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Low Density Lipoprotein Cholesterol–Lowering Strategies and Population Health

Time to Move to a Cumulative Exposure Model

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Lifetime medication burden from current approaches to low-density lipoprotein cholesterol (LDL-C) lowering relies on small molecules requiring daily dosing, with the burden of responsibility placed on patients. Patient-related factors (risk perception, health literacy) affect adherence and persistence. Adherence to statins and ezetimibe correlates with LDL-C reduction and risk, potentially accounting for ≈12 000 avoidable cardiovascular events per 500 000 patients annually.[1] Attempts to improve adherence have had mixed results, with only text-messaging reminders, community health worker–based reinforcement, and fixed-dose combination pills shown to be effective at improving adherence and clinical events.[2] Patient-tailored strategies combining multiple approaches, including in-person consultations, may yield better outcomes, but implementation is complex, consuming both time and resources. Obesity and smoking cessation have been tackled with monetary compensation. Technology offers scalable low-cost options for pill and refill reminders through the use of telephone calls, text messages, and mobile apps. Finally, a crucial barrier to long-term adherence is the asymptomatic nature of cardiovascular risk factors, which may affect medication adherence. This could be facilitated by simplifying access to prescriptions and refills through electronic healthcare solutions that connect pharmacies to electronic patient records and enable automated prescriptions. Here, we draw on population studies and therapeutic developments to address the issue of adherence and lifetime exposure to LDL-C.

Comparison of Mendelian randomization, epidemiological studies, and trials comparing 50, 12, and 5 years of exposure, respectively, shows a log-linear relationship between relative risk and absolute difference in LDL-C. Because benefits are cumulative, for any given difference in LDL-C, for example, 39 mg/dL, genetic variants associated with lifelong lower LDL-C exposure are associated with greater risk reduction than a similar LDL-C reduction derived over a shorter period of time through pharmacological interventions.[3] Conversely, small and sustained differences in LDL-C of ≈13 mg/dL over 50 years appear to provide a benefit similar to a 39-mg/dL difference maintained over 5 years.

Imperfect adherence to any pharmacotherapy results in greater LDL-C variability, which in turn increases the average LDL-C exposure, thus diminishing the benefit of a therapy. Instead of an assessment of LDL-C reduction at an isolated time point, the concept of annual time-averaged LDL-C per person per year, which accounts for adherence and is more representative of the real world, is more meaningful for assessment of long-term benefit (Figure [A]).[1] This concept incorporates the potency and the medication burden/complexity of the lipid-lowering regimen, which in turn are affected by adherence. The concept of annual LDL-C exposure can be projected over different time horizons to estimate short- and long-term benefits. Because relative risk reduction is proportional to the absolute reduction in LDL-C and the duration of that reduction but is independent

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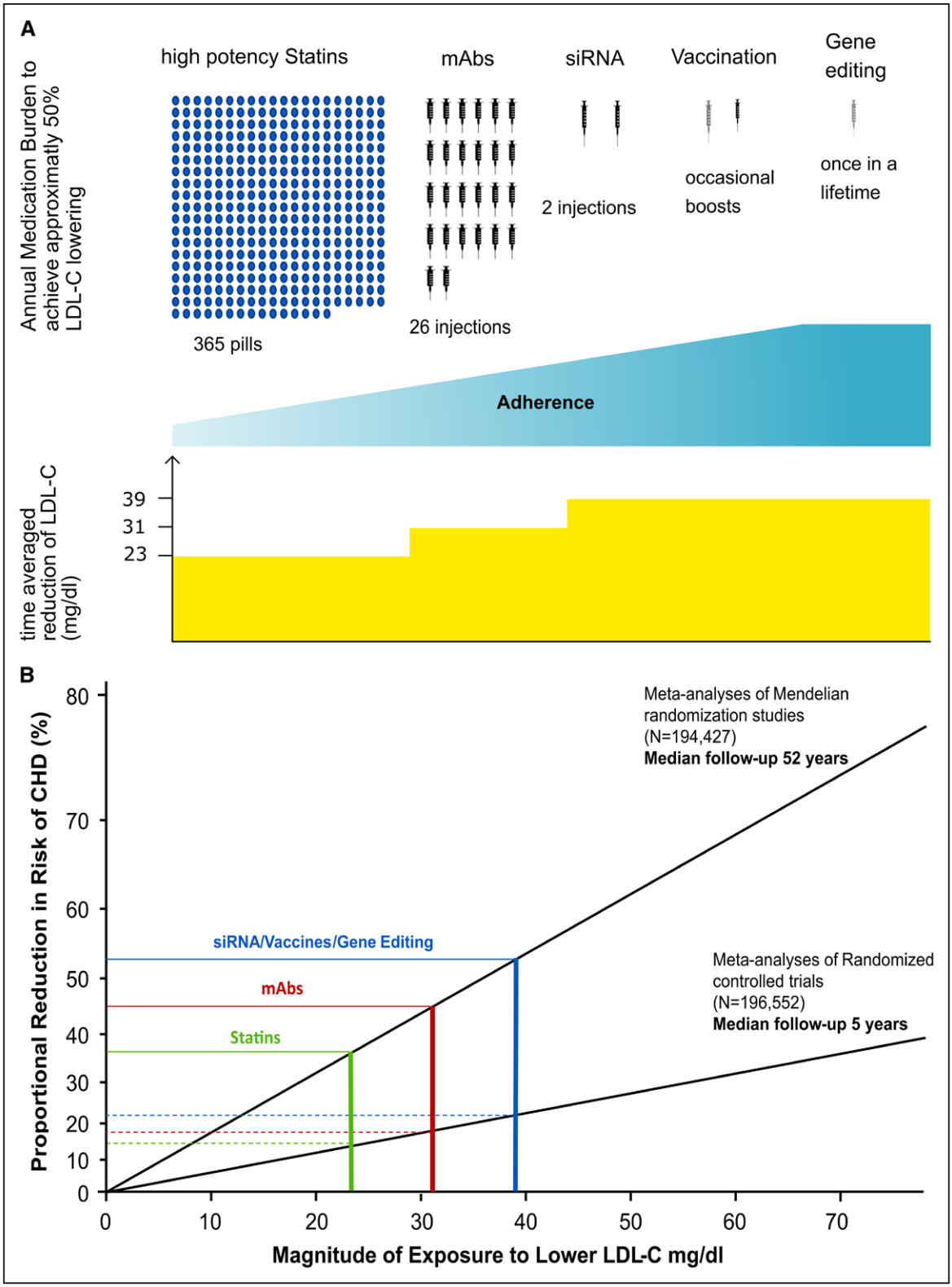

Figure. The impact of LDL-C-lowering strategies on adherence, annual LDL-C exposure and CHD risk reduction over different time horizons. **A**, Medication burden impairs adherence and average low-density lipoprotein cholesterol (LDL-C) reduction over time. Current annual medication burdens for lipid-lowering regimens are shown here. The highest medication burden is with statins, followed by monoclonal proprotein convertase subtilisin/kexin type 9 antibodies (mAbs), which could lead to imperfect adherence. New therapeutic agents are associated with lower administration frequency. Perfect to near-perfect adherence may be feasible with infrequent dosing regimens (siRNAs, vaccines) administered by medical professionals and with permanent interventions such as gene editing. The impact of adherence to these therapies on average LDL-C reduction is shown in yellow and assumes that an annual average LDL-C reduction of 39 mg/dL is maintained with perfect adherence (siRNAs, vaccine, gene editing), an annual average LDL-C reduction of 31 mg/dL is maintained for mAbs with imperfect adherence, and an average LDL-C reduction of 23 mg/dL is maintained for statins. (*Continued*)

Figure Continued. B, Impact of imperfect adherence on the proportional risk reduction of coronary heart disease (CHD) on the population level. This graph shows the log-linear relationship between absolute differences in LDL-C exposure from different therapeutic approaches (after accounting for adherence) and the relative risk reduction in heart disease over 5 and 52 years. The impact of the exposure duration on relative risk reduction is indicated with horizontal dashed lines for an exposure duration of 5 years and with horizontal solid lines for 52 years. The graph shows the impact of an annual average LDL-C reduction of 39 mg/dL potentially with perfect adherence (siRNAs, vaccine, gene editing; shown in blue), the potential impact of an annual average LDL-C reduction of 31 mg/dL for mAbs (shown in red) with imperfect adherence, and the potential impact of an annual average LDL-C reduction of 23 mg/dL with statins (shown in green).

of how LDL-C reductions are achieved, emerging approaches, if safe, effective, and affordable, may help to maintain long-term reductions in LDL-C through pharmacotherapy. If we take the scenario of a 50% lowering in LDL-C, this can currently be achieved with 365 statin tablets per year or 26 injections of a monoclonal antibody (mAb) to proprotein convertase subtilisin/kexin type 9 (PCSK9) per year or potentially in the future 2 injections per year of an siRNA-based therapy such as inclisiran. Even combination therapies of small molecules such as statins and ezetimibe or potentially bempedoic acid and ezetimibe, although they reduce pill burden with fixed dosed combinations, still require daily dosing and thus 365 tablets.

If we assume that imperfect adherence at a population level causes suboptimal reductions in LDL-C, then a theoretical 39-mg/dL reduction observed soon after initiation will not be sustained when the therapeutic time horizon is extended. Differences in adherence to treatment regimens will differentially affect therapies that have different durations of action. For instance, according to real-world data,[1] over a 5-year treatment cycle, the time-averaged reduction in LDL-C might be attenuated from 39 to 23 mg/dL for statins. Phase 1 data from mAbs suggest that LDL-C levels return to baseline 1 month after administration; hence, imperfect spacing of dosing intervals beyond the recommended schedule attenuates peak LDL-C reduction by 4% to 5%.[4] Over a 5-year cycle, a recurring modest attenuation of the peak effect through imperfect adherence could translate into an attenuation in the absolute reduction in LDL-C from 39 to 31 mg/dL and thus an ≈20% attenuation in the absolute LDL-C exposure over 5 years for mAbs. A physician-administered siRNA should still provide a 39-mg/dL lowering, assuming no loss of efficacy and no major or recurring delay in recommended dosing; otherwise, the average LDL-C exposure may not fit with the assumptions made. That said, LDL-C returns toward baseline at ≈2%/mo, with inclisiran allowing greater flexibility over 5 years than therapies with shorter half-lives. Therefore, the population-level impact of each of these 3 approaches might produce less than the expected 22% lowering of risk expected per 39–mg/dL LDL-C lowering over 5 years, with a predicted 13.5% proportional risk reduction for statins, a 17.5% reduction for mAbs, but a 22% reduction for siRNAs. Projecting over a 50-year therapeutic window,[3] the cumulative benefits of maintaining the same LDL-C differences are even more marked at a population level, where one might expect a 31.2% relative risk reduction for statins, 41.6% relative risk reduction for mAbs, and 52% relative risk reduction for siRNAs (Figure [B]).

The concepts of infrequent or 1-time therapeutic interventions could be further extended through PCSK9 vaccination approaches. Animal studies suggest that a safe PCSK9 antibody response and LDL-C lowering are feasible in mice and nonhuman primates with a maximum in vivo half-life of ≈5 months.[5] In the future, a longer-lasting immune response requiring an occasional boost may be feasible. A lifelong permanent therapeutic effect with only a single treatment could become feasible through gene editing with the use of the CRISPR-Cas9 platform and the introduction of loss-of-function mutations into the PCSK9 gene. In mice, circulating PCSK9 fell, resulting in LDL-C reductions of 35% to 40%.[5]

In summary, therapeutic advances reducing the burden of long-term adherence and hence exposure to risk factors for the patient could improve population health through an earlier, more effective strategy that preserves health rather than treating disease.

ARTICLE INFORMATION

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