Current Treatment Strategies for Coronary Disease in Japan

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Abstract
Despite the remarkable progress in diagnosis and treatment, acute coronary syndrome (ACS) remains an important public health problem demanding much effort from cardiologists.

A comparison of the Japanese and the U.S. guidelines for ACS shows that they differ in the provisions concerning institutional requirements and the skill of persons performing the procedure. If we apply the U.S. guidelines to the situation in Japan, 46.9% of PCI cases are receiving PCI at centers failing to meet the U.S. standards.

While the inclination toward the use of PCI in Japan is considered to expand further, care providers are expected to make self-imposed effort aiming at the establishment of more stringent institutional requirements and further skills accumulation. They should improve the ability to deduce well-balanced conclusions through the process of analyzing actual needs based on the combination of social, basic, and clinical medicine.

Key words Acute coronary syndrome, Acute myocardial infarction, Institutional requirements, Pre-hospital care system, Guidelines, Drug-eluting stent

Introduction
According to the Vital Statistics Report published by the Ministry of Health, Labour and Welfare (MHLW), heart disease was responsible for 152,000 deaths in 2002 in Japan. It was the second most important cause of death representing 15.5% of all deaths.1 The 5th National Survey of Circulatory Disorders indicated that a history of myocardial infarction (MI) was found in 2.4% of males and 1.1% of females, while a history of angina pectoris was found in 3.6% of males and 2.9% of females.2

In the recent analysis of MI patients from the Japanese Coronary Intervention Study, Nishigaki et al.3 of Gifu University reported that the occurrence of MI in Japan (about 52 per 100,000 population) was 4 times lower than that in the U.S. (192 per 100,000 population). The majority of this difference may be due to diet and other acquired factors, in addition to hereditary factors.

Among the various types of heart disease, acute coronary syndrome (ACS) including MI remains the main challenge for cardiologists, although the diagnosis and treatment of ACS have progressed remarkably in recent years by the use of diagnostic imaging, reper-
fusion therapy, and other techniques. The difficulty arises from the facts that ACS shows rapid progression in a very concentrated time span; it requires approaches not only in the area of cardiology but also from emergency medicine, social medicine, and medical economics; and that careful initial assessment and accurate treatment definitely contribute to the survival prognosis of patients.

For these reasons, this review focuses on ACS among other types of coronary disease.

Definition

ACS is defined as a clinical syndrome characterized by acute myocardial ischemia resulting from coronary plaque rupture and thrombosis. It encompasses a wide range of conditions from acute MI and unstable angina to sudden cardiac death.

Coronary Disease Practice in Japan

The geography and health care systems of Japan are important factors in considering ACS in Japan. Japan has a very high population density: 90% of the 127 million people inhabit coastal areas occupying a small proportion of the 378,000-km² national land area. With this densely distributed population, effective emergency care systems have been established under the lead of the government.

In particular, the MHLW and the Fire and Disaster Management Agency, Ministry of Internal Affairs and Communications have been developing a system for providing pre-hospital care. The scope of medical treatment that emergency medical technicians (EMTs) are allowed to perform has been expanded gradually. For example, they have been allowed to perform electrical cardioversion under the general direction of a physician (without specific instruction) since April 2003. Endotracheal intubation has been permitted for EMTs completing schooling and hospital training under the specific instruction of a physician since July 2004. As for drug use, a study on the minimal use of epinephrine and other drugs was conducted to evaluate the efficacy and safety in the use by EMTs, and the government has decided to permit the use of epinephrine by EMTs from April 2006.

The MHLW has been leading the development of primary, secondary, and tertiary emergency care systems organized according to new function-based role sharing. As of March 2005, 176 emergency care centers have been established to provide medical services as tertiary emergency care facilities. Under this system, all Japanese citizens are given unrestricted access to any medical institution under the national health insurance system. A person developing ACS in Japan can visit any appropriate medical institution. At some medical centers, the unit prices of health care cost (drugs and medical supplies) are standardized uniformly according to the Diagnosis Process Combination (DPC) system. This factor is exerting a decisive effect on the behavior of patients.

Treatment Strategies for Coronary Disease

Several sets of guidelines are provided for the management of ACS in Japan. The guidelines for the management of acute MI have been developed by the MHLW study group led by Kanmatsuse. Those for non-ST-segment elevation ACS have been formulated by the joint study group of the Japanese Circulation Society, the Japanese College of Cardiology, the Japan Society for Intervention, the Japanese Coronary Association, the Japanese Association for Thoracic Surgery, the Japanese Society for Cardiovascular Surgery, and the Japanese Society of Intensive Care Medicine.

In the U.S., the American Heart Association (AHA) has established ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction, as well as
Comparison with Other Countries

The treatment strategies for ACS are divided into early invasive treatment and early conservative treatment according to the timing of coronary angiography (CAG) and revascularization. In the early invasive strategy, elective CAG is performed early in all hospitalized cases unless there is a contraindication, and revascularization is performed if indicated. In the early conservative strategy, CAG is selected only in cases that are considered clinically high risk and those experiencing repeated myocardial ischemic attacks despite adequate drug therapy. Thus, the timing of CAG is a major difference between these strategies. No conclusion has been reached as to which of these strategies is better.

As shown in Table 1, there is little difference in primary PTCA in acute MI between the Japanese and American guidelines.

In both countries, the recommendations for Class I conditions specify the following: “In patients with acute MI and ST-segment elevation or new or presumed new left bundle branch block (LBBB) who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist, if performed . . . by persons skilled in the procedure” and supported by experienced personnel in an appropriate laboratory environment.

Table 1: Comparison of Japanese and U.S. guidelines concerning primary PTCA and institutional requirements

<table>
<thead>
<tr>
<th>Primary PTCA</th>
<th>ACC/AHA guidelines for the management of patients with acute myocardial infarction</th>
<th>Guidelines for the diagnosis and treatment of acute myocardial infarction</th>
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<td>As an alternative to thrombolytic therapy in patients with AMI and ST-segment elevation or new or presumed new left bundle branch block who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist, if performed in a timely fashion by persons skilled in the procedure and supported by experienced personnel in an appropriate laboratory environment.</td>
<td>In patients with AMI and ST-segment elevation or new or presumed new left bundle branch block who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist, if performed by persons skilled in PTCA in an appropriate institutional environment (meeting the institutional requirements specified by MHLW).</td>
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Institutional requirements specified by MHLW:
1. A medical institution practicing in cardiovascular medicine.
2. At least 1 full-time physician with 10 or more years of experience in the procedure.
3. At least 1 full-time cardiovascular surgeon with 5 or more years of experience or a partnership with a medical institution employing a physician with such experience.
4. At least 1 full-time clinical engineer.
5. At least 100 cases in the institution per year.
Table 2 Comparison of medical therapies in Japanese and U.S. guidelines

<table>
<thead>
<tr>
<th>Treatment for ventricular tachycardia/ventricular fibrillation</th>
<th>ACC/AHA guidelines for the management of patients with acute myocardial infarction</th>
<th>Guidelines for the diagnosis and treatment of acute myocardial infarction</th>
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<tr>
<td>Class I Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mmHg) should be treated with one of the following regimens: a. Lidocaine. b. Procainamide. c. Amiodarone. d. Synchronized electrical cardioversion starting at 50 J (brief anesthesia is necessary).</td>
<td>Class I 4. Intravenous lidocaine or procainamide for sustained monomorphic VT not associated with angina, pulmonary congestion, or hypotension (systolic blood pressure less than 90 mmHg). 5. Synchronized electrical cardioversion for sustained monomorphic VT not associated with angina, pulmonary congestion, or hypotension (systolic blood pressure less than 90 mmHg) (brief anesthesia is necessary).</td>
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<tr>
<th>Antiplatelet and anticoagulation therapy</th>
<th>ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction</th>
<th>Guidelines for the management of acute coronary syndrome</th>
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<tr>
<td>● Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of evidence: A) ● In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of evidence: A), and for up to 9 months. (Level of evidence: B) ● In patients for whom a PCI is planned and who are at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (Level of evidence: A), and for up to 9 months. (Level of evidence: B)</td>
<td>● Chewable aspirin 162 to 325 mg should be administered as soon as possible, followed by long-term administration of 50 to 100 mg. ● Ticlopidine should be administered to patients who are unable to take aspirin.</td>
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Reimbursement standards of Japan, a center performing PTCA must have at least 1 full-time physician with 10 or more years experience and there must be at least 100 cases operated on at the center per year. There are no requirements concerning the skill of physicians and the number of cases operated on by each physician. On the other hand, the guidelines in the U.S. provide for specific numerical requirements that each physician must have experienced 75 or more cases of PTCA and each center must be performing 200 or more cases of PTCA per year.

Another difference between the Japanese guidelines and the AHA guidelines relates to arrhythmia. The Japanese guidelines do not indicate amiodarone for ventricular tachycardia and ventricular fibrillation (Table 2) because intravenous amiodarone is not provided for under the national health insurance. Nifekalant, a K ion channel blocker of Japanese origin, is already covered by the national health insurance, and this drug may appear in the Japanese guidelines ahead of Western countries after further accumulation of evidence.

In addition, the Japanese guidelines do not contain clopidogrel as an antiplatelet drug (Table 2). Like amiodarone, this drug is not provided for under the national health insurance. Since clopidogrel acts more quickly than ticlopidine and has a better safety profile, it is the first-choice drug among thienopyridine derivatives in the U.S.
Because ticlopidine causes granulocytopenia as a serious adverse effect, clopidogrel should be covered by the Japanese national health insurance as soon as possible.

**PTCA or CABG**

In the above-mentioned guidelines, recommendations concerning emergency or urgent bypass graft for Class I conditions differ little between Japan and the U.S. These are: “Failed angioplasty with persistent pain or hemodynamic instability,” “AMI with persistent or recurrent ischemia refractory to medical therapy in patients . . . who are not candidates for catheter intervention,” and “Postinfarction ventricular aneurysm associated with intractable ventricular tachyarrhythmias and/or pump failure.” A notable difference is found in the recommendations for Class III (conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful). While the AHA guidelines only state, “When the expected surgical mortality rate equals or exceeds the mortality rate associated with appropriate medical therapy,” the Japanese guidelines contain the following: “When PTCA has failed but reperfusion is impossible because of a no-flow condition,” “In the case of reperfusion beyond 12 hours of an ST-segment elevation (Q-wave) infarction without ongoing ischemia,” and “When the expected surgical mortality rate equals or exceeds the mortality rate associated with appropriate medical therapy.”

It is often pointed out that percutaneous coronary intervention (PCI) is performed much more frequently than coronary artery bypass graft (CABG) in Japan, while the difference is smaller in Western countries. According to the above-mentioned nationwide survey on coronary intervention performed in 2000, reported by Nishigaki et al., in 2003, there were 543,046 cases of CAG (428 per 100,000 population), 146,992 cases of PCI (116 per 100,000 population), and 23,584 cases of CABG (19 per 100,000 population) performed in Japan. The corresponding figures in the U.S. were 1,318,000 cases of CAG (468 per 100,000 population), 561,000 cases of PCI (199 per 100,000 population), and 519,000 cases of CABG (184 per 100,000 population) (Table 3). Because the prevalence of coronary artery disease (CAD) per 100,000 population was 4,584 in the U.S. versus 3,199 in Japan (data for 2000), the fraction of CAD cases receiving CAG was 1.4 times higher in Japan than in the U.S.

In Japan, 59.8% of the medical centers performing PCI were each performing less than 100 cases of PCI per year, and 20.9% of all PCI cases in Japan received PCI at such centers. Furthermore, 46.9% of PCI cases received this procedure at centers performing less than 200 cases of PCI per year.

Only 20.7% received PCI at the centers performing 400 or more cases of PCI per year.

With respect to the number of centers performing these procedures, the data from

<p>| Table 3 Number of coronary intervention cases in Japan and the U.S. in 2000 |
|------------------------------|------------------|------------------|------------------|------------------|
|                              | Japan            | United States    |
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this survey and those from a similar questionnaire survey conducted by Takeshita et al. in 1997 indicate that the number of centers performing PCI increased from 1,023 to 1,240, and those performing CABG increased from 486 to 581.

While CABG was performed in over 20,000 patients in the year, 91.7% of the centers performing CABG were each performing less than 100 cases of CABG per year, and as many as 71.2% of all CABG cases in Japan received CABG at such centers. The centers performing less than 50 cases of CABG per year represented 70.9% of the centers performing CABG and 37.2% of the patients receiving this procedure. The ratio of PCI to CABG was as high as 6.23 in overall average. It was “0 to 3” in 30% of centers, “3 to 5” in 20%, “5 to 8” in 23%, and “8 or more” in 27%. Larger numbers indicate a stronger bias toward the use of PCI relative to CABG. About 60% of centers were performing more CABG than PCI.

These data indicate that about half of patients with acute coronary disease in Japan are receiving PCI at centers that are performing less than 200 cases per year, failing to meet the AHA standards, and 91.7% of CABG cases are performed at centers treating less than 100 cases. This fact suggests the direction that should be pursued in future cardiovascular practice.

Although PCI is used actively for left main trunk (LMT) disease in Japan, a survey by Nishida showed that the mortality rate associated with elective PCI for LMT disease is significantly higher than that associated with CABG. Unfortunately, there has been no move to correct this perturbing situation.

Nishida et al. remarked, “While surgeons work with CABG and cardiologists work with PCI toward improvement of techniques and outcomes, they lack sufficient information exchange concerning the selection of treatment methods both at the level of individual hospitals and at the level of academic societies.” We need to promote closer communication among cardiologists and surgeons in order to realize better demarcation based on objective data.

**Toward Further Skill Accumulation**

While PCI and CABG are performed at many centers in Japan, 46.9% of PCI cases are performed at centers treating less than 200 cases, failing to meet the AHA standards, and 91.7% of CABG cases are performed at centers treating less than 100 cases. This fact suggests the direction that should be pursued in future cardiovascular practice.

In the present system, a patient developing coronary disease anywhere in Japan is sent to the nearest secondary care center on a free (uncontrolled) access basis. After the emergency room physician makes diagnosis of coronary disease, PCI, CABG, or other treatment is given, if the center is capable of performing the needed procedure. If not, arrangements are made for transporting the patient to a center with the necessary facilities.

The free access system may seem ideal, but it could end in loss of life, if the patient is sent to a center with little experience and insufficient technical skill. In fact, about half of the medical centers in Japan are deficient in skill according to the AHA guidelines. Ideal emergency cardiovascular care should begin with effective pre-hospital care. In our opinion, emergency personnel in the ambulance should be able to conduct initial triage, judge the presence of coronary disease, and transport the patient to a center treating a sufficient number of PCI or CABG cases with highly experienced, skilled physicians.

To this end, we need to build on the current efforts to develop the medical control system, to improve the abilities of EMTs such as advanced cardiovascular life support (ACLS), and to reinforce pre-hospital care systems in communities. On the side of health care providers, we need to continue further development of the guidelines both for PCI
and CABG, incorporating more stringent institutional requirements and establishing the potential for skill accumulation.

**Final Remarks and Remaining Problems**

As discussed above, the treatment selection for ACS in Japan is too biased toward the use of PCI. A new type of stent called drug-eluting stent (DES)\(^{12}\) came into clinical use recently, and was popularized quickly to be employed in over 70% of cases nationwide within months of introduction. We do not discuss the merits and demerits of this treatment here, but this device has the potential to intensify the excessive use of PCI. In addition, the antiplatelet agent used in Japan is ticlopidine hydrochloride, because clopidogrel has not been approved. Almost nothing is known about the short- and long-term outcome of ticlopidine hydrochloride administration in patients receiving DES, and the results of data analysis from DES patient registration in Japan (e.g., J-cypher) are awaited. This drug causes granulocytopenia as a serious adverse effect, which poses an important problem for clinicians in terms of patient’s safety.

On the other hand, the widespread use of DES and the further development of diagnostic imaging are expected to decrease the need for invasive CAG for follow-up purposes. This should be good news for patients.

Finally, patients with ACS in Japan are more frequently complicated with diabetes than those in Western countries, as a result of the genetic predisposition of the Japanese people. This fact is extremely important from the standpoint of prophylaxis.

Cardiologists and cardiac surgeons in Japan should not simply depend on the advancement of treatment methods and uncritically adopt the newest therapies. Rather, they should develop the ability to deduce well-balanced conclusions through the process of analyzing the actual needs based on the combination of social medicine, basic medicine, and clinical medicine.

**References**