# Lack of accurate evidence on non-statin medication in patients receiving high-intensity statin therapy: Re-evaluation of recommendations is needed

To the Editor,

Despite high-intensity statin therapy (HIST), cardiovascular events persist. Therefore, non-statin medication (NSM) drugs have been developed. However, the patient group to which these drugs should be administered is unclear. The American Heart Association (AHA) published a NSM recommendation to address this question (1). However, we believe that some elements of the updated 2017 recommendation warrant more investigation.

Five important studies pertaining to the guidelines on NSM have recently been published. However, the number of patients receiving HIST in all studies, with the exception of one study, was inadequate. The percentage of patients receiving HIST was as follows: ODYSSEY, 46.8%; FOURIER, 69%; SPIRE-II, 73%; SPRIRE-I, 91% patients; and IMPROVE-IT was conducted with 40-mg simvastatin; therefore, no HIST was used (2-5). Only the SPIRE-I study could suggest that NSM is beneficial or not for patients receiving HIST. However It was shown that adding PCSK9-I (bococizumab) in the regimen of patients receiving HIST has no additional benefit for patients with LDL-C ≥70<100 mg/dL. In SPIRE-II, bococizumab was found to be beneficial for patients with LDL-C ≥100 mg/dL.

Statin therapy not only reduces LDL-C levels but also has anti-inflammatory effect, particularly when used in HIST doses. The CANTOS study clearly showed that that the anti-inflammatory effect reduces cardiovascular events. The FOURIER-trial subgroup analysis suggests that in treatment strategies that reduce LDL-C levels without an anti-inflammatory effect and LDL-C levels remain >10 mg/dL, residual cardiovascular events continue. Perhaps, HIST therapy has additional beneficial effect independent of an effect on the LDL-C level.

For patients over 21 years with clinical coronary artery disease already receiving maximum tolerated statin therapy, AHA recommends addition of ezetimibe as first line therapy, followed by PCSK9-I, if necessary. However, the SPIRE-I study shows no benefit of the addition of PCSK9-I to patients with LDL-C levels ≥70 <100 mg/dL and receiving HIST. SPIRE-II suggests some efficacy of PCSK9-I in patients with LDL-C ≥100 mg/dL and receiving HIST with fairly weak evidence, but bococizumab is not approved by FDA. However, without sub-analysis comparing patients receiving HIST with those not receiving HIST, the benefit of adding NSM for all patients with LDL-C levels ≥70 mg/dL for preventing cardiac events remains unclear. Therefore, the recommendation for NSM treatment in patients receiving HIST is inappropriate. We suggest revision of the recommendation to include NSM therapy for all patients with LDL-C levels ≥70 mg/dL and not receiving HIST and PCSK9i for patients with LDL-C levels ≥100 mg/dL and receiving HIST with an indirect weak evidence. However, no additional treatment is required for patients with LDL-C levels ≥70 <100 mg/dL and receiving HIST. Sub-analysis of all studies by statin level must be performed for clarifying optimal treatment.

**Deniz Demirci, Duygu Ersan Demirci**
**Department of Cardiology, Health Sciences University, Antalya Training and Research Hospital; Antalya-*Turkey***

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**Address for Correspondence:** Dr. Deniz Demirci,
Antalya Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 07100 Antalya-*Türkiye*
Phone: +90 242 249 44 00
E-mail: dddemirci@gmail.com

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