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LDL-C Targets in Secondary Prevention: How Low Should We Go?

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Abstract

Purpose of Review The benefits of lowering low-density lipoprotein cholesterol (LDL-C), mainly using high-intensity statin therapy, and its impact on decreasing the recurrence of atherosclerotic cardiovascular disease (ASCVD) in secondary prevention has been well established. With the advent of non-statin medications, particularly PCSK-9 inhibitors, which can lower LDL-C to very low levels not seen before, it is important to answer some important questions regarding LDL-C lowering and the uses of these medications in clinical practice: how low should we go with LDL-C reduction? Is there a threshold beyond which lower LDL-C is not associated with any benefit and possibly harm? Does the benefit derived from more aggressive LDL-C lowering justify the cost of additional therapies?

Recent Findings Our review has found overwhelming evidence to support the conclusion that lower achieved LDL-C levels correlate with a decreased burden of atherosclerosis and better clinical outcomes in secondary prevention. The concern for adverse effects with very low LDL-C levels is not backed by the literature, and side effects appear to be medication-specific. There still remains a question of the cost-effectiveness of some non-statin therapies particularly PCSK9 inhibitors, in spite of recent price decreases, and whether the benefit is worth the cost.

Summary It is prudent to always pursue an individualized patient-level approach to LDL-C lowering that considers the patient's global cardiovascular risk, their side effect profile, and the cost-effectiveness of therapies in order to derive maximal benefit from aggressive lipid lowering.

Keywords Clinical guidelines · LDL lowering · Secondary prevention · PCSK9 inhibitors · Adverse effects

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Introduction

The benefits of lowering low-density lipoprotein cholesterol (LDL-C), mainly using high-intensity statin therapy (HIST), and its impact on decreasing the recurrence of atherosclerotic cardiovascular disease (ASCVD) in secondary prevention has been well established. In the last few years, several large-scale trials using non-statin LDL lowering therapies have also shown significant reduction in ASCVD. As such, the most recent 2018 AHA/ACC/Multi-Society guideline, in concordance with other worldwide guidelines, has shifted towards recommending HIST with a goal of ≥ 50% LDL-C reduction with consideration of adding non-statin therapies if LDL-C level remains ≥ 70 mg/dL or non-HDL-C level ≥ 100 mg/dL in an incremental fashion, particularly in very high-risk individuals [1••, 2••].

With the advent of non-statin medications, particularly proprotein convertase subtilsin-kexin type 9 inhibitors (PCSK9i), which can lower LDL-C to very low levels not seen before, it is important to answer some important questions regarding LDL-C lowering and the uses of these medications in clinical practice: how low should we go with LDL-C reduction? Is there a threshold beyond which lower LDL-C is not associated with any benefit and possibly harm? Does the benefit derived from more aggressive LDL-C lowering justify the cost of additional therapies? To answer these timely and crucial questions, we must review basic concepts of LDL-C lowering for ASCVD risk reduction and analyze the safety of very low LDL-C levels, as well as the cost-effectiveness of adding non-statin therapies.

Evidence for Lower Is Better

The formation and growth of atheromatous plaques, which underlie the pathophysiology of ASCVD, has been shown to be a consequence of circulating atherogenic apolipoproteins, mostly in the form of LDL particles. It has been argued that, when the lifetime burden of LDL-C measured by mg/dL years (age x [LDL-C] reaches a threshold of 5000 mg/dL-years, the accumulated atheroma begins to manifest as clinically overt ASCVD. Beyond this threshold, the risk of developing ASCVD increases logarithmically [3•, 4•].

Mendelian randomization studies have been referred to as a "natural randomization" for LDL-C levels [5, 6], revealing that those with genetically lower LDL-C levels have a resulting lower risk for ASCVD. Using a Mendelian randomization approach, over 112,000 individuals from 14 prospective cohorts were analyzed. Those with higher proprotein convertase subtilsin-kexin type 9 (PCSK9) or 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) scores, favoring lower LDL-C, had a 19% lower risk of myocardial infarction (MI) or death from coronary heart disease (CHD) per 10 mg/dL decrement in LDL-C. This effect was seen to be additive in a 2 × 2 factorial analysis of PCSK9 and HMGCR genetic scores [7••]. These findings were also seen in Niemann-Pick C1-Like 1 (NPC1L1) variants, the target mechanism in ezetimibe, who have low LDL-C. These studies suggest that genetically determined lifelong lower LDL-C levels are associated with a significantly reduced ASCVD risk, regardless of the underlying mechanism [8••].

Extending from the studies examining genetically determined LDL-C and cardiovascular risk, several meta-analyses have demonstrated a similar dose-dependent relationship between the lowering of LDL-C and decreased risk of ASCVD. The landmark meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration, examining the effect of LDL-C lowering via statin on risk of major vascular events (coronary death, non-fatal MI, coronary revascularization, or stroke), revealed a relative risk reduction of 22% for every 1 mmol/L (38.7 mg/dL) decrease in LDL-C [9]. More intensive statin therapy was beneficial, even if LDL-C was lower than 77 mg/dL, with a resulting relative risk reduction of 20% per 38.7 mg/dL for CHD, and 16% for cardiac death. More recently, Navarese et al. performed a meta-analysis that included 34 primary and secondary prevention studies examining statin and non-statin therapies [10]. More intensive LDL-C lowering was associated with a greater reduction in the risk of all-cause and cardiovascular mortality, but this effect did not extend to patients with baseline LDL-C < 100 mg/dL [10]. However, there continued to be a relative risk reduction of 10% in non-fatal MI, revascularization, and major adverse cardiovascular events (MACEs) in patients with baseline LDL-C < 100 mg/dL [10].

Another recent secondary prevention meta-analysis by Sabatine et al., which expanded on the CTT studies, further examined 3 studies of non-statins, and extrapolated a similar 21% relative risk reduction per 1 mmol/L (38.7 mg/dL) reduction in LDL-C even for a group of patients starting with median LDL-C levels of 1.6 mmol/L (63 mg/ dL) and achieving on-treatment levels of 0.5 mmol/L (21 mg/dL) [11••]. In summary, there is overwhelming evidence that LDL-C is causal in atherosclerosis and that the lower the LDL-C level, the lower the risk of recurrent ASCVD in secondary prevention. Individuals with lifelong genetically-determined low LDL-C levels achieve approximately fourfold the amount of ASCVD risk reduction per LDL-C decrement compared to those with low LDL-C on drug therapy. Finally, although greater absolute risk reduction is derived from patients with higher baseline LDL-C (> 100 mg/dL), there is consistent relative risk reduction in patients with very low baseline LDL-C < 70 mg/dL.

In addition to clinical outcome studies, serial coronary intravascular ultrasound (IVUS) imaging has allowed us to directly observe the effects of lipid lowering strategies on coronary atherosclerosis and establish a link between lower LDL-C levels and changes in atheroma volume. IVUS studies have shown that in patients with CHD, coronary atheroma

progression slows with statin therapy and even regresses with HIST. Lower LDL-C levels were associated with greater atheroma regression in several IVUS trials where patients were treated with HIST alone or in combination with non-statin therapies [12–14].

In the PRECISE-IVUS study, there was greater regression in atheromatous plaque with atorvastatin and ezetimibe combination therapy versus atorvastatin alone, corresponding with the lower LDL-C levels achieved with combination therapy [15]. The GLAGOV trial also demonstrated that patients with CHD on HIST had greater percent and total atheroma volume reduction with evolocumab compared with placebo, where the evolocumab group achieved lower mean, time-weighted average LDL-C levels (36.6 vs. 93.0 mg/dL; difference, − 56.5 mg/dL [95% CI, − 59.7 to − 53.4]; $P < .001$) [16]. Serial coronary IVUS trials have thus added further mechanistic evidence to clinical outcome trials that LDL-C levels are causal in the process of atherosclerosis, and the lower the achieved LDL-C levels the better, when using statins and non-statin therapies that upregulate LDL receptor expression.

Practical Application of "the Lower the Better" Approach to Individual Patients

It is important to note that despite the decrease in relative risk that can be achieved with LDL-C lowering therapies; there will still continue to be the question of whether this translates to a meaningful reduction in absolute risk. The absolute risk reduction in ASCVD is more appreciable in those with a higher baseline ASCVD risk, higher baseline LDL-C level, and those who achieve a greater absolute reduction in LDL-C with therapy. In Fig. 1, we demonstrate an example where we assume that 2 patients each has a similar global ASCVD risk of 25%. Patient 1 has a baseline LDL-C level of 100 mg/dL on HIST while patient 2 has a baseline LDL-C level of 70 mg/dL on HIST [11••]. Assuming both are treated with a PCSK9i, they will achieve 60% reduction in LDL-C levels. Patient 1 has a higher baseline LDL-C, and thus has a greater absolute reduction in LDL-C which results in a higher relative and absolute risk reduction. In Fig. 2, we show an example where patients 1 and 2 have different global ASCVD risk prior to treatment (patient 1–25% and patient 2–10%), but both have a similar baseline LDL-C level of 75 mg/dL. Assuming both are treated with PSCK9i, they will achieve a 60% reduction in LDL-C levels and approximately 24% relative risk reduction in ASCVD events, extrapolated from CTT. However, the absolute risk reduction in patient 1 is 6% vs. only 2.4% in patient 2. Therefore, when approaching each individual patient, it is important to think about whether further LDL-C lowering will achieve meaningful reduction in absolute ASCVD risk. This individualized approach is applicable even in patients who achieve an LDL-C level of < 70 mg/dL with HIST as there still remains a subset who continue to have an elevated residual risk [18, 19]. Such risk could be related to discordantly elevated lipoproteins such as apolipoprotein B (ApoB) and lipoprotein(a), or could be related to other factors such as elevated high-sensitivity C-reactive protein (hsCRP) and auto-immune diseases [18, 20]. In such

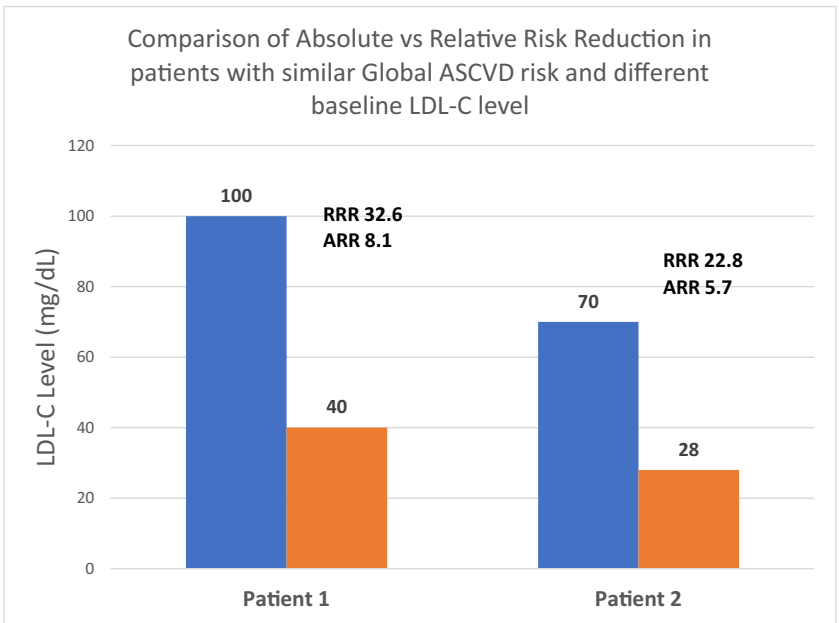

Fig. 1 Comparison of absolute risk reduction vs. relative risk reduction for two patients with a 25% global ASCVD risk, but different baseline LDL-C on HIST (patient 1–100 mg/dL vs. patient 2–70 mg/dL). Assuming both patients have similar reduction in LDL-C by 60% with a PCSK9i, the relative risk reduction is substantial in both patients; however, the absolute risk reduction is less in the patient with lower baseline LDL-C [17] (based on findings of PCSK9i studies with short term follow-up). ARR absolute risk reduction, RRR relative risk reduction, HIST high-intensity statin therapy, PCSK9i proprotein convertase subtilsin-kexin type 9 inhibitor, ASCVD atherosclerotic cardiovascular disease

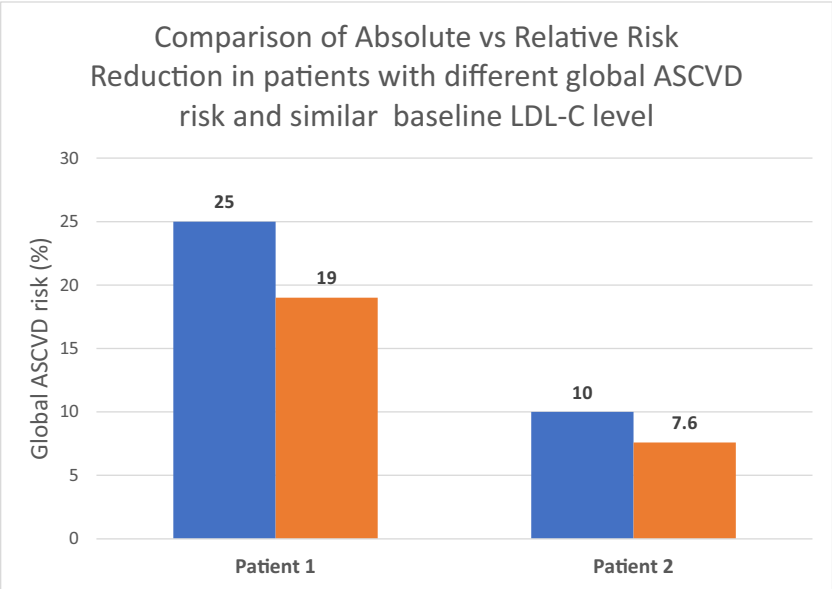

Fig. 2 Comparison of absolute risk reduction in patients with different global ASCVD risk (patient 1–25% vs. patient 2–10%), but the same baseline LDL-C on HIST of 75 mg/dL. Assuming both patients have a reduction in LDL-C by 60% with a PCSK9i, the relative risk reduction is equal in both patients (24%); however, absolute risk reduction is much less in patient 2 (2.4%) vs. patient 1 (6%) (based on findings of PCSK9i studies with short term follow-up). ASCVD atherosclerotic cardiovascular disease, HIST high-intensity statin therapy, PCSK9i proprotein convertase subtilsin-kexin type 9 inhibitor

patients with elevated residual risk, more aggressive reduction in LDL-C levels, even beyond 70 mg/dL, may translate into meaningful reduction in absolute ASCVD risk.

The 2018 AHA/ACC/Multi-Society Cholesterol guidelines have recommended an incremental approach to lowering LDL-C in secondary prevention. HIST is considered the mainstay of secondary prevention, with the expected decrease in LDL-C of approximately 50% from baseline. Despite maximum tolerated statin therapy, many patients continue to have LDL-C levels ≥ 70 mg/dL [21]. In patients above this LDL-C threshold who have very high ASCVD risk, such as those with multiple recurrent events or other high-risk factors, the guideline recommends further lowering of LDL-C by adding ezetimibe to HIST, which can result in a 24% reduction in LDL-C as shown in the IMPROVE-IT trial [22••]. Even with the addition of ezetimibe, there still remains a subset of patients who are still above the LDL-C threshold of ≥ 70 mg/dL [21] and may be considered for treatment with PCSK9i. PSCK9i outcome trials, FOURIER and ODYSSEY Outcomes, showed that the addition of PCSK9i to HIST in secondary prevention patients was associated with a relative risk reduction of around 15%; however, absolute risk reduction was 1.5–2% in this population. This has to be taken with caution because FOURIER followed patients for a median of only 2.2 years and the continued curve separation suggests that the treatment effect is expected to be larger on the long term. Therefore, it is imperative that clinicians take into consideration the patient's global ASCVD risk as well as the estimated absolute risk reduction before deciding to add non-statin therapies. Interestingly, an analysis of the FOURIER trial, which differentiated patients by their cardiovascular risk, noted a substantial difference in the absolute risk reduction derived by each group from therapy, ranging from > 3% to approximately 1% in the lower risk groups [23]. For example, one may consider targeting lower LDL-C in patients with diabetes with multiple recurrent ASCVD events despite an achieved LDL-C level of 65 mg/dL on HIST, especially when the addition of non-statin therapies is cost-effective and not associated with adverse side effects.

Adverse Effects of Very Low LDL-C Levels

LDL-C lowering with statins has been previously linked with several adverse effects, including new-onset type 2 diabetes mellitus, hemorrhagic stroke, myositis, and neurocognitive side effects, some of which have been refuted. The European consensus panel on statins has noted a discordantly higher rate of statin-associated muscle symptoms (SAMS) (7–29%) compared with RCTs [24]. Meanwhile, the STOMP randomized controlled trial showed a 9.4% rate of SAMS compared with 4.6% in controls [24]. However, the risk of myopathy was generally linked with the dose of statin, rather than the reduction of LDL-C achieved [24]. Moreover, the GAUSS-3 trial examined the use of ezetimibe or evolocumab monotherapy in patients with statin intolerance and showed that evolocumab was more efficient at reducing LDL-C in these patients and there were no significant SAMS reported [25].

On the other hand, an increased risk of type 2 diabetes mellitus has been reported in patients with very low LDL-C levels with conflicting evidence. In Mendelian randomization studies examining PCSK9i and HMGCR variants, those with a lower genetically determined LDL-C showed a respective 11.2% and 12.7% increase in the risk of diabetes, in a dose-dependent and additive manner [7••]. On the other hand, a meta-analysis [11••] examining patients with very low LDL-C levels at baseline who were further treated with LDL-C

lowering therapy showed no difference in the rate of new onset diabetes mellitus, cancer, or hemorrhagic stroke. In a pooled analysis of 10 studies from the ODYSSEY trials, which achieved a substantial decrease LDL-C levels as low as 30 mg/dL, the incidence of diabetes was not increased [26••]. Regardless of this reported risk of new onset diabetes, an analysis from the JUPITER trial showed that the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes. Overall, for every 1 incident case of diabetes, 4 or 5 ASCVD events are prevented [27]. Similarly for hemorrhagic stroke, initial concerns were obviated by a large meta-analysis of 180,000 patients from randomized trials showing no increased risk and that there is a large net benefit with statins even in those at high risk of hemorrhagic stroke [28] Another meta-analysis evaluating the risk of hemorrhagic stroke with different LDL-C lowering therapies, showed no increased risk, even with meta-regression of achieved LDL-C levels [29].

In a 2015 network meta-analysis of PCSK9i trials, there was an increased rate of neurocognitive adverse events with PCSK9i compared with placebo (OR 2.34 [95% CI 1.11–4.93] $P = 0.02$) [30]. However, the FOURIER trial, which examined the PCSK9i evolocumab compared to placebo for secondary prevention, showed no difference in the rate of neurocognitive effects [31]. In a subset of 1204 patients from the FOURIER study, neurocognitive testing was performed over a median follow up of 19.4 months comparing patients receiving PCSK9i vs. placebo on baseline HIST [32••]. The study revealed no association between adverse cognitive effects, even in those who achieved LDL-C < 25 mg/dL [32••]. This study is limited by its relatively short duration and that both arms of the study were already on statin therapy. However, the results match those from Mendelian randomization studies that show no neurocognitive side effects of having genetically determined very low levels of LDL-C [33]. Further studies and careful post-marketing surveillance of PCSK9i on the long term will help further clarify if neurocognitive side effects are associated with very low levels of LDL-C. In summary, it seems that there is no evidence to suggest significant short- or long-term side effects that are directly associated with having very low LDL-C levels, and most reported side effects are usually medication specific.

Cost-Effectiveness of LDL-C Lowering to Very Low Levels

A model of 215,000 patients with MI from a US population receiving HIST with on-treatment LDL-C $\geq$ 70 mg/dL was conducted to determine the cost-effectiveness of alirocumab. The model was based on the inclusion criteria in the ODYSSEY trial, and compared to statin and statin vs. ezetimibe [34]. The authors assigned a cutoff of $100,000 per quality-adjusted life year (QALY) to meet a willingness-to-pay threshold, which would only be feasible with 86% reduction of the price of alirocumab from its price of $14,560 annually in March of 2018. The recent decrease in the price of alirocumab to $5850 a year has been welcomed [35]; however, it still remains far from the recommended price of $874 proposed by the authors if it is to be comparable to ezetimibe. The contention with alirocumab is adherence because only half of patients who are prescribed the drug are approved by insurance, with only a third ever receiving treatment. Furthermore, the patients who receive treatment are not always the ones most likely to benefit from treatment based on their risk [36]. Baum et al. have appraised the utility of cost-analysis and identified that such analyses may rely on too many assumptions, including the acceptable cost goal, the baseline risk of a population, amongst others; without putting enough weight on the individual patient. Thus, while the benefits of extensive LDL-C lowering with non-statin therapies are apparent, their practical implementation is challenging and clinicians need to individually weigh the risks and benefits of additional therapies in each patient.

Applying the "Lower the Better" Concept in Primary Prevention

Primary prevention of ASCVD with LDL-C lowering therapies has mostly been recommended for those with high ASCVD risk scores. The exceptions are patients aged 40–75 years with diabetes mellitus (where at least a moderate-intensity statin is recommended regardless of 10-year risk score) and for those patients with severe primary hypercholesterolemia (where a high-intensity statin is recommended regardless of 10-year risk score). Risk scoring, which often weighs age as a strong predictor, is recommended for those without established risk factors [2••]. The CTT meta-analysis demonstrated that patients in the lower risk groups (5-year risk < 10%) also benefitted from more intensive statin therapy, with a relative risk reduction per 38.6 mg/dL of 43% in non-fatal MI and 48% in coronary revascularizations [37]. Following the CTT analysis, the HOPE-3 randomized controlled trial examined a diverse population of individuals without known ASCVD at moderate risk who were randomized to rosuvastatin 10 mg/day vs. placebo [38]. Rosuvastatin monotherapy was associated with a decreased risk of composite death from ASCVD, non-fatal MI, or non-fatal stroke (hazard ratio, 0.76; 95% CI, 0.64 to 0.91; $P = 0.002$) and a significant decrease in coronary revascularization, heart failure, and resuscitated cardiac arrest (hazard ratio, 0.75; 95% CI, 0.64 to 0.88; $P < 0.001$) [39••].

The results of these primary prevention trials as well as Mendelian randomized studies bring up the important concept of lifetime exposure to LDL-C. If the lifetime

exposure to LDL-C is taken into consideration, the age of onset at which ASCVD begins may be significantly delayed [40]. This likely explains the increase in the observed risk reduction seen with LDL-C lowering therapies as the duration of treatment extends. In terms of primary prevention, the duration of LDL-C lowering would have to be extended significantly compared with secondary prevention trials, in order to establish a meaningful reduction in ASCVD risk [41]. An analysis from the Framingham Offspring cohort demonstrated that early treatment of moderately elevated lipid level may theoretically return a fourfold benefit over time, in comparison to starting treatment later [40]. However, there continues to be practical difficulties in conducting long-term studies of aggressive LDL lowering, given that a large segment of the population may qualify for early treatment, the duration of follow-up will likely be unfeasible, while the expected treatment effect may be small and difficult to power. But rather than being handicapped by skepticism, we should pursue creative and innovative approaches to answer several important questions related to primary prevention: Would individuals derive benefit from aggressive lifelong reduction in LDL-C starting in early adulthood? How low should we go with LDL-C and what tools should we use? Is lowering LDL-C, at a very young age, cost-effective and safe, especially with novel long-term interventions like gene therapy or RNA interference?

Conclusion

We are in an era of emerging LDL-C lowering therapies. Combining an armamentarium of tools can potentially achieve dramatic reductions in LDL-C levels and subsequently reduce the risk for ASCVD events. The concern for adverse effects with such low LDL-C levels has been raised; however, clinical studies thus far have been reassuring and side effects appear to be medication-specific. There still remains a question of the cost-effectiveness of some non-statin therapies particularly PCSK9i, in spite of recent price decreases, and whether the benefit is worth the cost. Therefore, it is prudent to always pursue an individualized patient-level approach to LDL-C lowering that considers the patient's global cardiovascular risk, their side effect profile, and the cost-effectiveness of therapies in order to derive maximal benefit from aggressive lipid lowering.

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Compliance with Ethical Standards

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