Rationale and Design of a Large-Scale Trial Using Atrial Natriuretic Peptide (ANP) as an Adjunct to Percutaneous Coronary Intervention for ST-Segment Elevation Acute Myocardial Infarction

— Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by ANP (J-WIND-ANP) —

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Background The benefits of percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI) are limited by reperfusion injury. In animal models, atrial natriuretic peptide (ANP) reduces infarct size, so the Japan-Working groups of acute myocardial infarction for the reduction of Necrotic Damage by ANP (J-WIND-ANP) designed a prospective, randomized, multicenter study, to evaluate whether ANP as an adjunctive therapy for AMI reduces myocardial infarct size and improves regional wall motion.

Methods and Results Twenty hospitals in Japan will participate in the J-WIND-ANP study. Patients with AMI who are candidates for PCI are randomly allocated to receive either intravenous ANP or placebo administration. The primary end-points are (1) estimated infarct size (creatinine kinase and troponin T) and (2) left ventricular function (left ventriculograms). Single nucleotide polymorphisms (SNPs) that may be associated with the function of ANP and susceptibility of AMI will be examined. Furthermore, a data mining method will be used to design the optimal combinational therapy for post-MI patients.

Conclusions J-WIND-ANP will provide important data on the effects of ANP as an adjunct to PCI for AMI and the SNPs information will open the field of tailor-made therapy. The optimal therapeutic drug combination will also be determined for post-MI patients. (Circ J 2004; 68: 95–100)

Key Words: Acute myocardial infarction; Atrial natriuretic peptide; Data mining; Randomized clinical trial; SNPs

Reperfusion of the ischemic myocardium by percutaneous coronary intervention (PCI) reduces the size of the infarct and improves left ventricular function, both of which contribute to an improved clinical outcome for patients with acute myocardial infarction (AMI).^{1–3} However, in some patients who undergo reperfusion therapy, reperfusion per se adversely leads to tissue damage known as reperfusion injury.⁴ Several clinical trials targeting the prevention or reduction of reperfusion injury are now in progress^{5,6} and atrial natriuretic peptide (ANP) is

a promising candidate for an adjunctive therapy for AMI because it can suppress the renin–angiotensin–aldosterone system and endothelin-1, both of which modulate cardiac remodeling.^{7,8} In the clinical setting, however, the beneficial effects of nicorandil have been tested in single center studies only and the number of patients has been relatively small.^{9,10} Thus, larger multicenter studies are needed to assess whether the effects of ANP can translate into clinical benefits. Japan-Working groups of acute myocardial infarction for the reduction of Necrotic Damage by ANP (J-WIND-ANP) is a prospective, randomized, multicenter study designed to evaluate the beneficial effects of ANP as an adjunctive therapy for AMI. In the J-WIND-ANP, in addition to examining the effects of ANP treatment on clinical outcomes, including infarct size and left ventricular regional function, the association between single nucleotide polymorphisms (SNPs) of genes that may potentially influence either ANP function or the metabolism of ANP and the responsiveness of ANP therapy is also analyzed. Further, by comparing the prevalence of SNPs of genes that may influence the occurrence of AMI between normal subjects and AMI patients enrolled in J-WIND-ANP, we

(Received July 8, 2003; revised manuscript received October 21, 2003; accepted November 26, 2003)

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Table 1 Inclusion Criteria for J-WIND-ANP

1. Age 20–79 years
2. Chest pain of more than 30 min
3. 0.1 mV ST-segment elevation in 2 contiguous ECG leads
4. Admission to hospital within 12 h of symptom onset
5. First episode of AMI

Table 2 Exclusion Criteria for J-WIND-ANP

1. History of old myocardial infarction
2. Left main coronary artery stenosis
3. Severe liver and/or kidney dysfunction
4. Suspected aortic dissection
5. History of coronary artery bypass graft
6. History of allergic response to drugs
7. Severe hypovolemia
8. Right ventricular infarction

Table 3 Cessation Criteria for J-WIND-ANP

1. Patient's decision to cease attending the study
2. Prolonged hypotension
3. Difficulty in continuing the study because of an adverse event
4. Patient who does not match the inclusion criteria after registration
5. Patient who meets exclusion criteria after registration

can genetically predict the patient population that has the highest risks of AMI.

In conjunction, we plan to use a data mining method to determine the best therapeutic combination for decreasing the risk for cardiac events in patients with post-myocardial infarction (MI) because this method is useful for discovering combinational information from a database that is too large for traditional statistical methods.^{12,13} In the most recent clinical studies, the effects of single medication on the end-points have been assessed with no consideration of the effects of the drug combination. In addition, by examining SNPs information of the genes that may affect pharmacodynamics and the association rules of therapeutic combination with clinical outcomes, we should be able to provide important information for 'tailor-made' therapy of post-MI patients.

Methods

Study Population

Patients are eligible when all the inclusion criteria are fulfilled (Table 1). The exclusion and cessation criteria are listed in Tables 2 and 3, respectively. All patients sign written informed consent twice: immediately after hospitalization and a few weeks later when patients could decide on study participation under less urgent conditions. The principal investigator of each participating hospital will be in charge of the written informed consent forms (Appendix 1). The patients registered in the J-WIND-ANP are not able to participate in other clinical studies. Patients enrollment started on 31 October 2001, and will continue until 30 September 2005. Enrolled patients will be followed until 30 September 2007.

Protocol (Fig 1)

Immediately after the diagnosis of AMI, patients are randomly assigned to either an ANP or saline group by means of sealed envelopes containing the randomization schedule that was generated by computer before the beginning of the study. Randomization blocks are prepared for each participating hospital. The physicians responsible for giving the treatment are unaware of the randomization schedule. We adopted the envelope method instead of central randomization for the following reasons.

(1) It is not unusual for AMI patients not to be registered on the Web if the hospital presentation is an emergency, especially around midnight.

(2) There are some hospitals where physicians can not easily access the Web in the emergency room.

In the ANP group, ANP is continuously infused intravenously at $0.025 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 3 days. In the control group, 5% glucose solution is continuously infused at the corresponding dose in the same manner. Accordingly, most patients enrolled in J-WIND-ANP start to receive ANP before recanalization. The study protocol does not restrict or specify any other diagnostic or therapeutic strategies, including the recanalization method such as percutaneous transluminal coronary angiography or thrombolytic therapy. Blood samples for creatine kinase (CK) and CK-MB measurements are drawn before the procedure and at 1, 2, 6, 9, 12, 18, 24, 36, 48 and 72 h after reperfusion.¹⁴ Troponin T is measured 15 and 96 h after symptom onset. The right anterior oblique views of left ventriculogram (LVG) are

Fig 1. Overview of the J-WIND-ANP protocol. (White box) ANP administration; (Black box) CK measurement.

Table 4 Drug List for Data Mining

Angiotensin converting enzyme inhibitors:				
Cilazapril	Temocapril hydrochloride	Perindopril erbumi		
Imidapril hydrochloride	Enalapril maleate			
Others: _____ dose ____ mg				
Angiotensin II type I receptor antagonists:				
Valsartan	Candesartan cilexetil	Losartan potassium		
Others: medication _____ dose ____ mg				
Statins:				
Pravastatin sodium	Atorvastatin calcium	Simvastatin		
Fluvastatin sodium				
Others: _____ dose ____ mg				
Ca channel blockers:				
Nifedipine	Benidipine hydrochloride	Amlodipine besilate		
Others: _____ dose ____ mg				
-blockers:				
Carvedilol	Celiprolol hydrochloride	Metoprolol tartrate	Bisoprolol fumarate	
Others: medication _____ dose ____ mg				
Anti-platelet drugs:				
Aspirin	Ticlopidine hydrochloride	Cilostazol		
Others: _____ dose ____ mg				
Diuretics:				
Spironolactone	Azosemide	Furosemide		
Others: _____ dose ____ mg				
Nitrates:				
Isosorbide mononitrate	Nitorol-R	Frاندol	Nitroglycerin	
Others: _____ dose ____ mg				
Inotropic agents:				
Pimobendan	Digitalis	Docarpamine		
Others: _____ dose ____ mg				
Adenosine re-uptake inhibitor:		KATP channel opener:		
Dipyridamole	_____ mg	Nicorandil	_____ mg	
Anti-arrhythmic agents:				
Amiodarone	Pilsicainide	Propafenone	Mexiletine	
Disopyramide				
Others: _____ dose ____ mg				
Anti-diabetic agents:				
Glimicron	Euglucon	Voglibose	Acarbose	
Pioglitazone				
Others: _____ dose ____ mg				
Other medication:				
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analyzed in the acute phase and approximately 1 month later (2–6 weeks). End-diastolic volume and ejection fraction are measured by the area–length method. The regional wall motion (standard deviation per chord) of the area of the targeted artery is analyzed with the centerline method.¹⁵ Two angiographers who are unaware of the patients' allocation independently analyze the cinefilms.

After the completion of intensive care for AMI, patients are treated with cardiovascular drugs. We ask the participating physicians to select from the drugs listed in Table 4 in order to limit the number of drugs to be included in the data mining. Furthermore, once the drugs for each patient are decided, we ask the physicians not to change them for 2 years unless the patient's condition dictates a revision of therapy. By finding the association rules between the effectiveness of a set of treatments and clinical outcomes in patients with post-MI, we can identify the optimal therapeutic combination for these patients.

A blood sample for SNPs is drawn before discharge from patients with signed written informed consent. After extraction of the DNA of the sample, SNPs will be examined for the targeted genes that (1) influence the occurrence of AMI, (2) modulate the function and/or metabolism of

nicorandil, and (3) affect the pharmacological dynamics of the drugs listed in Table 4. The protocol of the J-WIND-ANP, including SNPs analysis, has been approved by the institutional review board and ethical committees of all hospitals involved. A counseling system to respond to the questions and requirements of the registered patients about the gene analysis has been established in the National Cardiovascular Center.

End-Points

The primary end-points are (1) estimated infarct size and (2) left ventricular function (left ventricular ejection fraction and end-diastolic volume) and regional wall motion. The infarct size is estimated by two methods: the area under the curve (AUC) of CK (and CK-MB) and a single measurement of troponin T.¹⁴ Left ventricular function and regional wall motion are evaluated by LVG that is performed at the time of hospital admission and 2–6 weeks later.¹⁵ The secondary end-points are (1) survival rate, (2) cardiovascular events (ie, cardiac death, nonfatal re-infarction, re-hospitalization because of cardiac disease, revascularization), (3) reperfusion injury (ie, malignant ventricular arrhythmia during reperfusion periods, re-elevation of ST-

segment, worsening of chest pain), and (4) the association of SNPs of ANP-related genes with response to ANP treatment. SNPs of genes that may influence the occurrence of AMI are compared between patients enrolled in J-WIND-ANP and normal subjects. In addition, the optimal combination of therapeutic drugs to treat patients post-MI will be retrospectively surveyed by data mining. Clinical characteristics and medication during the follow-up period must be reported to the J-WIND-ANP Data and Safety Committee at 3, 6, 12 and 24 months after registration.

Safety

The Safety and Data Monitoring Committee, comprising 3 physicians and a statistician not involved in the conduct of the trial, monitors all adverse events. Furthermore, research nurses visit the participating hospitals to check that the registration, administration of drugs and data collection are correctly performed according to the protocol. Interim analyses of study data will be performed when approximately 20%, 40%, and 60% of the expected number of patients have been enrolled. The committee members do not communicate any results to the Steering Committee, unless discontinuation of the study is recommended.

Sample Size

A previous single center study demonstrated that intravenously administered ANP decreased the peak CK value by 20% compared with placebo,⁹ although this value did not reach significance because of the small number of patients and large standard deviation. The estimated percent reductions in CK are 20% in the ANP treatment group and the standard deviation will be 5-fold larger than the mean value (>100%). There will be no changes in CK in the placebo group. To detect statistically significant differences with 80% power and with $\alpha=0.05$, a total of 600 patients (300 patients per group) is required as $p=0.021$ with 10% dropout.

SNPs

It has been suggested that common genetic variants, such as SNPs, may influence the effectiveness of pharmacological therapy and patient susceptibility to disease.¹⁶ In the J-WIND-ANP, genotype distribution will be analyzed among the patients with ANP treatment and will be compared between normal subjects and AMI patients, using SNPs of genes that may modulate the functions of ANP and that may affect the metabolism of ANP in the patients. The association of SNPs of targeted genes with patient responsiveness to ANP treatment will be examined in patients by comparing them with normal subjects. Furthermore, the SNPs of genes that may influence the occurrence of AMI will be investigated in AMI patients by comparing them with normal subjects. The SNPs information of the control subjects comes from the data base of Japanese SNP (JSNP: <http://snp.ims.u-tokyo.ac.jp/index.html>) officially opened in Japan. Finally, we will also assess the association of clinical outcomes with therapeutic drug combination in regard to the drug-related SNPs, such as SNPs of calcium-channel-related genes for calcium channel blockers. We have a list of ANP-related, infarct-related, and drug-related genes, but because of the sensitive nature of the information, including patents for SNPs analysis, we are unable to disclose it.

Data Management

Data for CK and the LVG cinefilms are collected by Koteisyo-kyokai (Tokyo), the organization established by the Japanese government for promoting large-scale clinical trials of Medical Frontier Strategy Research using Health and Labor Sciences Research Grants. Koteisyo-kyokai helps to manage the randomization, registration, data collection, and data analysis of the patients in the J-WIND-ANP. We also established a system that completely protects the private information of patients who agreed to SNPs analysis. In brief, the blood sample is labeled with a temporal code provided from the J-WIND office, and then it is sent to SRL where the DNA is extracted from the sample. From SRL, the sample is sent to the Individual Data Manager in the National Cardiovascular Center. The manager replaces the temporal code with an anonymous one and the samples are then analyzed by the HuBIT company. The SNPs data from HuBIT for the samples labeled with an anonymous code are strictly managed by the Individual Data Manager; however, the Individual Data Manager can never link the patients and their SNPs information. We have restricted the use of SNPs information to those specific aims described in the informed consent. DNA from patients is discarded after completion of the analysis.

Statistical Analysis

Continuous variables are reported as means and standard deviations. Because the primary end-points are comparing (1) infarct size estimated by the AUC of CK (and CK-MB) and by troponin T, and (2) the improvement in the regional wall motion scores evaluated by LVG in the AMI patients with and without ANP treatments, a two-tailed Student's *t* test for unpaired data will be used. All significant tests will be 2-sided, with type I error rate $\alpha=0.05$. Survival rates and cardiac events will be analyzed by survival analysis. For each clinical event outcome, the variable for analysis will be the time period between the beginning of the treatment and the first occurrence of the event of interest. Event rates in the placebo and ANP-treated groups are compared by the log-rank test. These analyses will be done on an intention-to-treat basis. Worsening of anginal status is defined as a worsening of at least one class in the Canadian Cardiovascular Society Foundation classification of angina. Relative frequencies of reperfusion injury (malignant ventricular arrhythmia during reperfusion periods, re-elevation of ST-segment, worsening of chest pain) are compared by chi-square test.

For the analysis of SNPs, genotype distributions is analyzed among the patients in the ANP treatment group, and between normal subjects and AMI patients. Multiple logistic linear regression analysis is used to show the genotype distributions between the groups, and the adjusted odds ratios and their 95% confidence intervals will be calculated. Genotypes that may affect pharmacological dynamics will be also analyzed in patients enrolled in the J-WIND-ANP. The prevalence of genotypes will be expressed as percentage and will be analyzed by chi-square test.

Traditional statistical analysis cannot work with a database of observations consisting of clinical information and data mining is used in such cases.^{12,13} It is currently being used in a number of other industries, such as financial and chemical companies. Essentially, this method identifies the association rules and patterns that reveal the relationship

among different items. The patterns investigated can be patient characteristics, medication used, and patient outcomes. Once the patterns have been validated, the results can be used to develop decision trees for patient care. The data mining method is especially useful for finding trends in drug interactions. In the case of J-WIND-ANP, we will generate for each patient a set of all medications administered and the clinical outcome, and by applying data mining, we can assess the association rules indicating relationships between medication and clinical outcome.

Funding Source

J-WIND-ANP is supported by Grants for Comprehensive Research on Aging and Health (H13-21seiki (seikatsu)-23) in Health and Labour Sciences Research from the Ministry of Health, Labour and Welfare, Japan. The ANP used in J-WIND-ANP is provided from the J-WIND office to the participating hospitals. The patients registered in the study do not pay extra cost to participate. The study is designed, conducted, analyzed, and interpreted by the investigators entirely independent of all funding sources.

Conclusion

The results of J-WIND-ANP will provide important data on the effects of ANP as an adjunct to PCI for AMI patients. Furthermore, by analyzing the SNPs of genes associated with the responsiveness to ANP therapy, the occurrence of AMI, and pharmacological dynamics, tailor-made therapy for patients post-MI will be established. Finally, the first application of data mining to a cardiovascular trial will discover the optimal therapeutic combination for post-MI patients. The broad range of data obtained by J-WIND-ANP will allow comprehensive assessments of the potential benefits of ANP, tailor-made therapy and optimal therapeutic combinations for patients post-MI.

Acknowledgments

This study is supported by Grants on Comprehensive Research on Aging and Health (H13-21seiki (seikatsu)-23) in Health and Labour Sciences Research from Ministry of Health, Labour and Welfare, Japan.

We thank Ms Yukiko Hanemoto, Satomi Ihara, Etsuko Fukuda, Megumi Yokoi, Ayako Kameda, Hiroko Kawakita and Masami Yokoyama for their excellent assistance. We also thank Drs Hitonobu Tomoike, Soh-ichiro Kitamura and Kunio Miyatake at National Cardiovascular Center and Masatsugu Hori at Osaka University Graduate School for their encouragement and support.

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Appendix 1

The following investigators and institutions are participating in the J-WIND-ANP study.

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