The composite of cardiovascular events, stroke, and MI in the HZ group was higher than in the non-HZ group (Table 1). The differences of absolute incidences for stroke and MI in HZ group when compared to non-HZ group were 1.34 per 1,000 person-years (95% confidence intervals [CI]: 0.71 to 1.97) and 0.80 per 1,000 person-years (95% CI: 0.41 to 1.18), respectively. The hazard ratios for stroke were highest in the subgroup under 40 years of age, a relatively younger population with fewer risk factors for atherosclerosis, and gradually decreased with age. Regarding temporal relationship, the risks of both stroke and MI were highest in the first year after the onset of HZ and then tended to decrease with time, whereas it was evenly distributed in the non-HZ group (data not shown).

The association of varicella-zoster virus (VZV) with stroke and MI is reminiscent of previous "infection hypotheses" such as the association between chlamydia infection and atherosclerosis, which was eventually rejected by the WIZARD (Weekly Intervention With Zithromax for Atherosclerosis and Its Related Disorders) study demonstrating that antibiotics against *C. pneumoniae* failed to improve outcomes in coronary artery diseases (2). This skeptical position with regard to the association of chlamydia with atherosclerosis should not be directly applied to the association of VZV with stroke and MI. VZV is the only virus for which there is clear evidence of viral DNA and antigen in areas of ischemia or infarction in cerebral arteries (3). Moreover, the diagnosis of HZ such as the presence of VZV in the saliva of patients with HZ is more direct than that of chlamydia infection, which was largely based on serology. There are several possible biological causes of stroke and MI after HZ: 1) VZV replication adjacent to an artery, which leads to inflammation of the artery and subsequent thrombosis and rupture; 2) repeated subclinical reactivation of VZV and a subsequent effect on the arteries; 3) transaxonal migration of VZV in a centripetal direction; 4) increased sympathetic tone, blood pressure, and adverse emotional reactions; and 5) the altered immunological status caused by VZV reactivation and subsequent vulnerability to cerebrovascular events.

In conclusion, we have demonstrated that HZ significantly increases the risk of stroke and MI even after rigorously adjusting possible confounding factors in a large population cohort. In propensity score-matched analysis, HZ raised the risks of the composite of cardiovascular events, stroke, and MI by 41%, 35%, and 59%, respectively. The risks were especially high in the relatively young who have fewer risk factors for atherosclerosis. Furthermore, there was a substantial temporal link between HZ and the occurrence of stroke and MI.

Min-Chul Kim, MD
Sung-Cheol Yun, PhD
Han-Bin Lee, MD
Pil Hyung Lee, MD
Seung-Whan Lee, MD
Sang-Ho Choi, MD, PhD
Yang Soo Kim, MD, PhD
Jun Hee Woo, MD, PhD
***Sung-Han Kim, MD, PhD**
Sun U. Kwon, MD, PhD

*Department of Infectious Diseases
Asan Medical Center
University of Ulsan College of Medicine
88 Olympic-ro 43-gil, Songpa-gu
Seoul 05505, Republic of Korea
E-mail: kimsunghanmd@hotmail.com

http://dx.doi.org/10.1016/j.jacc.2017.05.015

Please note: This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HI15C1763). This study was based on the National Health Insurance Service database of South Korea (NHS-REQ0000002692). The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Min-Chul Kim and Sung-Cheol Yun contributed equally to this work.

REFERENCES

1. Kwon SU, Yun SC, Kim MC, et al. Risk of stroke and transient ischaemic attack after herpes zoster. Clin Microb Infect 2016;22:542–8.

2. O'Connor CM, Dunne MW, Pfeffer MA, et al. Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. JAMA 2003;290:1459–66.

3. Nagel MA, Mahalingam R, Cohrs RJ, Gilden D. Virus vasculopathy and stroke: an under-recognized cause and treatment target. Infect Disord Drug Target 2010;10:105–11.

Are T-Inversions in Chest Leads Always Benign?

We read with great interest the paper by Malhotra et al. (1) who investigated the prevalence and significance of anterior T-wave inversions in young white adults. They reported that anterior T-wave inversions were present in 2.3% of the study population (of whom 20% were athletes), but T-wave inversions extended beyond lead V_2 in only 0.5% (0.2% of men; 1.2% of women). Although anterior T-wave inversions represent a major criterion in the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) (2), none of the participants fulfilled the

diagnostic criteria for ARVC after further evaluation or experienced adverse events during the 2-year follow-up.

These findings by Malhotra et al. (1) extend the previous observations on the benign clinical course of anterior T-wave inversions in young adults and athletes. However, contrary to what the investigators state in their paper, the prevalence and prognostic significance of T-wave inversions in right precordial leads V_1 to V_3 have been previously reported in white adults in >10,000 Finnish middle-aged subjects from the general population (3). In the Finnish study, the prevalence of anterior T-wave inversions was also 0.5%, with a surprisingly similar distribution between men (0.1%) and women (0.9%) as Malhotra et al. (1) reported. T-wave inversions normalized during the course of the study in only 20% of the subjects. During the mean follow-up of 30 years, no increase in mortality was observed among those with anterior T-wave inversions. In contrast, T-wave inversions beyond leads V_1 to V_3 were associated with increased risk of mortality and sudden cardiac death. Therefore, it should be emphasized that all T-wave inversions in chest leads may not be benign, even in young athletes.

Together, these data will help to reassure subjects with isolated anterior T-wave inversions about the benign nature of this finding. However, decisions about the need for further evaluation of patients with this electrocardiographic pattern need to be individualized based on the extent of T-wave inversions and other electrocardiographic and clinical features, as well as the estimated prevalence of ARVC in the specific geographic region.

*Aapo L. Aro, MD, PhD
M. Juhani Junttila, MD, PhD
Heikki V. Huikuri, MD, PhD
*Division of Cardiology, Heart and Lung Center
Helsinki University Hospital
Haartmaninkatu 4, PL 340
00029 HUS, Helsinki, Finland
E-mail: aapo.aro@helsinki.fi

http://dx.doi.org/10.1016/j.jacc.2017.01.079

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Malhotra A, Dhutia H, Gati S, et al. Anterior T-Wave inversion in young white athletes and nonathletes. J Am Coll Cardiol 2017;69:1–9.

2. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Circulation 2010;121:1533–41.

3. Aro AL, Anttonen O, Tikkanen JT, et al. Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. Circulation 2012;125:2572–7.

REPLY: Are T-Inversions in Chest Leads Always Benign?

We are grateful to Dr. Aro and colleagues for their interest in our paper (1). They cite their study of 10,899 middle-aged subjects, including 52% of males, that investigated the presence of anterior T-wave inversion over a substantial mean follow-up of 30 ± 11 years (2). The prevalence of T-wave inversion in leads V_1 to V_3 was 0.5% and similar to that reported in our study. There was no increase in mortality among this group, contrary to T-wave inversion in leads other than leads V_1 to V_3, which was associated with an increased risk of cardiac and arrhythmic death. This study supports our findings that T-wave inversion in the anterior leads may be a physiological variant among white individuals in the absence of symptoms or a concerning family history. Both studies suggest that electrocardiographic criteria used by the Task Force recommendations for arrhythmogenic right ventricular cardiomyopathy (ARVC) may be nonspecific in the general population (3). However, we did emphasize that the benign pattern pertained to T-wave inversion limited to leads V_1 to V_2, and that extension beyond this may warrant further investigation. We entirely agree that T-wave inversion in territories other than an anterior territory should be investigated further, particularly as these may be harbingers of cardiomyopathy (4).

We would like to highlight that our study included 14,646 young white athletes and nonathletes, aged between 16 and 35 years. The mean age of these subjects was 21.7 ± 5.4 years, which was significantly lower than the middle-aged Finnish subjects (mean age: 44.0 ± 8.5 years). It is important to note that a similar prevalence of anterior T-wave inversion seems to persist among individuals in the third to fifth decades. However, we do maintain that the rarity of T-wave inversion beyond lead V_2, especially in men (<0.3%), warrants further investigation. This is particularly relevant to the electrocardiograms of young athletes in light of recent studies that have suggested that exercise increases age-related penetrance and arrhythmic risk in ARVC (5).

Aneil Malhotra, MSc, MA, PhD
Harshil Dhutia, BSc
Sabiha Gati, PhD
Tee-Joo Yeo, BSc
Helder Dores, MBBS
Rachel Bastiaenen, PhD, MA
Rajay Narain, MBBS
Ahmed Merghani, BMedSci
Gherardo Finocchiaro, MBBS