sharing their models of care and the Johns Hopkins Clinical Research Network Hospitalists and General Internal Medicine Research in Progress Physicians for their comments on the model and quality measures.


Limit to Benefits of Large Reductions in Low-Density Lipoprotein Cholesterol Levels: Use of Fractional Polynomials to Assess the Effect of Low-Density Lipoprotein Cholesterol Level Reduction in Metaregression of Large Statin Randomized Trials

A recent metaregression of 25 large statin randomized trials involving 155,613 participants and 23,791 major vascular events reported a significant reduction in the risk of major vascular events associated with a reduction in low-density lipoprotein cholesterol (LDL-C) level. The question that naturally follows is whether there is a threshold for the benefit of LDL level reduction that can be achieved with statins or whether greater reductions in LDL level would bring greater reductions in vascular events.

Conventional metaregressions such as the one by Delahoy et al., however, rely on “linear” modeling, which assumes that the association fits a line (a constantly increasing or decreasing risk as the exposure increases or decreases) and does not allow for alternative associations such as threshold effects. We performed a “flexible” (not “linear”) unrestricted maximum-likelihood metaregression (inverse variance-weighted regression) based on fractional polynomials of the reduction in LDL-C level on the logarithmic relative risk (RR) for major vascular events.

Methods. The mean absolute reduction in LDL-C level at 1 year and the RR for major vascular events were abstracted from each individual randomized trial included in the recent metaregression. First-order and second-order fractional polynomial models take the forms log RR = β0 + β1x + β2x^2 + β3x^3, respectively. By choosing p and q from the predefined set [−2, −1, −0.5, 0, 0.5, 1, 2, 3], a rich set of possible functions, including some so-called U-shaped and J-shaped relations, may be accommodated. The powers are expressed according to the Box-Tidwell transformation, in which x^p denotes x^p if p ≠ 0 and log x if p = 0. When p = q, the model becomes β1 + β2x^p + β3(log x).

For each set of powers (p, q), we calculated β1, β2, and β3 that minimized the deviance (sum of inverse variance-weighted squared residuals) using Microsoft Excel Solver (Microsoft Corp). The best fit among the family of models thus generated is defined as that with the highest likelihood or, equivalently, that with the lowest deviance. The gain for a given model is defined as the deviance associated with the reference linear model (β1 = 0, p = 1; applied in the recent metaregression) minus that for the model in question; accordingly, a larger gain indicates a better fit.

Results. The conventional quadratic model (p = 1, q = 2) better fitted the data than the linear model (black line, Figure), with a gain in deviance of 12.87. The best-fitting model (p = −2, q = −2; red curve, Figure) offered a gain in deviance of 13.30 with respect to the reference linear model, representing an almost horizontal line when the reduction in LDL-C level is more than approximately 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) (RR [log RR] of 0.80 [−0.23], 0.79 [−0.24], 0.78 [−0.25], and 0.77 [−0.26] at the LDL-C level reductions of 40, 50, 60, and 70 mg/dL, respectively).

Discussion. Our fractional polynomials metaregression suggests almost no additional benefit in the use of statins beyond a 40 mg/dL decrease in LDL-C level in preventing major vascular events.

A traditional method of summarizing dose-response relations across studies is to estimate the change in the logarithm of the RR per unit of exposure within each study and to combine these estimates across studies. Such an approach could be misleading, however, because it assumes that the dose-response relation follows a specific model form, usually linear. Polynomial models, typically quadratic models, are used to represent nonlinearity. An alternative curve-fitting method,
fractional polynomial regression, has been described. Fractional polynomials are a family of models to consider, as covariates, power transformations of a continuous exposure variable restricted to a small, pre-defined set of integer and noninteger exponents. Such approaches are underused in epidemiologic research and have seldom been compared in a meta-analysis of dose-response aggregate data. Fractional polynomials provide great flexibility for a meta-analysis of dose-response aggregate data and are especially valuable when important nonlinearity is anticipated. Furthermore, they are easier to communicate mathematically, require the estimation of fewer parameters, and are less influenced by arbitrariness in the choice of the model than traditional approaches.

On the basis of the Cholesterol Treatment Trialists’ meta-analysis, Sniderman et al calculated that any potential gain from increasing the dose of atorvastatin calcium from 40 to 80 mg would be small, at best an additional 2% reduction in clinical events. The increase in dose, unfortunately, would likely be associated with increased adverse effects and decreased adherence. Accordingly, whether net benefit would be demonstrable cannot be assumed. It follows that definitive evidence supporting maximal lowering of LDL-C level or maximal dose of statins is still lacking and that guidelines, if they are to be evidence based, should acknowledge this uncertainty. Although we found, on the basis of flexible (not linear) metaregression, that using statins to reduce LDL-C level by more than approximately 40 mg/dl could produce almost no additional reduction in the risk of major vascular events, further analysis would be required to confirm our findings.

Hisato Takagi, MD, PhD
Takuya Umemoto, MD, PhD
for the ALICE (All-Literature Investigation of Cardiovascular Evidence) Group

Published Online: April 29, 2013. doi:10.1001/jamainternmed.2013.659

Author Affiliations: Departments of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan.
Correspondence: Dr Takagi, Departments of Cardiovascular Surgery, Shizuoka Medical Center, 762-1 Nagasawa, Shimizu-cho, Sunto-gun, Shizuoka 411-8611, Japan (kgfth973@ybb.ne.jp).

Author Contributions: Dr Takagi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Umemoto. Acquisition of data: Takagi. Analysis and interpretation of data: Both authors. Drafting of the manuscript: Takagi. Critical revision of the manuscript for important intellectual content: Umemoto. Statistical analysis: Takagi. Administrative, technical, and material support: Umemoto. Study supervision: Umemoto. Group Information: The members of the ALICE Group are Hisato Takagi, MD, PhD; Yusuke Mizuno, MD; Hirota Yamanoto, MD; Masao Niwa, MD; Shin-nosuke Goto, MD; Masafumi Matsui, MD; and Takuya Umemoto, MD, PhD.

Conflict of Interest Disclosures: None reported.

Because they assign patients to treatment conditions, randomized clinical trials (RCTs) offer unparalleled internal validity for drawing inferences about the efficacy of a medical treatment. Whether such inferences can be generalized is not always clear because many RCTs enroll a low and unrepresentative proportion of all patients. The challenges of judging the clinical utility of clinical trial results are increased by poor reporting. The study by Gross et al of trials published in leading medical journals from 1999 through 2000 found that only 28% reported the proportion of screened patients who were enrolled. These deficiencies may have been ameliorated in the past decade because the CONSORT statement was revised in 2001 to require more complete information on the enrollment process in reports of clinical trials, and because many treatment research fields have been showing greater concern about generating knowledge that better informs clinical practice. Accordingly, the present study assessed the extent to which low enrollment rates are still characteristic of widely cited clinical trials, and whether reporting of enrollment information has improved.

Methods. A Web of Science search was used to identify the 20 most influential English-language RCTs for each of 14 prevalent chronic disorders (alcohol dependence, Alzheimer disease, breast cancer, colorectal cancer, chronic obstructive pulmonary disorder, depression, diabetes mellitus, drug dependence, human immunodeficiency virus/AIDS, hypertension, ischemic heart disease, lung cancer, nicotine dependence, and schizophrenia) published from 2002 to 2010 (see eTable for search terms and citations returned; http://www.jamainternalmed.com). We sorted the results on citations per year rather than total citations so that recently published trials would still have the chance to rank as influential. Top-cited articles that were not RCTs (eg, major literature reviews) were excluded.