



Overview of the 78th Annual Scientific Meeting of the Japanese Circulation Society

– Cardiology in the Information Era: From Bench to Community –

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The 78th Annual Scientific Meeting of the Japanese Circulation Society was held in Tokyo on March 21–23, 2014. The main theme was “Cardiology in the Information Era: From Bench to Community”. Because of technological advancements, including computer networking, a vast amount of information from basic and clinical research is being generated in a short time period. This information has great potential to contribute to human health, and some of the results are presented. However, we must remain vigilant, for there are many risks inherent in information generation. To ensure high-quality information, we need to obtain enough knowledge to focus on not only the medicine, but also ethics, and methodology. Moreover, we need to train the specialists, establish economic support, and create a regulatory framework. More than 15,000 people, including paramedical specialists, attended this meeting. The most popular sessions included those on “Transcatheter Aortic Valve Implantation for Aortic Stenosis,” “Diabetes Mellitus,” “Atrial Fibrillation,” “Pulmonary Hypertension,” and “Diuretics To Treat Heart Failure”. Even in rather small sessions, attendees participated in discussion, identified opportunities to expand or start research, and were able to update their clinical knowledge. The meeting was successfully completed with a discussion of the future of cardiology.

Key Words: Cardiology; Future directions; Japanese Circulation Society

Overview and Meeting Theme

The 78th Annual Scientific Meeting of the Japanese Circulation Society (JCS) was held in Tokyo, Japan, on March 21–23, 2014, with the theme of “Cardiology in the Information Era: From Bench to Community.” The Tokyo International Forum (**Figures 1A,B**) was the main venue, but the JP Tower and the Tokyo Chamber of Commerce and Industry were also used. These venues are located in central Tokyo near the Tokyo station (**Figure 1C**), which has been partially restored to its original condition when it was built 100 years ago. The JP Tower, which was reopened last year after renovations, was built on the site of the historic “old Tokyo Central Post Office”, preserving part of its original appearance. Together, these buildings offered enough space for the meeting to be held in Tokyo for the first time in a decade. Furthermore, because of proximity to the imperial palace, “jog & walk around the palace” sessions were conducted on Sunday morning.

In addition to the scientific meeting, a medical history exhibition titled “The Dawn of Modern Medicine in Japan: From Dutch Medicine to German Medical Science” was hosted at the JP Tower, in collaboration with the Museum of the University of Tokyo. Thus, the meeting provided participants with

the opportunity to enjoy both the scientific meeting itself and the interesting coexistence of modern and historic Tokyo.

Ryozo Nagai, MD, PhD, President of Jichi Medical University was Congress Chairperson and introduced the main theme (**Figure 2A**). In daily medical practice, clinicians need to process a vast amount of medical information. In clinical research, numerous clinical trials, physician-led clinical research and epidemiological studies are conducted. Moreover, basic research is generating tremendous amounts of information in a short period of time because of technological advancements. Therefore, we should thoroughly examine how that information is produced and interpret it with care. Only by having enough knowledge to eliminate the risks, can this enormous information base contribute to improving human health outcomes.

In the current information era, the use of registries is symbolic of clinical research. Many registries exist for both local purposes and restricted diseases, and some that are currently in progress were presented in Symposium 11. Each registry has the potential for significant impact in clinical medicine; however, of the registries in Japan, the only national database that gathers patient numbers and causes of cardiovascular disease is The Japanese Registry of all Cardiac And Vascular Diseases (JROAD). The progress of this unique registry was

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Figure 1. (A,B) Tokyo International Forum. (C) View of Tokyo Station (Marunouchi-side). Photo courtesy of Dobun Hayashi.

reviewed in the Congress Chairperson's Special Session 3. Initially, the registry was launched as a nationwide annual survey on the management of cardiovascular disease, and was intended to assess the clinical activities of general hospitals with cardiovascular beds. Later, the JCS expanded and renamed JROAD. It now truly reflects the real world of cardiovascular medical care in Japan, and could help drive future medical care policy.

Unfortunately, some Japanese clinical research into cardiovascular disease has received criticism for scientific misconduct. Therefore, several sessions were dedicated to lectures and discussions regarding sloppiness, forging, falsification, and fabrication. In the Congress Chairperson's Special Session 4, titled "How Can We Conduct Sensible Investigator-initiated Clinical Research (IICR)?" Dr Kohro summarized the data management problems of the Kyoto Heart Study and explained how to improve the rigor of the study data. In Plenary Session 4, "Medical Guidelines for the Management of Cardiovascular Diseases and EBM in Japan," Dr Ueshima pointed out the weaknesses of the prospective randomized, open, blinded endpoint (PROBE) studies. He emphasized that hard or objective endpoints are necessary for such studies to prevent biased results. In addition, he recommended asking whether the result was consistent with previous studies. The main discussion of this session focused on whether IICR should be regulated by law or the Good Clinical Practice (GCP) guidelines. Although

all agreed on the importance of regulation, there were differences of opinion on the form that regulation should take.

Conflict of interest (COI) is an essential but difficult concept for researchers to understand. The lecture titled "Thought on COI" at Congress Chairperson's Special Session 7, explained that although the original concept of COI was developed as a fine tuning tool, during the past decade or two it has needed to deal with the inherent conflicts between business-academia collaborations and the public nature of medicine. An important principal of COI is to ensure transparency with everybody involved, including patients.

Throughout these sessions, it was apparent that there was a sincere eagerness to conduct good clinical studies that benefited patients. In the future, clinical studies could be improved by greater collaboration among clinical doctors, epidemiologists, and medical statisticians. Moreover, a monitoring system is necessary to ensure the quality of data. We can surmount the risks of excess information generation through sound medical, ethical, and methodological knowledge.

Attendees and Sessions

This meeting comprised 45 lectures and more than 100 organized sessions. In total, 3,649 abstracts were submitted, of which 2,331 were accepted, including 125 abstracts for the featured research session (acceptance rate, 63.9%). The total

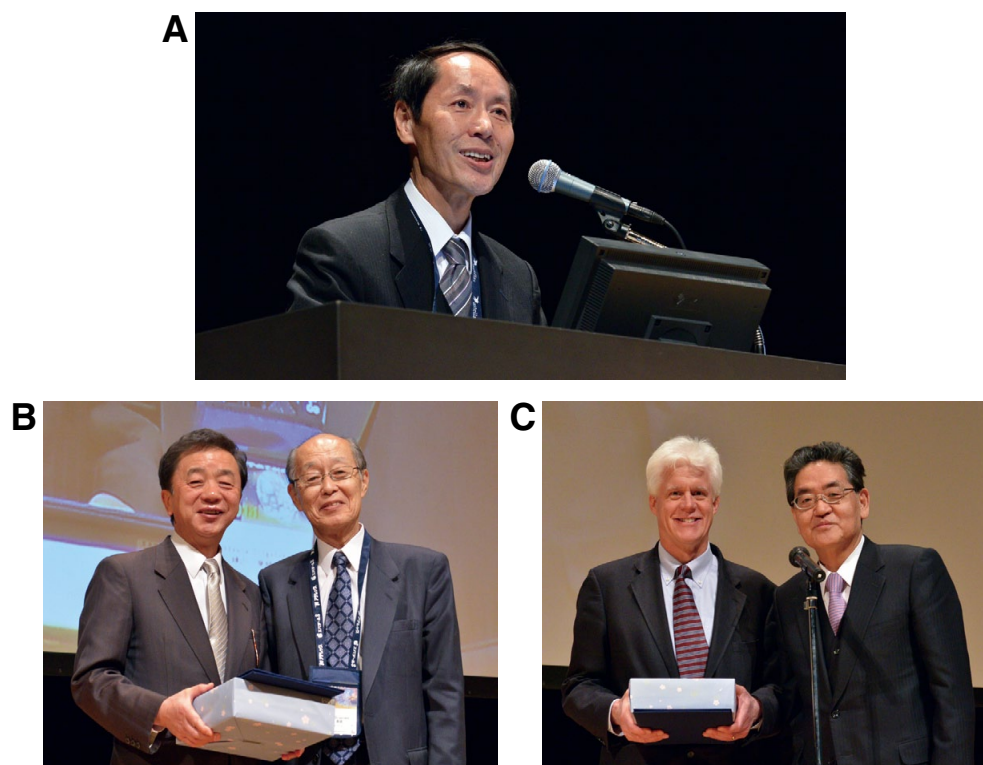


Figure 2. (A) Ryozyo Nagai, MD, PhD, President of Jichi Medical University, presenting the Congress Chairperson's Lecture. (B) Tadatsugu Taniguchi with the session's chairperson, Shigetake Sasayama, at the Mashimo Memorial Lecture. (C) Eric N. Olson with the session's chairperson, Yoshio Yazaki, at the Mikamo Lecture.

number of attendees was 15,175, and although most were Japanese doctors, attendees included 174 resident physicians, 193 medical students, 33 international students, and 1,736 co-medicals. Specific sessions for co-medicals included 5 symposiums, 30 oral presentations, and 318 presentations. Moreover, the meeting offered an open lecture to the public at the Tokyo International Forum, titled “How to Live with Heart Disease”, which included a talk by a famous TV newscaster. The session was attended by 1,180 citizens. In total, the meeting welcomed 191 foreign attendees. Notably, 58% of the oral presentations and 49% of the poster presentations were in English. Several symposiums were organized in collaboration with the American Heart Association, the American College of Cardiology, and the European Society of Cardiology.

To assess the subjects that were most attractive to the attendees, the numbers attending each session were counted. Those requiring more than 80% of the room's capacity are summarized in order of attendance number in [Table](#). Although these data are undoubtedly affected by many factors that make for imprecision (eg, size and location of the room, the schedule, etc), it does suggest what attendees considered to be important questions.

Arrhythmia

Atrial fibrillation (AF) was a major topic of this meeting, as a result of the new JCS guidelines for the pharmacotherapy of AF and the recent emergence of several nonvitamin K antago-

nist oral anticoagulants (OACs). The most popular session on arrhythmia was “The First-Line Therapy for Paroxysmal AF” (Controversy 2). However, there was no definite answer to the question of whether we should select antiarrhythmic drug therapy or pulmonary vein isolation using radiofrequency catheter ablation. The arguments for catheter ablation emphasized 2 core arguments: when conducted by a skillful doctor, catheter ablation is better than drug therapy and lacks the potential risks of antiarrhythmic drug. Conversely, the drug therapy argument focused on the complications of catheter ablation therapy. The session on Controversy 4 concerning whether OAC therapy should be applied to patients with AF at relatively low risk for stroke was equally popular. Most presenters favored OAC therapy in such patients, but stressed the need to consider many factors, including economic ones, before making a decision.

Considering the emergence of new OACs (NOACs), the usage of OACs was another topic of great interest. In Symposium 10, “Prevention and Treatment of Atrial Fibrillation for the Prevention of Cerebral Infarction-Update,” Dr Inoue summarized the results of the J-RHYTHM Registry, which described AF management in the warfarin era. Although Western guidelines have been validated for Japanese patients with non-valvular AF, it may be necessary to lower the target INR levels.¹ In the same session, Dr Akao reported the 1-year follow-up results of the prospective community-based Fushimi AF registry, which suggested that under-use and under-dosing with OACs are major problems.² In Oral Presentation 15, the sub-

Table. Top 10 Popular Organized Sessions at 78th Annual Scientific Meeting of the Japanese Circulation Society

Controversy 5
The Interventional Treatment of Valvular Heart Disease in the Elderly
Plenary Session 6
Cardiovascular Diseases in Diabetes Mellitus: Where are We Now?
Special Lecture 4 (by Christine E. Seidman)
Genetic Causes of Human Heart Disease
Special Lecture 3 (by Peter Libby)
Update on the Pathophysiology of Acute Myocardial Infarction
Controversy 2
The First-line Therapy for Paroxysmal Atrial Fibrillation
Controversy 4
How can We Prevent Ischemic Stroke in Patients with Atrial Fibrillation at Relatively Low Risk?
Controversy 1
Changing Strategy for Treatment Aortic Aneurysm
Symposium 17
New Treatment Methods Expected for Pulmonary Hypertension
Plenary Session 4
Medical Guidelines for the Management of Cardiovascular Diseases and EBM in Japan
Roundtable Discussion 5
How to Use Diuretics in Patients with Acute Decompensated Heart Failure

analysis of these registries suggested that sex does not relate to the risk for thromboembolic events among Japanese non-valvular AF patients, despite female sex being a risk factor in Western guidelines.

Although several NOACs have demonstrated similar or better efficacy and safety when compared with warfarin in global clinical trials, concerns remain. For example, the following questions were discussed: Can we directly extrapolate the results of these trials to patients with nonvalvular AF in Japan? Are there any beneficial biomarkers for monitoring NOACs? How should we perform antithrombotic therapy in AF patients undergoing coronary intervention? Are there ethnic differences in hemorrhagic stroke and bleeding between warfarin and NOACs?

In addition, genetic factors were shown to contribute to AF treatment. A recent meta-analysis of genome-wide association studies for AF has successfully identified 10 genotypes that are susceptible to AF.³ In Featured Research Session 7, Dr Fujii presented the newly developed genotype risk score that is based on these single nucleotide polymorphisms, and reported that the risk score was significantly associated with AF in patients with heart failure (HF).

HF and Heart Implantation

Diuretics, which are frequently used to treat HF patients, have limited evidence of effectiveness for HF. The vasopressin receptor antagonist, tolvaptan, became available more than 3 years ago, and clinical data have accumulated. The Round Table Discussion 5, “How to Use Diuretics in Patients with Acute Decompensated Heart Failure”, was the most popular session on HF. In this session, tolvaptan was reported to be effective for volume control in patients with endstage renal failure undergoing peritoneal dialysis. Moreover, tolvaptan had similar effects and less adverse events when compared with carperitide for acute decompensated HF. Urine osmolality (U-OSM) was proposed as a response determinant for tolvaptan because

the baseline U-OSM and relative decreases in U-OSM after tolvaptan administration had a positive correlation with increased urine volume. In Late-Breaking Cohort Studies 2, Dr Kinugawa reported on the safety and efficacy of tolvaptan in HF patients from an interim post-marketing surveillance conducted as a prospective, multicenter, observational study. Given that this drug is expensive and has a unique functional mechanism, care should be taken when deciding who may benefit from this drug, in terms of both immediate effect and long-term prognosis.

The management of cardiovascular disease is increasingly complex; therefore, the importance of collaboration was emphasized in Symposium 5. An example of cooperation is the Heart Team, which presents medical information and recommendations to patients and families to assist them in deciding on the treatment of choice. For patients with HF, whether heart transplantation is necessary and whether a left ventricular assist device (LVAD) should be implanted are very important decisions. A similar situation arises in other cardiovascular areas, such as cardiac endarterectomy or carotid artery stenting, and in the selection of percutaneous coronary intervention or coronary artery bypass grafting. Another principal area of collaboration in HF treatment would be between cardiologists and cardiac surgeons, and the symposium reported on the practical aspects of collaboration for ventricular assist device therapy in the pre-, peri-, and postoperative care settings.

Topic 5, “The Latest Heart Failure Management for the Oldest-old,” was also popular. As aging of the population advances, it is important to understand the characteristics of HF in the elderly. Previous illnesses and comorbidities are common and the treatment of elderly patients can be long. With the numbers of elderly persons living with only the spouse or alone increasing, community support is not necessarily adequate, and many encounter difficulties with hospital visits and rehabilitation. Based on these factors, we must provide appropriate treatment and establish adequate daily support.

In younger patients, heart transplantation is available. In

Meet the Expert 7, the present state and future of heart transplantation in Japan were reported. Since the Organ Transplantation Law was established in 1997, there have been 185 heart transplantations in Japan. The mean assist duration was reported to be approximately 2.3 years and the mean waiting duration for Status 1 patients was approximately 2.4 years. The primary disease among recipients was dilated cardiomyopathy. The 10-year survival rate is approximately 90%, which is superior to that of the International Society for Heart and Lung Transplantation registry. Despite the severe shortage of donors and the long waiting times on LVAD, the outcomes from heart transplantation in Japan are excellent.

Ischemic Heart Disease (IHD)

The number of popular sessions related to IHD was less than expected in this meeting. Special Lecture 3, titled "Update on the Pathophysiology of Acute Myocardial Infarction", was the most popular session on this topic. Peter Libby talked about the role of inflammation in the pathophysiology of acute myocardial infarction (AMI) and acute coronary syndromes, and described the roles of interleukin-1 β , the matrix metalloproteinase family, tissue factor, and the CD40 ligand. In addition, he argued that hemodynamic conditions of low shear stress may alter the interstitial collagenases. Finally, he mentioned 2 ongoing trials to test whether antiinflammatory therapy could reduce cardiovascular events. The first is the Cardiovascular Inflammation Reduction Trial (CIRT), which uses low-dose methotrexate and the other is the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial, which uses the human monoclonal antibody, canakinumab to selectively neutralizes IL-1 β . If either is effective, it will support the inflammatory hypothesis and provide a novel cytokine-based therapy.

In clinical practice, although fractional flow reserve (FFR) is widely used to estimate whether an intermediate coronary stenosis produces significant myocardial ischemia, there are several unsolved problems. A new technique and strategy for FFR and relative coronary flow reserve were presented in Symposium 1. Over the past decade, stent thrombosis following drug-eluting stent (DES) implantation has been a major topic. In the late-breaking cohort studies 1 session, late catch-up phenomenon of first generation sirolimus-eluting stents relative to bare-metal stents regarding stent thrombosis and target-lesion revascularization was reported from the data of the CREDO-Kyoto registry Cohort-2. In contrast, second-generation DES have been recently shown to have very low incidence of stent thrombosis. Their impact, and the role of novel antiplatelet agents, were reviewed and discussed in Round Table Discussion 3. There is increasing concern that aggressive antithrombotic therapy can increase the risk of stroke in patients with coronary artery disease (CAD), particularly those with elevated systolic blood pressure. In another late-breaking cohort study of patients with CAD registered in the Japanese Coronary Artery Disease study (JCAD) study, antithrombotic therapy was found to have negligible effect on either ischemic or hemorrhagic stroke, if the systolic blood pressure was ≤ 140 mmHg.

Control of Coronary Risk Factors

The number of patients with diabetes mellitus (DM) is increasing, and many unanswered questions were discussed in Plenary Session 6. Glucose fluctuation and insulin resistance were proposed as the primary target for DM treatment in AMI.

Glucose fluctuation, including the daily glucose profile, was also reported to affect coronary plaque vulnerability in patients with CAD who are pretreated with lipid-lowering therapy. In addition, cardiologists expect DM drugs to lower the incidence of cardiovascular events. Although some trials suggested pioglitazone may be promising, this theory was supported in a Japanese randomized trial (The J-DESSERT study), which analyzed patients with DM and CAD after DES implantation. We are expecting new DM drugs to have similar effects. Late-breaking clinical trials reported the new dyslipidemia medication, AMG-145, which is a monoclonal antibody to PCSK9. The Phase II randomized, double-blind, placebo-controlled YUKAWA Study reported that AMG-145 significantly reduced low-density lipoprotein cholesterol compared with placebo and was tolerated in high-risk Japanese patients.

After a series of angiotensin-receptor blockers, no new classes of antihypertensive drugs are due to be released. Therefore, the main topic of Symposium 7, "EBM in Hypertension", focused on the optimal target ranges for blood pressure according to disease, such as type 2 DM, post-AMI, and HF. Topic 11 discussed the unsolved question of renal denervation (RD), which is expected to lower blood pressure. To reduce sympathetic nerve activity, catheter-based renal nerve ablation was performed in a patient with resistant hypertension in 2009.⁴ Furthermore, after this demonstrated clinically relevant blood pressure reduction, subsequent trials have provided further evidence of its safety and effectiveness. In addition, preliminary data obtained from small and uncontrolled studies indicate additional benefits for hypertensive end-organ damage, congestive HF, cardiac arrhythmias, chronic renal failure, insulin resistance, and sleep apnea. However, because those studies did not include a sham-control arm, the Symplicity HTN-3 study was designed to assess the efficacy of RD against controls undergoing a sham procedure. The primary endpoint was any change in systolic blood pressure after 6 months. Unfortunately, just 2 months before this meeting, and despite a lack of safety concerns, this phase 3 study was suspended, having failed to achieve its primary endpoint. Given that RD is available in Europe, the presenter remains hopeful that it may be proven effective. Specifically, it was discussed why this study failed, the purported mechanism of lowering blood pressure, how to assess whether the procedure is sufficient to ablate the nerve, and which patients are most likely to respond to RD.

Valve Disease and Other Diseases

More than 700 people attended the Controversy 5 sessions, titled "The Interventional Treatment of Valvular Heart Disease in the Elderly". To date, no effective drug therapy exists to treat or prevent the progression of aortic stenosis (AS). Though aortic valve replacement is the standard treatment, transcatheter aortic valve implantation (TAVI) has recently become available. Although TAVI has only just been introduced in Japan, it is increasingly popular in Europe because of its relatively less invasive nature. In late-breaking clinical trials 2, Dr Sawa reported on the first clinical trial of a self-expandable transcatheter heart valve in Japanese patients with symptomatic severe AS. In addition, TAVI was the main theme of topic 3, "Forefront of Hybrid Therapy in Cardiac and Vascular Therapy", and Meet the ESC, "TAVI update". Furthermore, transcatheter therapy could be aimed at mitral regurgitation (MR). Although early repair surgery for patients with degenerative MR is advocated, percutaneous transcatheter mitral valve repair may be used in the near future as an alternative for elderly patients with MR and high surgical risk.

Close to 600 attendees participated in symposium 17, “New Treatment Methods Expected for Pulmonary hypertension (PH)”. Several drugs are available to treat PH, but their effects are limited and new drugs or therapeutic strategies are awaited. Proposed salvage therapies for refractory PH included dual phosphodiesterase type 5 inhibitors (sildenafil and tadalafil) or the use of riociguat. Riociguat is an oral, soluble guanylate cyclase stimulator, which acts in synergy with endogenous nitric oxide and directly stimulates guanylate cyclase. Animal experiments suggest that nanoparticle-mediated delivery of prostaglandin I₂ may also be promising. Topic 10 then discussed interventional or surgical treatment. For example, the efficacy of balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic PH was reported. The high incidence of reperfusion pulmonary injury remains unresolved.

Basic Research

Congress Chairperson, Dr Nagai, has contributed to the establishment of chronic inflammation as a concept in cardiovascular research. The Mashimo Memorial Lecture was given by Tadatsugu Taniguchi from the University of Tokyo, and titled “Signaling and Gene Expression for Cytokine Activity in Inflammation and Immunity: Contributions to Medical Science” (Figure 2B). He talked about his research surrounding High-mobility group box protein 1 (HMGB1), which works both as a transcriptional regulator in the nucleus and as an inflammatory cytokine-like molecule when secreted.

Regenerative medicine is a major topic in cardiovascular research. Eric N. Olson from the University of Texas (Southwestern Medical Center, USA), presented “Molecular Control of Heart Development, Disease, and Regeneration” at the Mikamo Lecture (Figure 2C). His research is based on the gene regulatory networks that govern development, disease, and regeneration in the heart. He has identified microRNAs that influence several aspects of cardiac biology, and has discovered several novel cardiac regulatory genes that are important for heart function. Induced pluripotent stem (iPS) cells have several applications in medicine. They could be used as a platform for drug development and screening. In the joint American Heart Association-JCS symposium, iPS cells were discussed as model disease cells. Dr. Furukawa described human iPS cell-derived cardiomyocytes established from a patient with *SCN5A E1784K* mutation. Dr Wu described the human cardiomyocytes derived from iPS cells from a patient with familial hypertrophic cardiomyopathy, while Eric Olson discussed the direct induction of cardiomyocytes without iPS cells by reprogramming fibroblasts involved in heart repair. Dr Shimizu from the Institute of Advanced Biomedical Engineering and Science, Tokyo Women’s Medical University, Tokyo, reported on the results of translational research on cell sheet-based heart tissue reconstructed from iPS cells, and was awarded the Japan Heart Foundation Satoh Memorial Award.

Another important area in cardiovascular research is genomic analysis. Since the genome sequence project was completed, a tremendous amount of information has accumulated about the mutations and genome disorders associated with cardiovascular disease. In Special Session 6, “Advances towards Genomic Medicine,” the cost of genome analysis was presented; in 2001, it took several months and cost ¥10 billion to complete the whole genome sequence, whereas it now takes several hours and costs several hundred thousand Japanese yen. Therefore, large amounts of data can be generated easily, but human resources, super-computers, money, and energy are required to analyze them. Western countries appear to be preparing resources and connecting data with electronic medical records to embrace a “tailored medical era”. However, this is not yet the case in Japan, and the strategy required to apply these genomic analysis to clinical medicine was summarized by Dr Seidman in her keynote lecture in Symposium 22. Discovering the genetic basis of disease may enable us to identify patients prior to overt disease, thereby providing opportunities for intervention that may delay the disease onset or attenuate its severity.

Closing Remarks

The 78th Annual Scientific Meeting of JCS successfully offered future perspectives in cardiology. This report was based on abstracts⁵ and videos of the meeting.

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