Nationwide Actions Against Heart Failure Pandemic in Japan
—What Should We Do From Academia?—

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Heart failure pandemic is rapidly approaching in Japan, requiring nationwide actions. In particular, the Japanese Circulation Society and related societies launched the Stroke and Cardiovascular Disease Control Act, which was passed by the National Diet, as the first ever legislative policy measure against stroke and cardiovascular disease. In association with this, actions against heart failure pandemic from the scientific field are also important. Because heart failure pandemic is a critical problem not only in Japan but also in many developed countries, we believe the nationwide approach, as summarized here, will greatly contribute to the development of cardiovascular medicine, particularly the management and treatment of heart failure worldwide.

Key Words: Heart failure; Nationwide action; Stroke and Cardiovascular Disease Control Act

Heart failure is on the brink of becoming a pandemic in Japan. Against this, the Japanese Circulation Society (JCS) is taking nationwide actions including the Five-Year Plan for Overcoming Stroke and Cardiovascular Disease, the Stroke and Cardiovascular Disease Control Act, and the Yokohama Declaration.

In 2016, JCS and the Japan Stroke Society jointly made the Five-Year Plan for Overcoming Stroke and Cardiovascular Disease with 19 related societies, aiming to extend healthy life expectancy, and heart failure is listed as 1 of 3 major therapeutic targets. We have suggested 5 major strategies: Training and development, Contemporizing healthcare, Patient registry/database development, Patient and public outreach, and Accelerating clinical and basic research. In Japan, the Cancer Control Act was passed in the National Diet in 2006, but countermeasures against cardiovascular disease have been far inferior to those against cancer. Therefore, activities to establish the Stroke and Cardiovascular Disease Control Act were launched in cooperation with JCS, the Japan Heart Foundation, and the Japan Stroke Association. After overcoming many hurdles, the Stroke and Cardiovascular Disease Control Act was unanimously passed by the National Diet in December 2018, as the first ever legislative policy measure against stroke and cardiovascular disease. Finally, the Yokohama Declaration, which underscores the importance of preventive cardiology for heart failure pandemic was adopted at the 83rd Annual Scientific Meeting of the JCS in March 2019.

To overcome heart failure pandemic, we believe contributions from the scientific field are required in association with these nationwide approaches. In this article, we would like to take a general view of what we should do for heart failure pandemic from an academic perspective.

Heart Failure Pandemic in Japan

In Japan, cardiovascular disease accounts for approximately one-quarter of deaths, and the prevalence of heart failure is rapidly increasing. The JCS conducted the Japanese Registry of All Cardiac and Vascular Diseases (JROAD) to collect data from almost all teaching hospitals with cardiovascular beds. According to JROAD, the annual number of patients with heart failure hospitalization increased by 22% from 212,793 in 2012 to 260,157 in 2016 (while that of acute myocardial infarction (AMI) increased by 6% during the same period).1 This critical epidemiological condition is known as “heart failure pandemic.” Aging is closely associated with the development of heart failure. The percentage of the elderly population (>65 years) has rapidly increased 4-fold, from 6% in 1960 to 23% in 2010. This rate of change in aging in Japan is the fastest worldwide, and Japan has the highest proportion of older people. Therefore, the crisis of heart failure pandemic...
is utmost critical for Japan.

**Nationwide Surveillance of Heart Failure**

Overviewing the current status and management of patients with heart failure through nationwide surveillance in Japan is primarily needed to overcome heart failure pandemic. So far, there are no nationwide surveillance data regarding heart failure in Japan. It is estimated there are approximately 1 million heart failure patients in Japan, and the number of patients with heart failure is predicted to increase continuously, reaching 1.3 million by 2030. However, this is just an estimation based on local epidemiological data. The Sado Heart Failure Study is a hospital-based research conducted by all hospitals on the island of Sado, but because it is an isolated island and Sado City has a major proportion of the elderly population, such data might not accurately represent the general Japanese community. Therefore, we need nationwide surveillance to identify the current status of heart failure in Japan.

Nationwide surveillance is also necessary for the maintenance of the medical system and development of human resources. Currently, the medical system for cardiovascular diseases in Japan mainly focuses on emergency care for AMI. As a result, primary percutaneous coronary intervention for AMI is well penetrated. However, according to JROAD, the annual number of patients hospitalized for heart failure (260,157) is currently 3.5-fold that of patients hospitalized for AMI (73,421). Therefore, the optimal medical system, including a comprehensive and seamless medical system for the acute, recovery, and chronic phases, should be promptly rebuilt for heart failure. For example, network coordination of local clinics and hospitals, visiting care system, continuous cardiac rehabilitation, and interdisciplinary palliative care need to be promoted. Accordingly, human resource development, including not only physicians specialized in heart failure treatment but also health professionals other than physicians, is required based on the balance of supply and demand, which can be also evaluated by nationwide surveillance.

**Nationwide Registry Focusing on Features of Treatment for Heart Failure in Japan**

There are substantial differences in the characteristics and outcomes of patients with heart failure between Western countries and Japan because of racial and genetic variations, non-cardiac comorbidities and socioeconomic and environmental factors. The unique healthcare system, “kaihoken” (health insurance for the entire Japanese population), which was launched in 1961, assures access to health services for the entire Japanese population and also contributes to the Japanese features of heart failure management. For example, average length of hospital stay is >20 days in Japan, which is substantially longer than in other countries. However, the 30-day heart failure readmission rate is lower in Japan (5%) than in the U.S. (25%). Longer hospital stay and hospital readmission seemingly have a trade-off relationship, and we need to explore the optimal hospital care for heart failure to improve long-term clinical outcomes.

Moreover, there is a difference in the standard treatment for heart failure. Guideline-directed medical therapy (GDMT) is also different for heart failure. It currently remains unclear whether standard treatment for heart failure in Western countries is applicable in Japan, and several standard medications, such as ivabradine and sacubitril/valsartan, are not yet approved. Nonetheless, Japan has some unique pharmacological treatments for heart failure, which are not adopted in Western countries. These include tolvaptan (an oral vasopressin type 2 receptor antagonist), carperitide (an intravenous recombinant atrial natriuretic peptide), pimobendan (an oral inotropic agent that has both phosphodiesterase-inhibiting and calcium-sensitizing effects), nicorandil (an agent that has a vasodilatation effect through activating adenosine triphosphate-sensitive potassium channels), and landiolol (an ultra-short-acting intravenous β-blocker). These agents are widely used in Japan for heart failure. For example, carperitide is very frequently used for acute heart failure according to the Class IIa recommendation in the Japanese guidelines. However, the clinical benefit of these agents still remains unclarified. Hence, GDMT for heart failure must be established through the upcoming nationwide registry in Japan.

There are other features of heart failure treatment in Japan. Various medical devices that are available in Western countries are not approved in Japan because of “device lag.” Moreover, even if a medical device is approved, the indication is sometimes different in Japan. To overcome device lag and drug lag, which are both long-standing issues, we need to participate in the global clinical trials of novel drugs and innovative devices, and enroll enough patients to convince the Pharmaceuticals and Medical Devices Agency for approval in Japan. Additionally, because Japanese patients with cardiovascular diseases generally have a lower incidence of adverse clinical events, it is difficult to prove the effect of novel drugs and innovative devices by a statistically significant difference in clinical events. Therefore, it is necessary to establish trial design and methodology to assess the effect of new treatments by surrogate markers such as biomarkers and non-invasive functional tests. The number of heart transplantation procedures is also limited in Japan (the annual number in 2018 was 55) and the waiting period for heart transplantation is very long (>3 years). Furthermore, ventricular assist devices used as destination therapy have not been approved yet. A prospective nationwide real-world registry should focus on these features and limitations of heart failure treatment in Japan. In conjunction with the Stroke and Cardiovascular Disease Control Act, we held a meeting for establishing a surveillance registry in January 2019 with the Ministry of Health, Labour and Welfare and decided to start the registry focusing on heart failure as well as acute coronary syndrome (ACS) and aortic dissection. We are now making a concrete study protocol, and will launch a nationwide registry including as many hospitals as possible that are treating acute-phase patients suffering from heart failure, ACS, and aortic dissection. In order to enhance the function and potential of this registry, we are also considering combining the collected information with other big data and epidemiological data.

**Promoting Basic Research**

It is a big problem that scientific research activity is gradually declining in Japan. Particularly, the number of basic research papers regarding cardiovascular medicine is about half compared with 10 years ago. In contrast, there has been a tremendous progress in scientific research related to cancer, resulting in various groundbreaking curative
treatments such as molecular targeted therapy and cancer immunotherapy. A Japanese scientist Tasuku Honjo received the Nobel Prize in Physiology or Medicine in 2018 for the discovery of a protein on immune cells (called PD-1), which paved the way to a novel therapeutic approach (Opdivo) to cancer. Despite the poor prognosis, there has been no curative treatment for heart failure because the pathophysiological mechanisms of heart failure remain unclear. To overcome this, JCS launched a council forum on basic cardiovascular research in 2018. With the passage of Stroke and Cardiovascular Disease Control Act, we expect a significant increase in research activity. We believe that this movement will help Japan make progress in basic research, particularly in genomic science, omics analysis, establishment of standardized cardiovascular disease models, and regenerative medicine using induced pluripotent stem cells and other stem cells, and translational research as the foundation of clinical research, drug discovery and novel device development.

Preventive Cardiology Against Heart Failure Pandemic

Preventive cardiology, including primary prevention of heart failure and secondary prevention of recurrent heart failure, is also crucial, and actions from academia are required in this field. Recently, JCS adopted the Yokohama Declaration, which emphasized the necessity of awareness of preventive medicine for heart failure through lifestyle modification and optimal management of risk factors. Furthermore, the latest guideline of the JCS underscores the importance of population at risk for heart failure, including Stage A (at high risk for heart failure but without structural heart disease or heart failure symptoms) and Stage B (structural heart disease but without heart failure signs or symptoms) in the ACC/AHA guideline for the management of heart failure. Given that a considerable part of the population is categorized as Stage A or B, establishing evidence-based medical treatment for these subsets is of the utmost importance and its socioeconomic impact is expected to be enormous. However, because the population categorized as Stage A or Stage B has lower event rates than that categorized as Stage C or Stage D, a large-scale comprehensive epidemiological database with long-term follow-up is required to obtain scientifically convincing data. From this perspective, Japan has a potential advantage because the annual health check-up is theoretically applicable for almost the entire Japanese population. Employers offer annual health screening to their employees, and local city offices ensure annual health screening even for non-employees. Moreover, voluntary health check-ups, “Ningen Dock,” including more advanced examinations, are also very common in Japan (>3 million of Japanese citizens undergo “Ningen Dock” annually). Therefore, combining all these health check-up data will enable us to build a database with a larger sample size with long-term follow-up period. We believe that such a large-scale database will supply scientifically relevant findings, enabling citizen (patient) education that raises awareness regarding prevention of heart failure (including primary and secondary prevention). As well as citizen (patient) education, interactive communication between health professionals and patients (and their families) is also important. At the 83rd Annual Scientific Meeting of the JCS, we invited patients with cardiovascular diseases to the scientific meeting, and had the opportunity to hear and to share their thoughts and experiences for the first time. We should continue such activities as a society to deliver the voice of patients and their families to the government and together make the nationwide healthcare system more sophisticated and patient-oriented.

Conclusions

Given the huge number of patients suffering from heart failure in Japan, the nationwide approach of the cardiology societies should provide comprehensive epidemiological data of heart failure patients, particularly in our super-aging society, and shed light on novel scientific insights into the pathophysiology and treatment for heart failure. Furthermore, such nationwide action is important for patients currently suffering from heart failure and their families, as well as for the next generation of Japanese citizens to spend a healthy and high-quality life. Risk factors for the development of heart failure are closely related to an industrialized lifestyle and aging; therefore, heart failure pandemic is a critical problem not only in Japan but also in many developed countries. We believe that our nationwide approach as detailed here will greatly contribute to overcoming the heart failure pandemic in Japan and serve as an excellent model for other countries.

References