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Letter to the Editor

Mortality benefit and reduced need for repeat revascularization with statin therapy among patients undergoing percutaneous coronary intervention

To the Editor:

In their article on statin therapy for patients with coronary artery disease, [1] Nakamura and colleagues discussed the effect of statin therapy on all-cause mortality, target lesion revascularization (TLR), and a composite endpoint of death, myocardial infarction, and readmission for heart failure among a prespecified subgroup of patients undergoing percutaneous coronary intervention (PCI). Their findings showed a discrepancy between mortality and cardiovascular events. Statin therapy decreased the risk of fatal events, but not TLR, or the composite triple endpoint. However, we think that these results need to be cautiously interpreted because a not ideal adjustment of confounding by indication together with insufficient power may have affected the validity and precision of their effect estimates.

Although the association between statin therapy and all-cause mortality among PCI-patients were statistically significant in this study, the reported magnitude of protection, in our opinion, may have been overestimated. Based on a cohort of PCI-patients with similar enrollment periods (February 2004 to May 2004; February 2006 to July 2006) from the US National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, 83% of whom received at least one drug-eluting stent, we found a reduction of 42% in all-cause mortality [2] as compared with 73% in their study. It is noteworthy that up to today no clinical trials have confirmed the mortality benefit of statins among PCI-patients [3].

On the other hand, their evidence of lack of effect on TLR or the composite endpoint of cardiac events seems unreliable. Given the observed effect on mortality, it could not be explained only by false negatives due to small sample size. Based on the NHLBI Dynamic Registry, we found post-discharge statin therapy significantly reduced the need for repeat revascularization after adjusting for a wide array of covariates via propensity score models (hazard ratio: 0.74, 95% confidence interval: 0.56—1.00, $P = 0.05$) [2]. A meta-analysis of randomized clinical trials consistently showed a similar magnitude of reduction in repeat revascularization with statin therapy which was initiated after PCI procedures (risk ratio: 0.73, 95% confidence interval: 0.55—0.98, $P = 0.04$) [3].

As the authors pointed out in the Discussion, confounding cannot be completely controlled in an observational study due to unobserved covariates. Notably, several important prognostic factors in Tables 1 and 3 were not adjusted in their final multivariate model, although significant differences were observed between treatment groups. Small sample size may have limited the ability of a statistical model to accommodate covariates as needed. In this sense, adjustment through propensity score approach could possibly be an appropriate method to deal with their scenario [4].

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Zhi-Jiang Zhang (MD, PhD)*
Department of Epidemiology, School of Public Health, Shanghai Jiao Tong University, 227 South Chongqing Road, Shanghai, China

* Tel.: +86 21 63846590; fax: +86 21 63846590.
E-mail address: zhang.zj@msn.com

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Author's reply

We appreciate Dr Zhang's interest in our study [1] and the opportunity to discuss some issues. We also congratulate Dr Zhang and coworkers for their studies of the US National

Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, which showed the effect of statins on reduction in mortality after percutaneous coronary intervention (PCI), consistent with our results, and the meta-analysis, which showed that statins were significantly associated with reduced repeat revascularization, but are unfortunately not associated with reduced mortality rate in patients undergoing PCI.

As stated in our article, the relatively small size of the study population is one of the limitations. Propensity score analysis may be helpful for adjusting confounding factors efficiently. Moreover, the small number of events could lead to overestimation of the drug effects. We agree on these points with his comment. Therefore, a study with a larger population is now in progress and should allay his concerns. However, several previous studies using propensity score analysis have shown that the effect of early-initiated statins against death provided a similar level of risk reduction to our results in coronary artery disease (CAD) patients with or without PCI [2,3].

We think the main topic in Dr Zhang's letter is, at least from the clinical perspective, whether statins, especially early-initiated statins, can reduce the repeat revascularization rate. Our study cannot reveal the effect of early statin initiation on reduction in target lesion revascularization (TLR). Here, we need to underscore the necessity to distinguish precisely between TLR and target vessel revascularization or non-target vessel revascularization (and combined repeat revascularization) when discussing the endpoint about repeat revascularization. It has not been clearly established whether statins can provide a benefit in reducing the incidence of restenosis after stent implantation. In fact, both the NHLBI Dynamic Registry and the meta-analysis performed by Dr Zhang et al. showed no effect against TLR, consistent with our result. In addition, when we consider these revascularization rates, especially TLR, the procedures during stent deployment, such as with or without intravascular ultrasound guidance, have been reported to be an indispensable factor [4,5]. Revascularization rate could be also influenced by the follow-up method because routine angiographic follow-up increases the detection rate in restenosis and de novo stenosis. For these reasons, the conclusions drawn from Dr Zhang and coworkers' reports of their studies may not apply to our study populations with CAD who underwent PCI because of the differences in endpoint, patient backgrounds, and follow-up method.

As mentioned in our article, there are some possible explanations for the discrepancy between the effects of early initiation of statins on mortality and TLR. Although we do not have the clear answer for this discrepancy, we believe from our results and previously published reports that early-initiated statins can produce a beneficial risk reduction in mortality for Japanese CAD patients in real-world clinical practice.

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Michinari Nakamura (MD)
The Cardiovascular Institute, Tokyo, Japan
E-mail address: nmichi-kyu@umin.ac.jp

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