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Editorial

Opposing View: A Blind Faith in Meta-Analyses in Academia Could Be a Threat to Public Health

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Evidence-based medicine (EBM) is the process of making clinical decisions by integrating the best research evidence, clinical expertise, and patient values.[1] The practice of EBM generally consists of formulating a clear clinical question, searching for relevant articles, critically appraising evidence for its validity and usefulness, and applying findings to clinical practice.[2] Meta-analysis is a statistical method combining and synthesizing all available evidence on outcomes of interest from independent studies. Meta-analyses can improve the precision of effect size estimates, identify common treatment effects, and help identify people whose results are consistent.[3] They also allow the evaluation of rare events. Well-conducted meta-analyses with systematic reviews reflect the actual process of EBM practice and provide information for decision-making that maximizes the overall benefits of prevention or treatment. Hence, professional societies and organizations often incorporate meta-analyses when developing recommendations in guidelines and statements. However, some researchers have challenged placing meta-analyses at the top of the evidence pyramid owing to between-study heterogeneity and uncertainty of the evidence.[4] In addition, as the number of systematic reviews and meta-analyses increases, clinicians may face difficulties in interpreting results with different levels of evidence. These issues have recently led to umbrella reviews, or reviews of reviews, to consolidate higher-level evidence.[5] Therefore, when performing meta-analyses, we should prioritize addressing clinical and statistical heterogeneity and implementing methodological principles to explore and avoid biases.[6]

In a recent issue of *JAMA Internal Medicine*, Byrne and colleagues published a systematic review and meta-analysis evaluating the association between reductions in low-density lipoprotein cholesterol (LDL-C) levels with statin therapy and all-cause mortality, myocardial infarction, and stroke.[7] This study included 21 randomized controlled trials (RCTs) examining the efficacy of statins in reducing total mortality and cardiovascular (CV) outcomes in adults, with a planned duration of 2 years or longer and more than 1,000 participants. The included studies were equally distributed between primary prevention (7 studies), secondary prevention (6 studies), and primary or secondary prevention (8 studies) trials. The meta-analysis showed an absolute risk reduction (ARR) of 0.8% (95% confidence interval [CI], 0.4%–1.2%) for all-cause mortality, 1.3% (95% CI, 0.9%–1.7%) for myocardial infarction, and 0.4% (95% CI, 0.2%–0.6%) for stroke in people who received statins compared with placebo or usual care. The relative risk reduction (RRR) was 9% (95% CI, 5%–14%), 29% (95% CI, 22%–34%), and 14% (95% CI, 5%–22%), respectively. These findings were consistent in primary prevention and secondary prevention populations. However, significant clinical and statistical heterogeneity was observed depending on the outcomes and study populations.

Meta-regression revealed little association between the magnitude of LDL-C reduction and the size of the treatment effects. Based on these findings, the authors argued that the absolute benefits of statins for individual clinical outcomes were modest in both primary and secondary prevention. They also stated that the mediating associations between LDL-C reduction and treatment effects were inconclusive.

Meta-analyses of dichotomous outcomes use measures of treatment effects that represent the ARR (e.g., absolute risk differences) and RRR (e.g., risk ratios or odds ratios). The ARR is a difference in absolute risk of events between control and treatment groups. The RRR is the ARR divided by the absolute risk in the control group. Although the RRR has been frequently used to assess the efficacy of treatments in clinical trials, it may exaggerate the effect size when the incidence of events is low. The ARR is a direct measure of treatment effect. However, as the ARR is occasionally counterintuitive, we can also use the number needed to treat (NNT). The NNT is the reciprocal of the ARR, indicating the number of people who need to be treated to prevent one adverse outcome. In the study by Byrne and colleagues,[7] the NNT was 125, 77, and 250 for all-cause mortality, myocardial infarction, and stroke, respectively. When making shared decision-making, it is important to understand the absolute and relative effects of the intervention.

In this meta-analysis,[7] the authors emphasized the importance of the ARR for clinical decision-making. The ARR or NNT can be useful when evaluating the comparative effectiveness of different treatment options, as well as for discussing the benefits and harms of treatments with patients. However, since the ARR or NNT depends on the disease risk of individuals,[8] they may not provide appropriate information for person-centered care. The LDL-C-lowering effects and CV benefits of statins are greater in people with higher CV risk at baseline.[9] In addition, an increasing number of CV risk factors causes an exponential increase in the risk of cardiovascular disease (CVD).[10] For these reasons, the American College of Cardiology/American Heart Association guideline recommends determining statin therapy based on clinical atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus (DM), age, the 10-year ASCVD risk, and risk enhancers in people with or without established ASCVD.[11] The European Society of Cardiology guidelines recommend similar approaches to statins considering established ASCVD, DM, CVD risk, treatment benefits, risk modifiers, comorbidities, and individual preferences.[12,13] The guidelines of the Korean Society of Lipid and Atherosclerosis provide a strategy for statin therapy according to CV risk, LDL-C levels, and adverse effects.[14] Consequently, clinical decision-making based on the ARR or NNT without the corresponding RRR may lead to unintended negative consequences in people with established CVD or at high CV risk.

Byrne and colleagues[7] thoroughly evaluated the ARR and RRR in individual outcomes of all-cause mortality, myocardial infarction, and stroke rather than the composite outcome mainly focused on in previous meta-analyses.[15-17] They conducted meta-regression analyses of absolute risk differences after adjusting for control event rates and the length of follow-up to control between-trial differences in baseline characteristics. Their study showed inconsistent associations between LDL-C reduction and individual clinical outcomes. The authors also identified significant clinical and statistical heterogeneity,[7] which had received little attention in prior meta-analyses of statins using individual participant data (IPD).[9,15] A meta-analysis of 26 RCTs, conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration, showed a 22% RRR in major vascular events and a 10% RRR in all-cause mortality per 1.0 mmol/L of LDL-C reduction with statin therapy.[15] In people at low risk of major vascular events, statin

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therapy produced an ARR in major vascular events of about 11 per 1,000 over 5 years for each 1.0 mmol/L reduction in LDL-C.[9] In a trial-level meta-regression analysis of 49 RCTs, statin and non-statin therapies that upregulate the expression of LDL-C receptors to reduce LDL-C were associated with a 23% RRR in major vascular events per 1.0 mmol/L of LDL-C reduction.[16] A linear relationship was also found between achieved LDL-C levels and major vascular events in both primary and secondary prevention trials.[16] No significant heterogeneity was observed.[16] Thus, the results of this meta-analysis[7] conflict with many studies that have reported significant associations between LDL-C reductions and major CV events.

Several explanations for these differences are possible. Byrne and colleagues[7] included similar studies to the CTT meta-analysis in their analysis, however, trials of high-dose versus low-dose statins were excluded due to the limitations of active control trials.[18] Statin intensity was also not considered. In the CTT meta-analysis, the effects of statin on major vascular events were higher in trials of more versus less intensive statin therapy than those of statin therapy versus control.[15] In addition, since they conducted the meta-analysis based on aggregated trial data, not IPD, an independent inspection was prevented except for traditional weighting for individual trial variance. Statin dosage and intensity, adherence to statin therapy, and the characteristics of study participants, including baseline levels of LDL-C, could contribute to heterogeneity, which may reduce the certainty of the evidence. We have learned lessons from the rosiglitazone story that meta-analysis should be cautiously conducted when pooling heterogeneous trials.[19-21] Insufficient consideration of participants' characteristics, the definition of primary outcomes, and the adjudication of events of included studies caused excessive harm to people with type 2 diabetes.[19-21] Inherent heterogeneity in a meta-analysis may also challenge the application of the results to each person.[6] Therefore, we should understand the meaning of this study[7] in consideration of these limitations.

Nonadherence to statin therapy is a common and challenging problem.[22-24] Despite the favorable risk-benefit profile of statins,[25,26] concerns about potential adverse events have unfortunately led to discontinuation of or nonadherence to statin therapy.[27,28] A decrease in statin adherence is closely related to adverse health effects. In a population-based cohort study, discontinuation of statin therapy following acute myocardial infarction was associated with higher all-cause mortality.[29] A subgroup analysis of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial also showed an increased risk of a composite of death, myocardial infarction, and recurrent myocardial ischemia after the withdrawal of statins.[30] In a retrospective cohort study in the United States, low adherence to statin therapy was associated with a greater risk of mortality in people with established ASCVD.[31] Given the consistent results of RCTs[32] and the role of statins as the cornerstone of preventing CVD, Byrne and colleagues' conclusion[7] that the absolute benefits of statins are modest should be interpreted carefully and not misread.

CVD is a leading cause of death globally.[33] The control of modifiable CV risk factors is crucial for the prevention and management of CVD.[13] According to the INTERHEART study, nine modifiable risk factors accounted for 90% to 94% of the population attributable risk (PAR) of myocardial infarction, of which lipid levels had the highest PAR in both men and women.[10] LDL-C is unequivocally recognized as the primary diver of atherogenesis.[34] Mechanistic and clinical studies have shown that increased LDL-C levels and cumulative exposure to LDL-C are significantly associated with the lifetime risk of developing ASCVD.[35] Strong evidence from RCTs suggests that statins reduce the ASCVD risk in primary and secondary prevention, primarily by lowering LDL-C.[32] The absolute benefits of statins depend on the absolute

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risk of individuals and achieved LDL-C levels.[32] Beyond LDL-C lowering, statins also exert pleiotropic effects on inflammation, vascular dysfunction, and immunomodulation,[36,37] which may have a beneficial role in reducing CVD. Although there are concerns about adverse events, statins are effective and generally tolerable in a wide range of populations.[32,38] Since continuous statin use has been shown to reduce the risk of vascular disease, larger absolute benefits would accrue with prolonged therapy.[32,39] In conclusion, shared clinical decision-making in conjunction with a critical appraisal of the evidence is necessary for person-centered care of dyslipidemia and statin therapy.

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