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GUEST EDITOR'S PAGE

Trends in Characteristics of CVD in Asia and Japan

The Importance of Epidemiological Studies and Beyond

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Longevity is a positive consequence of the battle against cardiovascular disease (CVD) (1); however, attempts to decrease the incidence of CVD or the prevalence of its risk factors have been in vain. Metabolic syndrome, or its components such as hypertension, dyslipidemia, and diabetes, have been recognized as independent potential risk factors for CVD (2). The prevalence of these factors seems to have decreased in the United States and Europe but has seemingly increased in Asia, especially in Japan.

To respond to this unfavorable trend, the Japanese government launched the National Health Promotion Movement in the 21st Century (Health Japan 21) between 2001 and 2012. The major targets in the field of CVD are: 1) reduction of salt intake; 2) promotion of exercise; and 3) reduction of the prevalence of diabetes, hypertension, dyslipidemia, smoking, and metabolic syndrome. For >10 years, this movement decreased the prevalence of high blood pressure only, whereas other factors remained unchanged or even worsened. This resulted in unchanged mortality due to coronary artery disease (CAD). In addition, according to NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged) (3), the prevalence of hypertension in men and women in 2010 remained high at 62% and 48%, respectively; among the hypertensive population who were compliant with medications, the prevalence was lower at 32% and 40%, respectively. When these proportions of hypertensive subjects are compared with that of the baseline survey in 1980 (50.5% for men and 41.4% for women) (4), it appears that Health Japan 21 was not successful in reducing the prevalence of hypertension. This increasing incidence was also observed in China, although the absolute values were less than those in Japan (5). In fact, a total of 26.6% Chinese adults had hypertension in 2007 to 2008, with a higher prevalence in men and women at 29.2% and 24.1%, respectively, when compared with 20% and 17%, respectively, in 2002 (6). This resulted in a cardiovascular (CV) mortality of 240 per 100,000 persons in China (7).

SUCCESS AND FAILURE TO CONQUER CV EVENTS IN THE UNITED STATES AND ASIA

These recent trends in the prevalence of CV risk factors in Asia are completely different from those in the United States or Europe (8). In the United States, the rates of hypertension did not change between 1999 and 2000 (28.5%) and 2007 and 2008 (29.0%). This resulted in a decline in CAD-associated mortality by approximately one-half (542.9 to 266.8 deaths per a population of 100,000) from 1980 to 2000; this decline was attributed to reductions in the prevalence of major risk factors and the promotion of evidence-based medical therapies (9). On the contrary, CV deaths in Japan have increased from 143 to 156 per a population of 100,000 in 2009 and 2012, respectively (10). The reason for this low absolute value of CV death in Japan is not entirely clear, but it may be attributable to differences in the definitions of CV death, the social or health insurance system, and the prevalence of other risk factors. Interestingly, the prevalence of diabetes and other potential CV risk factors was 6% in 2005 and

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7% to 8% in 2008 in the United States (11), 5.5% in 2000 to 2002 in Japan (12), and 11.6% in 2010 in China (13), although epidemiologists and diabetes specialists in Japan predict that the prevalence of diabetes would further increase in the future. Therefore, the prevalence of risk factors or CVD *per se* is increasing in Asia, especially in Japan, compared with that of Western countries. On top of this trend is the increasing majority of the aged population in Japan, and because aging is the most important risk for CVD, the CV crisis is expected to increase further. Because these trends and their mechanisms could not be precisely investigated by basic or clinical studies, a worldwide epidemiological analysis should be emphasized to understand the pattern of progression of CVD.

ADDITIONAL EFFECT OF EPIDEMIOLOGICAL INVESTIGATION

For 10 years, our group has worked on a resident-based cohort study at Arita-cho in Saga, Japan, and found that the prevalence of hypertension, diabetes, dyslipidemia, metabolic syndrome, and current smoking in 2005 were 42%, 7%, 37%, 19%, and 14%, respectively (14). We also found that plasma B-type natriuretic peptide (BNP) levels can predict the 10-year risk for CAD and may be considered for inclusion in the recommendations for a comprehensive annual health care check of CV risks in each resident. Indeed, when the Department of Healthcare Promotion in Arita-cho routinely measured blood BNP and adiponectin levels and performed echocardiograms during its annual health care checkup of the residents, they found that the prevalence of hypertension, diabetes, and dyslipidemia decreased within 10 years, compared with those of residents of neighboring prefectures. This, in turn, decreased the cost of medical care in Arita-cho compared with the other areas.

EPIDEMIOLOGICAL INVESTIGATION OF HEART FAILURE IN JAPAN

Despite these programs to reduce the prevalence of risk factors, CVD occurs and can eventually cause heart failure (HF). The issue that has gained attention recently is heart failure with preserved ejection fraction (HFpEF), which is tightly linked with the components of the metabolic syndrome and aging (15), as demonstrated by epidemiological studies. In the United States, HFpEF is becoming more prominent (16). In Japan, data collected from JCARE-CARD (Japanese Cardiac Registry of Heart Failure in Cardiology), a nationwide observational study, showed that the rate of HFpEF has increased to about 30% among patients with HF (17,18). In addition, when patients with HF with reduced ejection fraction were compared with those with HFpEF, this study reported that the prevalence of CV death, including sudden death, was slightly higher in HF with reduced ejection fraction (68% vs. 58%); HF death, the most common cause of death, was similar between groups (37% vs. 35%); and non-CV mortality was significantly higher in HFpEF (28% vs. 18%). Furthermore, 2 longitudinal observational studies—the CHART (Chronic Heart Failure Analysis and Registry in the Tohoku District)-1 in 2004 and CHART-2 in 2010 (19,20) evaluating HF patients in the Tohoku area in Japan—reported several changes in the pathophysiology of HF, and specifically, increases in the following: 1) the prevalence of comorbidities, such as hypertension (from 47% to 74%) and diabetes mellitus (from 20% to 23%); 2) the prevalence of ischemic heart failure from 26% to 47%; 3) the prevalence of obesity; 4) the prevalence of HFpEF from 51% to 69%; and 5) HF severity, gauged by plasma BNP levels. The reason for the higher prevalence of HFpEF among patients in Tohoku compared with those in JCARE-CARD may be attributed to the high prevalence of hypertension in the Tohoku area. Miura et al. (3) also pointed out that physical activity and frailty were important determinants of mortality and morbidity in patients with HF (21), which could be explained by the increased ratio of the aged population in Japan. In our hospital cohort of HF patients, we found that the lack of a spouse/partner and presence of constipation and/or sleep disturbance in addition to cardiac dysfunction were closely related to the rate of rehospitalization due to HF (22). Because Japan leads the world with regard to an aging society, we should focus not only on cardiac dysfunction but also on the general condition of the entire body and the social circumstances of the patient. All countries may follow the pattern of CVD that Japan goes through in advance. Therefore, Japan has a responsibility of providing caution on how to avoid CVD in the older population.

HOW TO SEEK THE NOVELTY BEYOND THE STATISTICS OF EPIDEMIOLOGICAL BIG DATA?

On the basis of the results of epidemiological studies, data from patients with CVD and HF are important for primary, secondary, and tertiary prevention. The significant question is whether the primary purpose for data collection is academic. The goal seems to have been for epidemiological studies, but it would

be better to translate this clinically by seeking for unknown factors, alone or in combination, to explain CV events.

How do we do this type of analysis? One answer is by using "data mining," which is a technique of obtaining unexpected information using methods of data analysis, such as pattern recognition, artificial intelligence, and statistics (23). These methods provide only the necessary conditions for candidates that could explain the pathophysiology of CVD. Simply speaking, all possible combinations of each element are provided to explain outcomes. For example, if there are 4 candidates (A, B, C, and D) for CV events, data mining will test the effects of A, B, C, D, A + B, A + C, A + D, B + C, B + D, C + D, A + B + C, B + C + D, C + D + A, D + A + B, and A + B + C + D on CV events. Furthermore, we can study all elements that do not seem to be superficially linked to CV events and test the combinations that are linked to significant CV events (24). This type of analysis has not been possible in medicine. To increase the analytical power and obtain convincing results, we need to collect a lot more data. However, the obtained results are still within the necessary conditions and need to be tested whether they are sufficient.

A PROPOSAL FOR NEW TRENDS OF THE CLINICAL RESEARCH

Furthermore, to identify target molecules or drugs for CVD treatment from a large medical database for basic research, we need to narrow down the criteria and validate the candidates that will fulfill the necessary and sufficient conditions between the target goals and pathophysiology of CVD. Importantly, the effectiveness of such molecules or drugs in clinical practice needs to be re-evaluated by large-scale clinical trials. This cycle of clinical/basic/clinical studies, along with data mining methods, constitutes the best strategy for inventing novel drugs in the medical field, especially in cardiology.

Last but not least, to understand the current status and future directions of CVD and HF, data collection from patients with either CVD or HF, both with and without CV risks, is encouraged nationwide, Asia-wide, and worldwide.

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