References

1. Gül İ, Yücel O, Zararsız A, Demirpençe Ö, Yücel H, Zorlu A, et al. Prognostic role of soluble suppression of tumorigenicity-2 on cardiovascular mortality in outpatients with heart failure. Anatol J Cardiol 2017; 18: 200-5.
2. Mueller T, Jaffe AS. Soluble ST2--analytical considerations. Am J Cardiol 2015; 115(7 Suppl): 8B-21B.
3. Yucel O, Gul I, Zararsiz A, Demirpence O, Yucel H, Cinar Z, et al. Association of soluble ST2 with functional capacity in outpatients with heart failure. Herz 2017 Jun 26. doi: 10.1007/s00059-017-4590-1. [Epub ahead of print]

Address for Correspondence: Dr. İbrahim Gül,
Cumhuriyet Üniversitesi Tıp Fakültesi,
Kardiyoloji Anabilim Dalı,
Sivas-*Türkiye*
Phone: +90 346 258 18 06
Fax: +90 346 219 12 68
E-mail: dribrahimgul@hotmail.com

Interleukin-1 gene cluster polymorphisms associated with coronary slow flow phenomenon

To the Editor,

We found the publication "Association of Interleukin-1 Gene cluster polymorphisms with coronary slow flow phenomenon (CSFP)" (1) very interesting. Mutluer et al. (1) concluded that "IL-1ß+3954 SNP mutations are significantly more common in patients with CSFP" and "It may suggest that the tendency for inflammation may contribute to the presence of this phenomenon." In fact, based on the present study, a conclusion can be made only regarding genetic frequency. It is not possible to propose any pathophysiology regarding the inflammation process since no inflammatory parameter was assessed. In fact, if there is a direct pathological process as a result of the polymorphism, similar findings should be observed for both IL-1ß+3954 SNP and IL-1ß+3954 SNP. Finally, other SNPs of IL-1ß, which were not investigated by Mutluer et al. (1), such as IL-1ß -634SNP (2), can also have the same effect on CSFP.

Sora Yasri, Viroj Wiwanitkit[1]
KMT Primary Care Center; Bangkok-*Thailand*
[1]Hainan Medical University; Haikou-*China*

References

1. Mutluer FO, Ural D, Güngör B, Bolca O, Aksu T. Association of Interleukin-1 Gene cluster polymorphisms with coronary slow flow phenomenon. Anatol J Cardiol 2018; 19: 34-41.
2. Liu CL, Xue ZQ, Gao SP, Chen C, Chen XH, Pan M, et al. The Relationship between Interleukin-6 Promotor Polymorphisms and Slow Coronary Flow Phenomenon. Clin Lab 2016; 62: 947-53.

Address for Correspondence: Sora Yasri, MD,
KMT Primary Care Center, Bangkok, Thailand 10160
Bangkok-*Thailand*
Tel: +6624245687
E-mail: sorayasri@outlook.co.th

DOI:10.14744/AnatolJCardiol.2018.26429

Author`s Reply

To the Editor,

We would like to thank authors for their valuable comments on our recently published study titled "Association of Interleukin-1 Gene cluster polymorphisms with coronary slow flow phenomenon (CSFP)" (1). We cannot disagree on their comment on the association between inflammation tendency and IL-1 gene polymorphisms. We would like to clarify that there is a thin line between drawing conclusions and suggesting hypotheses, and we stay on the side of just suggesting hypotheses. The main weakness of small-sized genetic case-control studies is their lack of power to draw conclusions from the results. This is the reason why the methodology of genetic studies is moving toward genome-wide association studies (2). It would have been better if serum interleukin-1ß and interleukin-1RA levels were evaluated in our study. This is among the limitations of our study. However, it should be noted that the effects of mutations on inflammatory mechanisms might as well be simply beyond increasing and decreasing the synthesis of the gene product. Conflicting results testing the same hypothesis that these mutations have effects on the course of diseases associated with inflammation also underline this complexity. Additionally, we should emphasize that the co-occurrence of single nucleotide polymorphisms is not a rule. Associations might vary between different polymorphisms in the same gene as a result (3). Finally, screening for all defined mutations and even describing new mutations is possible with next-generation sequencing. However, with conventional methodologies, how many different mutations can be studied is a matter of time and resources (4).

Ferit Onur Mutluer, Dilek Ural, Barış Güngör[1], Osman Bolca[1], Tolga Aksu[2]
Department of Cardiology, Koç University Hospital; İstanbul-*Turkey*
[1]Department of Cardiology, Siyami Ersek Training and Research Hospital; İstanbul-*Turkey*
[2]Department of Cardiology, Kocaeli Derince Trainig and Research Hospital; Kocaeli-*Turkey*

References

1. Mutluer FO, Ural D, Güngör B, Bolca O, Aksu T. Association of Interleukin-1 Gene cluster polymorphisms with coronary slow flow

phenomenon. Anatol J Cardiol 2018; 19: 34-41. [CrossRef]
2. Howson JMM, Zhao W, Barnes DR, Ho WK, Young R, Paul DS, et al. Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms. Nat Genet 2017; 49: 1113-9. [CrossRef]
3. Lee YH, Bae SC. Associations between interleukin-1 and IL-1 receptor antagonist polymorphisms and susceptibility to rheumatoid arthritis: A meta-analysis. Cell Mol Biol (Noisy-le-grand) 2015; 61: 105-11.
4. Behjati S, Tarpey PS. What is next generation sequencing? Arch Dis Child Educ Pract Ed 2013; 98: 236-8. [CrossRef]

Address for Correspondence: Dr. Tolga Aksu,
Kocaeli Derince Eğitim ve Araştırma Hastanesi
Kardiyoloji Kliniği,
Kocaeli-*Türkiye*
Phone: +90 262 317 80 00
Fax: +90 262 317 60 65
E-mail: aksutolga@gmail.com

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*

References

1. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic cardiovascular Disease Risk A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017; 70: 1785-822.
2. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372: 1489-99.
3. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376: 1713-22.
4. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. N Eng J Med 2017; 376: 1527-39.
5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372: 2387-97.

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

DOI:10.14744/AnatolJCardiol.2018.76753