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The Role of Early LDL Lowering to Prevent the Onset of Atherosclerotic Disease

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Abstract Coronary atherosclerosis is a chronic progressive disease that begins early in life and progresses slowly over several decades before becoming clinically manifest. The causal relationship between low-density lipoprotein cholesterol (LDL-C) and the risk of coronary atherosclerosis is well established. Multiple randomized trials have demonstrated that lowering LDL-C levels during treatment with a statin reduces the risk of major atherosclerotic coronary events. However, individuals being treated with a statin continue to experience a high residual risk of events. Here we review the evidence that lowering LDL-C levels beginning earlier in life, and therefore earlier in the atherosclerotic disease process, can prevent or substantially delay the development of atherosclerosis and thereby substantially improve the clinical benefit of therapies that lower LDL-C levels. We focus on providing a critical appraisal of the naturally randomized evidence that is emerging from recently conducted genetic association studies.

Keywords Low-density lipoprotein cholesterol · Statins · Primary prevention · Genetic polymorphism · Mendelian randomization

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Introduction

The causal relationship between low-density lipoprotein (LDL) cholesterol (LDL-C) and the risk of atherosclerotic coronary heart disease (CHD) is well established. Multiple laboratory, genetic, and clinical studies support a central role for LDL-C in the initiation, development, and progression of coronary atherosclerosis. Numerous prospective epidemiologic cohort studies and two large meta-analyses of individual-patient-level data from over one million participants enrolled in more than 100 prospective studies have demonstrated a continuous, graded, and approximately log-linear relationship between increasing plasma LDL-C levels and the risk of CHD [1, 2•]. Furthermore, multiple randomized controlled trials have demonstrated that lowering LDL-C levels during treatment with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) reduces the risk of CHD, stroke, and other major vascular events [3].

A meta-analysis of individual-level data from 170,000 participants enrolled in 27 statin trials conducted by the Cholesterol Treatment Trialists' Collaboration demonstrated that the risk of CHD is reduced by approximately 21 % [odds ratio (OR), 0.79; 95 % confidence interval (CI), 0.77-0.81] for each 1 mmol/l (38.7 mg/dl) reduction in LDL-C concentration [4]. The observed proportional risk reduction in the statin trials appears to be independent of a person's baseline LDL-C level, age (within the limited age range of persons enrolled in these trials), gender, baseline short-term risk of developing CHD, or the presence or absence of a history of clinically manifest atherosclerotic disease [3, 4, 5•]. These data suggest that lowering LDL-C levels at any stage of the atherosclerotic disease process can reduce the risk of CHD events.

However, individuals being treated with a statin continue to experience a high residual risk of CHD events. Indeed, a

20 % proportional risk reduction per 1 mmol/l lower LDL-C concentration still leaves an 80 % residual risk. On the basis of the log-linear association between the magnitude of LDL-C concentration reduction achieved during treatment with a statin and the associated CHD risk reduction observed in the randomized trials, even a more aggressive reduction in LDL-C concentration of 2 mmol/l (77.4 mg/dl) would only reduce the risk of CHD by approximately 38 % ($0.79 \times 0.79 = 0.62$), thus leaving a still considerable residual risk of CHD events. It would appear, therefore, that more aggressive lowering of lipid levels by itself may not be enough to substantially reduce this residual risk.

In an attempt to determine the cause of and potentially reduce the residual risk of CHD events among individuals being treated with a statin or other lipid-lowering therapy, much attention has focused on the role of other lipid risk factors (e.g., high-density lipoprotein cholesterol, triglycerides) and nonlipid risk factors (e.g. hypertension, inflammation, diabetes) in the pathogenesis and progression of atherosclerotic CHD. With the exception of hypertension, however, randomized trial evidence demonstrating that treating these other risk factors further reduces the risk of CHD, and thereby reduces the corresponding residual risk of CHD events, is lacking [6–10].

An alternative, and complementary, hypothesis that may explain much of the residual risk of coronary events among individuals being treated with a statin is that initiating therapy to lower LDL-C levels beginning later in life, after atherosclerosis has already developed, may limit the potential clinical efficacy of lowering LDL-C levels as a therapeutic strategy to reduce the risk of CHD. It is well accepted that coronary atherosclerosis is a chronic progressive disease that begins early in life and slowly progresses over several decades before becoming clinically manifest. However, the mean age at the time of randomization in the statin trials was 63 years [5•]. Therefore, at the time of randomization, individuals enrolled in the statin trials had already been exposed to a lifetime of circulating LDL-C, with the subsequent development of a variable underlying atherosclerotic burden. Lowering LDL-C levels beginning later in life, after the development and progression of atherosclerosis, may serve merely to stabilize existing atherosclerotic plaques. These plaques, however, can continue to progress and eventually cause symptoms by obstructing epicardial blood flow, or disrupt to cause acute coronary syndromes, thus resulting in a high residual risk of coronary events. By contrast, lowering LDL-C levels beginning much earlier in life, and therefore much earlier in the atherosclerotic disease process, may prevent or substantially delay the progression of coronary atherosclerosis and thereby substantially reduce the risk of CHD events, and thus substantially reduce the correspondingly residual risk of CHD.

Rationale for Early Intervention to Lower LDL-C Levels

Coronary atherosclerosis appears to be initiated by the entry of LDL-C into the coronary artery wall, a process that triggers a cascade of inflammatory events [11]. This process begins relatively early in life with the formation of fatty streaks that consist largely of cholesterol (predominantly LDL-C) filled macrophages. The nascent plaque progresses over time to form a raised lesion consisting of a fibrous layer of scar tissue overlying a lipid-rich core. These raised fibrous plaques then further progress over time at a rate that is proportional to the circulating level of plasma LDL-C (and to the levels of other risk factors for CHD) to ultimately form larger and more complex lesions. These complicated lesions continue to progress over time and can eventually become vulnerable to disruption [12].

The earliest stages of the atherosclerotic process can be detected on gross pathological examination of coronary arteries beginning in adolescence and early adulthood [13–17]. Approximately 75 % of young men killed in the Korean and Vietnam wars (mean age 22 years) had fibrous plaques detected at autopsy [18, 19]. In the Pathological Determinants of Atherosclerosis in Youth study, autopsies performed on 2,876 individuals aged 15–34 years who died of noncardiovascular causes found that the presence and extent of fatty streaks and raised lesions increased with age, and the extent of these lesions was log-linearly associated with plasma non-LDL cholesterol level [20–22]. In the Pathological Determinants of Atherosclerosis in Youth study, the prevalence of advanced coronary lesions increased slowly between the ages of 15 and 29 years, but then increased by twofold among women and threefold among men between the ages of 30 and 34 years [20].

The well-established causal association between LDL-C and the risk of atherosclerosis, and the consistent finding that atherosclerosis begins in late childhood and progresses slowly throughout adolescence and young adulthood into middle age raises the intuitive hypothesis that lowering LDL-C levels beginning much earlier in life than is currently recommended may substantially delay the progression of coronary atherosclerosis and thus potentially prevent the development of the advanced atherosclerotic plaques that eventually become clinically manifest.

The notion that lowering plasma LDL-C levels can slow the progression of coronary atherosclerotic lesions is supported by observations from multiple studies that have measured the effect of lipid-lowering therapies on the progression of coronary atherosclerosis using intravascular ultrasonography. These studies have demonstrated that the rate of progression of coronary atherosclerotic lesions among individuals being treated with a statin or other lipid-lowering therapy appears to be linearly associated with the plasma LDL-C level achieved, and that

more intensive lowering of LDL-C levels leads to less plaque progression [23–25]. Indeed, these studies suggest that plaque progression can be arrested (or even marginally reversed) at LDL-C levels in the putatively normal range of 50-70 mg/dl [26•, 27].

Furthermore, nonrandomized long-term follow-up studies of two landmark statin trials have demonstrated that the clinical benefit associated with lowering LDL-C levels during treatment with a statin appears to persist for up to 10 years after completion of the trial. In the West of Scotland Coronary Prevention Study, treatment with pravastatin as compared with placebo among men with elevated LDL-C levels (mean 192 mg/dl) but without a history of CHD reduced the incidence of a first coronary event from 6.0 % to 3.7 % [hazard ratio (HR), 0.60; 95 % CI, 0.48-0.75] during a median of 5 years of treatment [28]. During the subsequent 10 years of additional follow-up, 38.7 % of individuals originally randomized to treatment with pravastatin and 35.2 % of persons originally randomized to placebo treatment were treated with a statin. At the end of the 15-year total follow-up period [29], individuals originally randomized to statin therapy had a persistently lower risk of CHD, 11.8 % versus 15.5 % (HR, 0.73; 95 % CI, 0.63-0.83). Similarly, in the Heart Protection Study, treatment with simvastatin as compared with placebo among 20,536 individuals at high risk of vascular disease reduced the risk of major vascular events by 23 % [relative risk (RR), 0.77; 95 % CI, 0.72-0.81] per 1 mmol/l reduction in LDL-C concentration during a mean follow-up of 5.3 years [30]. During a further 5.7 years of post-trial follow-up, treatment with a statin and plasma LDL-C levels were similar between the two original treatment allocation groups. After a total of 11 years of follow-up [31], the reduction in the risk of major vascular events observed during the trial period was largely unchanged during the subsequent 6 years of posttrial follow-up.

Taken together, the intravascular ultrasonography studies and the long-term observational follow-up of statin trials suggest that lowering LDL-C levels can slow the progression of coronary atherosclerosis and that this effect appears to be durable over time without evidence of attenuation of effect. It seems reasonable to assume, therefore, that if lowering LDL-C levels beginning later in life can slow the progression of advanced atherosclerotic plaques that have developed over several decades, then lowering LDL-C levels, or approximately equivalently keeping LDL-C levels low, beginning much earlier in life should also be able to slow the progression of less advanced fatty streaks and raised fibrous plaques, and thereby potentially prevent advanced atherosclerotic plaques from ever developing.

Observational Epidemiologic Evidence

The evidence from laboratory, autopsy, imaging, and long-term observational follow-up studies of randomized trials provides a compelling rationale for lowering LDL-C levels beginning early in life in an attempt to slow the development and progression of coronary atherosclerosis. The salient question, however, is not whether the atherosclerotic process can be slowed by earlier lowering of LDL-C levels, but rather whether or not long-term exposure to lower LDL-C levels will translate into a reduced risk of CHD and other major atherosclerotic vascular events, and whether the magnitude of this risk reduction is sufficiently compelling to change clinical practice and public health policy.

The possibility that prolonged exposure to low levels of LDL-C may result in a large clinical benefit is suggested by the observation that CHD appears to be rare in societies that maintain low LDL-C levels throughout adulthood [32–35]. Furthermore, differences in the observed rate of CHD between populations appear to be strongly influenced by differences in the mean cholesterol level in those populations. In the Seven Countries Study, the investigators measured diet-influenced differences in mean total cholesterol level among 11,579 men between the ages of 40 and 59 years living in 18 regions of seven countries [36]. They found that there was a more than tenfold variation in subsequent CHD mortality between these regions, and that the baseline mean total cholesterol level in each region, which presumably reflects lifelong differences in exposure to plasma cholesterol, strongly predicted CHD mortality. Indeed, a subsequent analysis of these data found that differences in mean baseline cholesterol level between regions explained nearly 80 % of the difference in CHD mortality [37]. These ecological studies, however, are generally considered to provide only weak evidence of causality, and they do not permit a reliable estimate of the magnitude of the CHD risk reduction that can be achieved with long-term exposure to lower LDL-C levels.

Data from a limited number of prospective cohort studies also suggest that long-term exposure to lower plasma cholesterol levels may result in a greater than expected reduction in the risk of CHD. In a subgroup analysis of younger participants enrolled in three prospective cohort studies, an analysis that included 81,578 men between the ages of 18 to 39 years followed for a median of 17 years, during which time 1,036 fatal CHD events occurred, the association between plasma total cholesterol level and CHD mortality was continuous and graded [38]. When data from the younger subgroups across all three studies are combined in a meta-analysis, each 1 mmol/l (38.7 mg/dl) increase in total cholesterol concentration was associated with a 64 % increased risk of CHD mortality (RR, 1.64; 95 % CI, 1.52-1.77).

Framed another way, these data also suggest, therefore, that long-term exposure to each 1 mmol/l lower total cholesterol concentration was associated with an approximately 39 % reduction in CHD mortality (RR, 0.61; 95 % CI, 0.56-0.66). Importantly, the observed reduction in CHD mortality was greater among the younger subgroups than for the remaining participants in these three cohort studies. Similar results were reported in a prospective study of 1,017 young men (mean age 22 years) followed for a median of 30.5 years, during which time 97 CHD events occurred [39]. In this study, each 1 mmol/l increase in baseline total cholesterol level was associated with a twofold greater risk of CHD (RR, 2.01; 95 % CI, 1.59–2.53). Although the data are limited, these prospective epidemiologic cohort studies support the hypothesis that lowering cholesterol levels beginning earlier in life may lead to larger reductions in CHD risk as compared with similar LDL-C level reductions later in life.

Evidence from observational studies, however, are vulnerable to confounding (including residual confounding), selection bias, regression dilution bias, and other forms of bias that can affect the validity of nonrandomized evidence. As a result, the observational studies cannot provide an unconfounded and unbiased estimate of the potential magnitude of the clinical benefit associated with long-term exposure to lower LDL-C levels. Instead, some form of randomized evidence is necessary to reliably estimate the potential clinical benefit of long-term exposure to lower LDL-C levels.

Ideally, the hypothesis that lowering LDL-C levels beginning early in life can prevent or substantially delay the progression of coronary atherosclerosis would be tested in a long-term randomized controlled trial. Owing to the low short-term risk of CHD among young adults, a definitive randomized trial would necessarily have to enroll a very large number of young asymptomatic adults, randomly allocate them to a lipid-lowering therapy or to usual care, and then follow them over several decades to accrue enough CHD events to produce reliable estimates of the effect of prolonged exposure to lower LDL-C levels. Such a trial would be extremely expensive and logistically complex. More importantly, it would also take several decades to produce definitive results. As a result, such a trial is unlikely to ever be conducted. However, in the absence of a long-term randomized trial, it may still be possible to evaluate the effect of random allocation to lower LDL-C levels beginning early in life on the risk of CHD by appealing to the principle of Mendelian randomization.

Naturally Randomized Evidence

Multiple single-nucleotide polymorphisms have been reported to be associated with small differences in circulating plasma LDL-C levels [40••]. These genetically mediated effects likely represent lifelong differences in LDL-C levels. Each of these polymorphisms is inherited approximately randomly at the time of conception in a process sometimes referred to as Mendelian randomization. Therefore, inheriting an allele associated with lower LDL-C levels is analogous to being randomly allocated to a therapy that lowers LDL-C levels beginning at birth, and inheriting the other allele is analogous to being randomly allocated to usual care. If certain assumptions are satisfied [41–43], then measuring the effect of an allele associated with lower LDL-C levels on the risk of coronary disease should provide a naturally randomized and unconfounded estimate of the effect of lifelong exposure to lower LDL-C levels on the risk of CHD in a manner analogous to a long-term randomized trial comparing a therapy that lowers LDL-C levels beginning early in life with usual care.

For example, individuals who inherit a polymorphism in the proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) gene have been reported to have both a lower lifetime exposure to LDL-C and a much larger than expected corresponding reduced risk of CHD. Among African Americans in the Atherosclerotic Risk in Communities (ARIC) study, the 85 participants who inherited a nonsense mutation in the PCSK9 gene had a 0.93 mmol/l (36 mg/dl) lower LDL-C level and a dramatic 88 % lower risk of CHD (RR, 0.11; 95 % CI, 0.02-0.81) as compared with the 3,278 participants without this polymorphism. Among Caucasians in the ARIC study, the 301 participants who inherited a missense mutation (46 L allele) in the PCSK9 gene had a 0.54 mmol/l (21 mg/dl) lower LDL-C level and a substantial 50 % lower risk of CHD (RR, 0.50; 95 % CI, 0.22-0.79) as compared with the 9,223 participants without this allele [44].

Subsequent studies of the PCSK9 46 L allele reported generally similar results for the effect of this polymorphism on circulating levels of LDL-C, but less dramatic and more variable results for the effect of the 46 L allele on the risk of CHD [45, 46]. For example, among 10,032 participants in the prospective Copenhagen City Heart Study, 46 L allele carriers had a similar 0.55 mmol/l (21 mg/dl) lower LDL-C level but only a 6 % lower risk of CHD (RR, 0.94; 95 % CI, 0.68-1.30). Among 4,654 cases and 5,000 controls in the Copenhagen Ischemic Heart Disease Study, 46 L allele carriers had a 0.50 mmol/l (19 mg/dl) lower LDL-C level but only an 18 % lower risk of CHD (RR, 0.82; 95 % CI, 0.55-1.21), whereas among 26,013 participants in the cross-sectional Copenhagen General Population Study, 46 L allele carriers had a 0.35 mmol/l (13.5 mg/dl) lower LDL-C level and a 46 % lower risk of CHD (RR, 0.54; 95 % CI, 0.39-0.77). In a meta-analysis combining data from the ARIC study, the three Copenhagen studies, and three other studies, PCSK9 46 L allele carriers had a 0.43 mmol/l (16.6 mg/dl) lower LDL-C level and a 28 % lower risk of CHD (RR, 0.72; 95 % CI, 0.62-0.84) as compared with noncarriers [46].

Although the summary estimate of the effect of the PCSK9 allele on the risk of CHD from the meta-analysis is somewhat less dramatic than in the original report in the ARIC study, the variability in the reported associations between the 46 L allele and the risk of CHD is not surprising given the low frequency of the 46 L allele in the general population (1-3 %). Taken together, the PCSK9 studies provide powerful evidence that lifelong exposure to lower LDL-C levels may result in a much greater reduction in the risk of CHD than expected on the basis of the results of short-term statin trials. However, it is not clear from the PCSK9 data alone whether the much greater than expected reduced risk of CHD is due entirely to the effect of lifelong exposure to lower LDL-C levels or to the combined effect of lower LDL-C levels plus some other potential pleiotropic effects mediated by the 46 L allele.

Meta-analysis of the Naturally Randomized Evidence

Recently, we evaluated the effect of multiple different polymorphisms associated with lower LDL-C levels on the risk of CHD [47••]. Because each of these polymorphisms is allocated approximately randomly at the time of conception, the results of these Mendelian randomization studies should be unconfounded by other lipid and nonlipid risk factors for CHD, and therefore can be thought of as approximately analogous to a series of natural randomized trials evaluating the effect of long-term exposure to lower LDL levels on the risk of CHD. We then combined these Mendelian randomization studies in a meta-analysis to obtain a more precise estimate of the effect of long-term exposure to lower LDL-C levels on the risk of CHD and compared it with the effect of lowering LDL-C levels during treatment with a statin. Our objective was to reliably quantify the magnitude of the association between long-term exposure to lower LDL-C levels and the risk of CHD, and to assess whether this effect varies according to the mechanism by which the LDL-C level is lowered.

We evaluated the effect of nine polymorphisms located in six different genes, each of which presumably lowers LDL-C concentration by a different mechanism. The effect of these polymorphisms on circulating levels of LDL-C varied by more than sixfold, ranging from 0.06 mmol/l (2.5 mg/dl) to 0.43 mmol/l (16.5 mg/dl) lower LDL-C concentration per copy of the exposure allele. Despite these differences in circulating levels of LDL-C, however, each of the nine polymorphisms was associated with a highly consistent reduction in the risk of CHD when measured per 1 mmol/l lower LDL-C concentration [47••]. For example, the 46 L allele of the PCSK9 gene was associated with a 0.43 mmol/l (16.5 mg/dl) lower LDL-C concentration and a 53 % reduction in the risk of CHD per 1 mmol/l lower LDL-C concentration (OR, 0.47; 95 % CI, 0.33-0.67), whereas a commoner polymorphism in the PCSK9 gene was associated with only a 0.08 mmol/l (2.9 mg/dl) lower LDL-C concentration, but a very similar 57 % reduction in the risk of CHD per 1 mmol/l lower LDL-C concentration (OR, 0.43; 95 % CI, 0.34-0.54). In addition, a polymorphism in the 3-hydroxy-3-methylglutaryl coenzyme A reductase gene (the pharmacologic target of statin therapy) was associated with a 0.07 mmol/l (2.6 mg/dl) lower LDL-C concentration and a 59 % reduction in the risk of CHD per 1 mmol/l lower LDL-C concentration (OR, 0.49; 95 % CI, 0.38-0.65), whereas a polymorphism in the LDL receptor gene had a much greater effect on plasma LDL-C concentration, resulting in a 0.19 mmol/l (7.5 mg/dl) lower LDL-C concentration, but a very similar 51 % reduction in the risk of CHD per 1 mmol/l lower LDL-C concentration (OR, 0.49; 95 % CI, 0.38-0.65). The lack of heterogeneity of effect among these polymorphisms per 1 mmol/l lower LDL-C concentration strongly implies that the effect of each of these nine polymorphisms on the risk of CHD is mediated largely or entirely through its effect on circulating levels of LDL-C, rather than through some other pleiotropic effect. Furthermore, the highly consistent effect of each of these polymorphisms on the risk of CHD when measured per unit lower LDL-C concentration strongly argues that the effect of long-term exposure to lower LDL-C concentrations on the risk of CHD appears to be independent of the mechanism by which the LDL-C concentration is lowered.

In a meta-analysis of the Mendelian randomization studies, long-term exposure to each 1 mmol/l (38.67 mg/dl) lower LDL-C concentration was associated with a substantial 54 % reduction in the risk of CHD (OR, 0.46; 95 % CI, 0.41-0.51) [47••]. This finding was subsequently validated by two other studies that reported a very similar 57 % reduction in the risk of CHD per 1 mmol/l lower LDL-C concentration estimated from a weighted genetic LDL-C score consisting of 13 LDL-C-associated polymorphisms [48•], and a 53 % risk reduction estimated from a weighted LDL-C score consisting of 12 LDL-C-associated polymorphisms [49•]. The magnitude of the effect of long-term exposure to lower LDL-C concentrations observed in each of these studies represents threefold greater reduction in the risk of CHD per unit lower LDL-C concentration than that observed during treatment with a statin started later in life (p for difference of 8.4×10^{-19}).

Furthermore, the association between long-term exposure to lower LDL-C concentrations and the risk of CHD appears to be approximately log-linear [47••]. This relationship is very similar to the log-linear association between LDL-C concentration and the risk of CHD observed in both epidemiologic studies and in the statin trials [1, 2•, 3]. On the basis of this log-linear relationship, if long-term exposure to 1 mmol/l (38.67 mg/dl) lower LDL-C concentration reduces the risk of CHD by approximately 55 %, then long-term exposure to 2 mmol/l (77.3 mg/dl) lower LDL-C concentration can potentially reduce

the risk of CHD by up to 80 % (0.45×0.45=0.20). These data imply, therefore, that long-term exposure to very low levels of LDL-C has the potential to dramatically reduce the risk of CHD.

The results of the Mendelian randomization studies demonstrate that the potential CHD risk reduction that can be achieved by lowering LDL-C levels depends not only on the magnitude of the reduction of LDL-C levels, but also on the timing and total length of exposure to lower LDL-C levels. Therefore, a primary prevention strategy that promotes keeping LDL-C levels as low as possible, beginning as early in life as possible, and sustaining those low levels of LDL-C throughout the whole of one's lifetime has the potential to dramatically reduce the risk of CHD.

Conclusion

The naturally randomized evidence that is emerging from recently conducted Mendelian randomization studies demonstrates that lifelong exposure to lower LDL-C levels is associated with a threefold greater reduction in the risk of CHD for each 1 mmol/l lower LDL-C concentration than that observed during treatment with a statin started later in life, and that this effect appears to be largely independent of the mechanism by which the LDL-C concentration is lowered. The totality of the evidence thus strongly suggests that promoting prolonged exposure to lower LDL-C levels beginning earlier in life, before the development of significant atherosclerosis, is likely to be substantially more effective at reducing the risk of CHD than the current practice of lowering LDL-C levels beginning later in life after atherosclerosis has already developed. Indeed, the apparently reduced efficacy of lowering LDL-C levels beginning later in life after atherosclerosis has already developed may explain much of the residual risk of coronary events experienced by individuals being treated with a statin or other lipid-lowering therapy.

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Papers of particular interest, published recently, have been highlighted as:
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