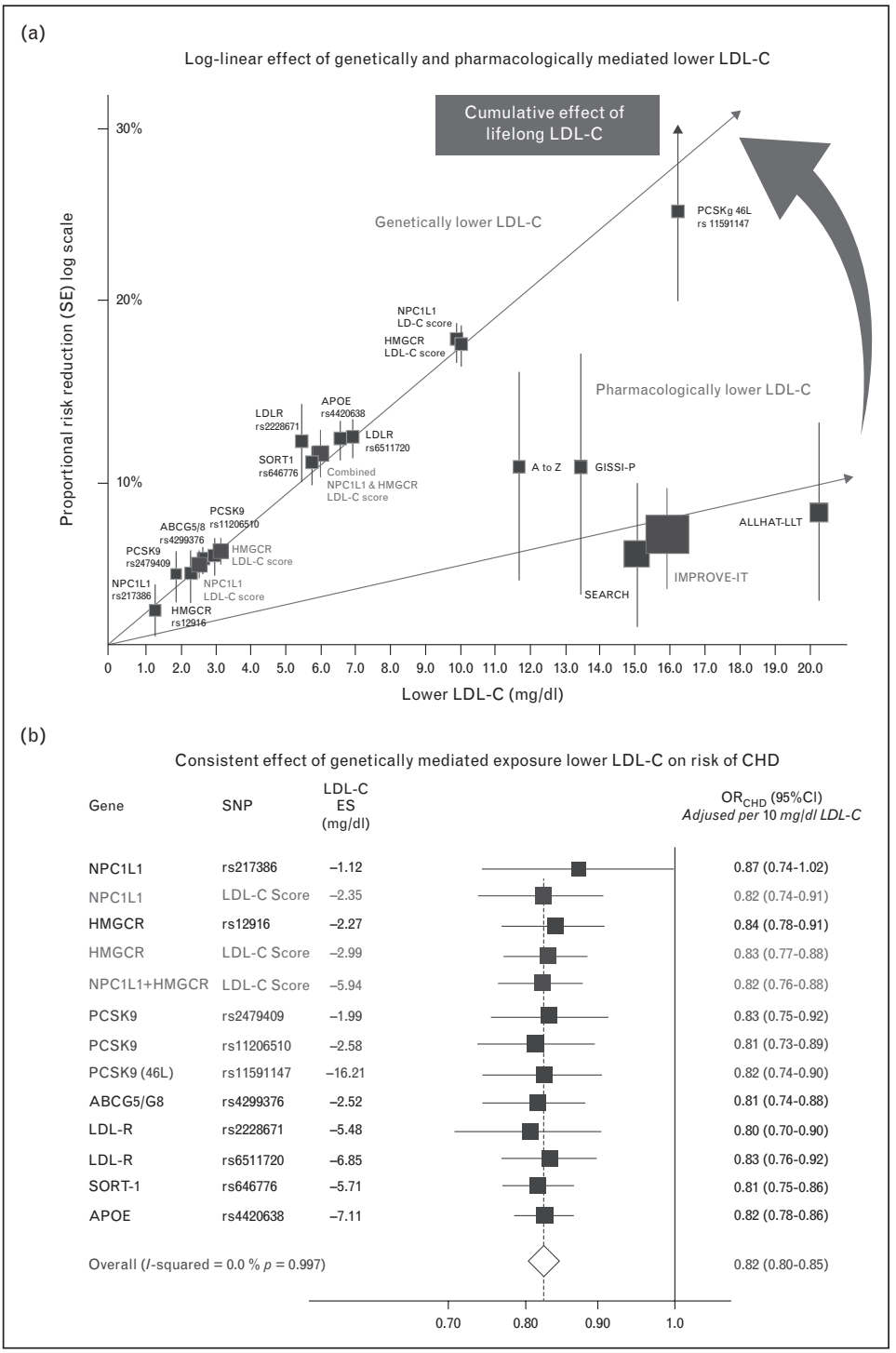

FIGURE 1. (a) Boxes represent proportional CHD risk reduction (1 – OR) for each exposure allele plotted against the absolute magnitude of lower LDL-C associated with that allele (top line), or the proportional CHD risk reduction (1 – RR) for each trial plotted against the mean absolute difference in LDL-C between treatment arms at 1-year follow-up for that trial (bottom line). Vertical lines represent one SE above and below point estimate of proportional risk reduction. SNPs and trials are plotted in order of increasing absolute magnitude of exposure to lower LDL-C. The lines (which are forced to pass through the origin) represent the increase in proportional risk reduction of CHD per unit exposure to lower LDL-C. (b) Boxes represent the OR for the association between the exposure allele (defined as the allele associated with lower LDL-C) and risk of CHD for each polymorphism or genetic LDL-C score. Bars represent 95% CI. Effect estimates and standard errors are adjusted for a standard decrement of 10 mg/dl (0.25 mmol/l) lower LDL-C using the usual ratio of effect estimates method. CHD, coronary heart disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; RR, Relative Risk; SE, Standard Error.

COMPARATIVE EFFECTIVENESS OF EARLIER AS COMPARED WITH LATER LOW-DENSITY LIPOPROTEIN CHOLESTEROL LOWERING

We are now in a position to use the naturally randomized genetic evidence to test the hypothesis that long-term exposure to lower LDL-C is associated with a greater reduction in the risk of CHD as compared with short-term reduction started later in life. We can do this by comparing the results of the meta-analysis of Mendelian randomization studies with the meta-analysis of statin trials.

In these analyses, long-term exposure to each mmol/l lower LDL-C appears to be associated with a substantially greater reduction in the risk of CHD events than the 20% relative reduction in risk observed during treatment with a statin started later in life (P value of 10^{-19}) [17]. Indeed, long-term exposure to lower LDL-C appears to be associated with a three-fold greater reduction in the risk of CHD per unit lower LDL-C (on the log scale) as compared with treatment with a statin started later in life. For example, if long-term exposure to each mmol/l lower LDL-C is associated with a 55% reduction in the risk of CHD, then to achieve this same relative risk reduction starting later in life would require lowering LDL-C by 3 mmol/l (relative risk $= 0.8^{*}0.8^{*}0.8 \approx 0.5$) [17].

The substantially greater effect of long-term exposure to each unit lower LDL-C on the risk of CHD, as compared with short-term LDL-C lowering during treatment with a statin, strongly implies that LDL-C has both a causal and a cumulative effect on the risk of atherosclerotic cardiovascular disease. As a result, the naturally randomized genetic evidence strongly supports the hypothesis that lowering LDL-C beginning earlier in life (and therefore earlier in the atherosclerotic disease process) would substantially improve the apparent clinical efficacy of lowering LDL-C. Thus, with regard to lowering LDL-C, the naturally randomized genetic evidence suggests that both 'lower is better' and 'earlier is better'. Indeed, the apparently reduced efficacy of lowering LDL-C beginning later in life may explain much of the residual risk associated with treatment with a statin.

DOES THE MECHANISM OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL LOWERING MATTER?

Although randomized trials of statins have consistently demonstrated that lowering LDL-C reduces the risk of CHD, several randomized trials have failed to demonstrate that further lowering LDL-C by adding niacin, a fibrate or a cholesterol-ester transfer protein inhibitor to a statin further reduces the risk of cardiovascular events [4–7]. The results of these trials have created uncertainty about whether the mechanism of lowering LDL-C influences the expected clinical benefit of exposure to lower LDL-C. Mendelian randomization studies can help to resolve this uncertainty.

Adjusting the effect of LDL-C lowering polymorphisms on the risk of CHD for a standard increment in LDL-C to create a genetic LDL-C score, or equivalently meta-analyze the Mendelian randomization studies to generate a summary estimate of the effect of genetically mediated exposure to lower LDL-C on the risk of CHD, also permits us to make inferences about whether the mechanism of lowering LDL-C influences the corresponding risk of CHD. Mendelian randomization studies have reported that polymorphisms in multiple different genes, each of which presumably acts to lower LDL-C by a different mechanism or pathway, have a remarkably similar effect on the risk of CHD when measured per unit lower LDL-C [17]. Similarly, other Mendelian randomization studies have compared polymorphisms in multiple different genes that each acts to lower LDL-C through the same common final pathway involving upregulation of the LDL-C receptor [22▪▪]. These analyses included polymorphisms in the genes that encode for the targets of several commonly available LDL-C lowering medications including the statins, ezetimibe and the new monoclonal antibodies directed against PCSK9. Once again, polymorphisms in each of these genes had a remarkably similar effect on the risk of CHD when measured per unit change in LDL-C.

Taken together, the Mendelian randomization studies strongly suggest that the clinical benefit of lower LDL-C appears to be independent of the mechanism by which LDL-C is lowered. Instead, the clinical benefit of lower LDL-C appears to be determined by the absolute magnitude of exposure to lower LDL-C regardless of how LDL-C is lowered. This finding may also explain the failure of trials evaluating niacin, fibrates and dalcetrapib [4–7]. In these trials, the absolute achieved reductions in LDL-C were too small and the number of events accrued too few to translate into statistically significant effects on CHD risk.

ANTICIPATING THE RESULTS OF RANDOMIZED TRIALS

The question of whether the mechanism of lowering LDL-C influences the expected clinical benefit was directly tested in the recently reported IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [23▪▪]. That study

found that adding ezetimibe, a cholesterol absorption inhibitor, to treatment with a statin was associated with a 16 mg/dl absolute reduction in LDL-C and a significant 10% reduction in the composite end point of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke ($P = 0.003$). The magnitude of this event reduction was consistent with the expected effect for a similar reduction in LDL-C during treatment with a statin, thus supporting the notion that the benefit of lower LDL-C is independent of the mechanism by which LDL-C is lowered. Despite this finding, however, considerable uncertainty persists as to whether lowering LDL-C by inhibiting cholesterol absorption with ezetimibe is as effective at reducing the risk of CHD as is treatment with a statin. Once again, naturally randomized genetic evidence can help resolve this uncertainty.

To compare the biological effect of lower LDL-C mediated by inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) protein with ezetimibe and inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) with a statin, we conducted a 2×2 factorial Mendelian randomization study to approximate a 'naturally randomized IMPROVE-IT trial' [22▪▪]. We found that polymorphisms that mimic the effect of ezetimibe and polymorphisms that mimic the effect of statins, respectively, had approximately the same effect on the risk of CHD per unit lower LDL-C, and that when present together they had a linearly additive effect on LDL-C and a log-linearly additive effect on the risk of CHD. The results of this naturally randomized IMPROVE-IT trial thus predicted that adding ezetimibe to a statin should reduce the risk of CHD proportional to the absolute achieved reduction in LDL-C, because the effect of each unit lower LDL-C mediated by inhibition of HMGCR and NPC1L1 has essentially the same effect on the risk of CHD. Indeed, this is precisely what the IMPROVE-IT trial reported [23▪▪]. This Mendelian randomization study, both provides strong biological support for the results of IMPROVE-IT, and importantly it suggests that naturally randomized genetic evidence can closely anticipate the results of randomized trials.

FILLING EVIDENCE GAPS WITH NATURALLY RANDOMIZED GENETIC DATA

Even after publication of IMPROVE-IT, an important unresolved issue is whether the combination of low-dose statin and ezetimibe will be as effective at reducing the risk of CHD as treatment with high-dose statins. The naturally randomized genetic data strongly suggest that treatment with combination low-dose statin and ezetimibe should be as effective as high-dose statin therapy at reducing the risk of CHD because polymorphisms that mimic the effect of statins, polymorphisms that mimic the effect of ezetimibe and the combined effect of these polymorphisms each has the same effect on the risk of CHD when measured per unit change in LDL-C [22▪▪,20,24▪].

This issue is particularly relevant given the concern about apparent dose-dependent statin-induced side-effects. In a recent meta-analysis of statin trials, treatment with a statin was associated with a dose-dependent increase in the risk of new-onset diabetes [25,26▪▪]. In addition, a Mendelian randomization study reported that polymorphisms in the HMGCR gene that mimic the effect of statins were also associated with a slightly higher lifetime risk of diabetes, suggesting that at least some of the increased risk of diabetes may be an 'on-target' effect of statins [26▪▪].

By contrast, analyses of data from the 'naturally randomized IMPROVE-IT' study found that polymorphisms that mimic the effect of ezetimibe, unlike polymorphisms that mimic the effect of statins, are not associated with an increased risk of diabetes (Ference B.A., unpublished data). These genetic data once again accurately predicted the results of the IMPROVE-IT trial. In IMPROVE-IT, adding ezetimibe to treatment with a statin did not increase the risk of new-onset diabetes [27▪▪]. Therefore, the naturally randomized genetic evidence, combined with evidence from IMPROVE-IT, suggests that the combination of low-dose statin and ezetimibe may actually be preferred to treatment with high-dose statins because it will maximize LDL-C lowering (and thus maximize the corresponding reduction in CHD risk), while at the same time minimize the potential for dose-dependent statin-induced side-effects, including new-onset diabetes.

CONCLUSION

Mendelian randomization studies have the potential to reshape cardiovascular medicine by generating robust naturally randomized evidence that can help to fill evidence gaps when an actual randomized trial would be either impossible or impractical to conduct. Indeed, recent Mendelian randomization studies have begun to challenge current paradigms in lipidology by demonstrating that LDL-C has both a causal and a cumulative effect on the risk of CHD, and that the clinical benefit lower LDL-C appears to be independent of the mechanism by which LDL-C is lowered. These naturally randomized genetic data suggest that with regard to LDL-C,

it may be time to consider changing the notion of 'lower is better' to 'lower is better, and earlier is better' to maximize the potential lifetime benefit of exposure to lower LDL-C; and to reconsider the focus on 'high intensity statins' and instead focus on 'high intensity LDL-C lowering' as the preferred strategy to reduce the risk of cardiovascular events, while at the same time minimize the potential for dose-dependent statin-induced side-effects.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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