Heart failure and myocardial diseases: a message to the next generation

Cardiovascular disease prevention: lessons from heart failure

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Developed countries like Japan are suffering from an abrupt increase of medical burden due to an aged population and low fertility. In particular, the increase of this burden is mainly due to cardiovascular diseases. I began my life's studies on myocardial diseases. Consequently, my scientific focus has gradually moved to the clinical issues of heart failure. Fortunately, through such practice, I have been able to learn the importance of preventive medicine. Herein, I pass on a message to the next generation of physicians based on these valuable lessons. I want them to stress the importance of disease management, preemptive intervention just before the first onset and just before a recurrence, seamless regional and departmental collaboration, and improvement of their patients' walking ability. In the future, these themes will certainly become essential in the fields of medicine and medical care.

Midway of my study, the academic interest was robbed by the following two challenging themes. One was autoimmune myocarditis and/or autoimmune cardiomyopathy. I began to pursue this theme in Germany under the guidance of Professor B. Maisch in Wuerzbrug University to establish an animal model of myocarditis and cardiomyopathy. After returning to Japan, Professor Makoto Kodama and I seriously challenged this task using human cardiac myosin as an antigen and finally succeeded to establish a brand new animal model of autoimmune myocarditis and autoimmune cardiomyopathy in 1987. Since then, this rat model has played a major contribution to the better understanding of the mechanism development and treatment of myocardial diseases. On the other hand, clinical beta-blocker therapy for heart failure captured my full attention and continues to this day.

After getting the professor's position and chairman of the Department of Cardio-Angiology in Kitasato University School of Medicine, I was assigned to handle more than 200 high-risk patients with refractory heart failure every year, which still continues to date. Therefore, even if that were not the case, I am obligated to spend most of my time on and pay most attention to clinical issues. So, many patients with heart failure came to us in every stage of emergency; and, regardless of whether I liked it or not, my staff members and I were forced to treat many refractory patients right from the beginning. They were constantly calling us day and night.

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Consequently, I have learned a lot from these heart failure patients. I have thorough confidence in my mastery of preventive practice concerning cardiovascular diseases. Thus, when I became 60 years old, I declared I would change my scientific focus again and began to concentrate on preventive medicine earnestly. Here, I would like to give you an idea of some of my experiences and accumulation of knowledge, and to present an outlook based on these data and experiences that are so precious to me.

Why should prevention be stressed so much?
Population aging is the biggest issue among developed countries such as Canada, Germany, and Japan. As a matter of fact, this is the main reason why I changed my focus in medicine after I became 60 years old. In Japan, the elderly ratio has been increasing rapidly year by year. This tendency had been pointed out after the Second World War and become more evident in the 1980s. In 2000, the ratio reached 17% and after that has increased linearly. In 2055, it seems to be more than 40%. In addition to this tendency, low fertility in the population has gradually occurred; as a result, the total number of the population began falling from the maximum of 126,120,000 in 2005. Japanese women no longer give birth to fewer than 1.4 children on average. With such a population structure, the need for medical services for men and women has continued to increase exponentially as shown in Figure 1. According to a government report, a total of 18.6% of people aged more than 75 years need medical service every day. Out of those, cardiovascular patients account for 28.8% as inpatients and 24.3% as outpatients. That means, that of the total of patients who require medical services daily, more than half of them are elderly patients with cardiovascular diseases. Like a tsunami, a huge medical burden is attacking and bearing down on the next generation of Japanese that is currently mainly supporting the elderly. Thus, it is easy to understand why we should stress cardiovascular prevention at this time. Because of the increase in the ratio of elderly people, there are two main urgent tasks emerging that must be resolved: how to reduce the medical burden, and how to save our medical resources.

In therapeutic intervention, especially for the elderly, the medical effects, life expectancy and QALY (quality-adjusted life year) weight, must always be determined by the balance between cost and risk (Figure 2). Therefore,

Figure 1. The need for medical services in men and women
It has continued to increase exponentially in both sexes.
disease prevention is the most reasonable solution and the best compliant measure to meet such conditions.

For preventive procedures to be effective, in addition to traditional approaches, firstly, how to avoid and/or delay a first event; secondly, how to prevent a recurrence; and thirdly, how to add preemptive intervention just before the events are important. And after every effort for prevention, especially in advanced elderly people, how to determine, "Cure or Care," namely to cure the patient or merely care for the patient, is a final question. I have learned lot about these issues from treating heart failure patients who had dilated cardiomyopathy.

The natural course of cardiovascular disease and its intervention

The natural course of cardiovascular disease is very similar to that of submarine volcanoes (Figure 3). Cardiovascular disease is closely linked with aging. Thus, the level of this disease is deeply related to two types of factors, genetic and environmental. Just imagine that under the surface of the sea, this disease is slowly progressing at invisible levels of status. One day a virulent, fulminate sign suddenly appears without symptoms. If possible, you should intervene at this first

Figure 2. Therapeutic intervention for the elderly

In this framework, medical effects, life expectancy, and QALY (quality-adjusted life year) weight is determined by the balance between cost and risk.

Figure 3. The natural course of cardiovascular disease

This diagram depicts the natural course of submarine volcanoes used here as an analogy to show the most likely natural course of cardiovascular disease.
visible point, namely at the level of the aura. But most people overlook it, consequently causing a serious, fulminating first event. Thereafter, even if they sincerely follow a preventive program, some patients will be attacked by an even more serious recurrence of the disease despite their efforts. Therefore, two points for preventive intervention are designated in this debilitating disease, a point before the first onset and the next one before the recurrence.

To prevent heart failure, disease management is very useful especially employing BNP guiding (Figure 4). Systemic treatment continuously adding to the next intervention referring value of the plasma BNP level and/or body weight in early morning is conventional to achieve clinical targets, to prevent a cardiovascular event and/or to reduce the medical burden. In this framework, beta blocker therapy with the combined use of an ACE (angiotensin converting enzyme) inhibitor and comprehensive rehabilitation are strong measures to enhance clinical outcome. For example, an excellent report about BNP guiding for secondary prevention in dilated cardiomyopathy has been published. If you can keep a dilated cardiomyopathy patient’s BNP level under 190 pg/ml for 6 months after being discharged, you would likely succeed in preventing recurrence and the need for rehospitalization.

To control remodeling of the heart size and shape is the next step in dilated cardiomyopathy. In a well responsive case, although the heart indicates a big size and cubic shape like a volley ball before therapy such as cardiac resynchronizing, 1 year after pacing therapy, the heart volume reduces remarkably, and the shape is transformed to that of an oval more like a rugby ball. This favorite change is so called, “reverse myocardial remodeling.” The prevalence provoked by cardiac resynchronizing therapy is very high, around 60%, if the pacing is conducted appropriately; but it is currently very expensive.

It is also possible to achieve reverse remodeling in medical treatment as well as pacing. The prevalence in dilated cardiomyopathy is around 40%, comparatively low, but relatively not expensive. Its clinical significance is very clear. To achieve reverse remodeling means to improve the patient’s prognosis. In a good responder to the treatment, the T wave change in the ECG (electrocardiogram) is very suggestive. It moved from negative waves to positive from early medication.

Thus, I would like to emphasize two main checkpoints for heart failure prevention: the BNP level, and the achievement of reverse remodeling.

Ischemic heart and prevention
In ischemic heart, the scenario is not as clear but much more complicated in comparison with dilated cardiomyopathy. You are easily able to understand such circumstances, if you follow up the patient with acute myocardial infarction precisely using SPECT (single-photon emission computed tomography) imaging. Even if a patient visits a hospital within 2 hours after the onset of a myocardial infarction and an emergency physician quickly succeeds in reperfusion by catheter

Figure 4. Disease management employing the BNP guidelines

BNP, B type of natriuretic peptide; ACE, angiotensin converting enzyme
intervention, most of the ischemic heart left largely substantial damage has already been enlarged upon admission. With time, the heart is remodeled and 6 months later, the left ventricular end systolic volume reaches a considerable amount. Despite the progress in remodeling, the patient has no cardiac symptoms; but the disease remains in an invisible state as heart failure. This remodeling depends on the severity of the myocardial damage primarily caused by the infarction. Follow-up ultrasonographic study clearly supports this tendency. Even if in a small infarction, cardiac volume continues to increase at the level of 2-3 ml per year in the left ventricular end systolic volume, and cardiac function continues to deteriorate. This remodeling seems to be documented more clearly in the elderly.\textsuperscript{21}

**Preemptive prevention**

In order to overcome remodeling in the ischemic heart, you need further approaches like preemptive intervention not only for apparently healthy patients but also for high-risk patients. This approach will best be done just before the first event and again just before a reoccurrence. For those purposes, extremely correct and prompt diagnosing

![Cardiac Compass®](image)

**Figure 5.** How to early and accurately detect the beginning of a cardiovascular event

An exceptional case is shown here in which the beginning of heart failure is accurately diagnosed using very expensive technology - a remote monitoring system: Cardiac Compass (Medtronic, Minneapolis, MN, USA). This implantable cardiac diagnostic device helps in early detection of heart failure. When atrial fibrillation starts, body fluid retention starts at the same time, and, by that time, thoracic impedance has been lowered.
of the patient’s state very close to the manifestation of the first event or the recurrence is essential. As such, preemptive intervention is still quite challenging. No doubt we have been and still are groping around in the dark at this primitive problem, how to detect cardiovascular fragile lesions early and how to predict their damage like a weather forecast. Figure 5 shows Cardiac Compass data of an exceptional case in which the beginning was correctly diagnosed using very expensive technology - a remote monitoring system. Accurate and early detection of heart failure is very difficult at the present time. Moreover, without overcoming this difficulty, we could not expand to a new stage in preemptive medicine. For usual prevention, simpler accurate and early diagnostics, such as biomarkers, including gene expression profiling and/or cardiovascular imaging techniques, may develop as just exactly what we are waiting for in the future.\textsuperscript{22}

The expected clinical impact seems to be greater referring to the JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) results.\textsuperscript{23} This clinical trial was attempted with apparently healthy patients with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg/dl but high-sensitivity C-reactive protein levels of 2.0 mg/l or higher. The intervening agent was rosuvastatin, a strong statin. As a result, cardiovascular events were reduced dramatically, to 44%. And the need-to-treat patient number was surprisingly small, only 25. This result is expected to be close to practical applications of effective preemptive intervention even for low-risk patients. If it succeeds, this approach will significantly reduce the disease burden.

**Care program and knee extensor muscle force**

After all efforts have been exhausted, the physician must make the decision to care for the patient. What determines starting patient care is the most delicate problem. In my exploration of the medical front regarding terminal patient care, I have come to a remarkable discovery. Consequently, I propose this suggestive clue to the elderly. It is that of the ability to walk. This ability depends on lower limb muscle strength and balance capacity. For example, the knee extensor muscle force is a good indication of the prognoses of heart failure patients. In cases of muscle force <30% of body weight, the 2-year survival rate will be limited to ≤51%.

As a means of guidance for the prevention of heart failure, I propose two clinically convenient scales: BNP and lower limb muscle force (Figure 6). Ideally, within the range, the plasma BNP level is less than 100 pg/ml, and also the lower limb muscle force is >55% of body weight, the patient with heart failure is able to take an active part in a preventive program of a full reasonable range. In spite of every effort, if the patient remains more than 500 pg/ml in the BNP level at any time and remains at <30% in the lower limb muscle force despite any efforts in cardiac rehabilitation, the physician should not hesitate, but start a care program immediately (Figure 7).\textsuperscript{24}

**Regional collaboration system**

Undoubtedly, prevention for cardiovascular disease should be seamless from the beginning to the end of the disease. To achieve this, I have been developing a regional collaboration system (Figure 8). In this framework, our hospital is only responsible for acute treatment. Stable patients who have recovered from a cardiovascular event, such as myocardial infarction or heart failure, are introduced to certified home doctors. At the same time, they are enrolled in a secondary prevention center, with their consent. The home doctor and the center share in the responsibility of the patient’s care. The home doctor concentrates on outpatient work, while the center is responsible for annual heart check-ups and planning the patient’s disease management. These two entities always share clinical information with the patients even using clinical path and information technology. During the past decade, more than 4,000 patients took part in this system. From the hospital cohort, we are able to gather a great deal of precious data that. For example, even in the secondary prevention stage, salt restriction is very effective to help avoid a total cardiovascular event. And
Figure 7. Cure and/or care in cardiovascular disease

Whether you should select cure or care is determined by the degree of ease of the remaining points to intervene. In general, if outcomes are acceptable and if the medical burden seems to be small, cure should be selected. And, if outcomes would be small, and if the cost and risk seems to be high, care should be selected. But, I think the patient's own feelings and desires, the family's feelings and desires, and the refrained skill of medical staff will also be determining factors, in addition to such rationality. The process for reaching a decision is not linear. The decision, whether it is correct or not, often still worries the family and you even after the results are known. Modified from Adler ED et al.24

Figure 8. Schema of a regional collaboration system
also, in the maintenance phase, the effect of cardiac rehabilitation is dramatic. Patients who did not stop cardiac rehabilitation in the maintenance phase, after the recovery period, were able to live pleasant lives without the anxiety or dread of rehospitalization.

Conclusions

As summarized in Figure 9, to achieve cardiovascular disease prevention, risk profiling is very important using non-modifiable factors and diagnostic testing. These are fundamental. In the paradigm to reduce the disease burden and to minimize cost and/or risk with only the standardization of medications and thorough control of pleasant, rewarding, and extended life to all your elderly patients suffering from cardiovascular diseases.

References


