Circ J 2004; **68:** 95–100

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) ——

Masanori Asakura, MD; Kim Jiyoong, MD*; Tetsuo Minamino, MD**; Yasunori Shintani, MD†; Hiroshi Asanuma, MD†; Masafumi Kitakaze, MD*; the J-WIND Investigators

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 (Σcreatine 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 nariuretic 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 nariuretic 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)

*Research Fellow of the Japan Society for the Promotion of Science for Young Scientists, *Cardiovascular Division of Medicine, National Cardiovascular Center, **Research Resident of Japan Foundation for Aging and Health for Medical Frontier Strategy Research by Health and Labor Sciences Research Grants and †Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Suita, Japan*

Mailing address: Masafumi Kitakaze, MD, PhD, Cardiovascular Division of Medicine, National Cardiovascular Center, Suita 565-8565, Japan. E-mail: kitakaze@hsp.ncvc.go.jp

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 groupby 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 $0.025\,mg \cdot kg^{-1} \cdot min^{-1}$ 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

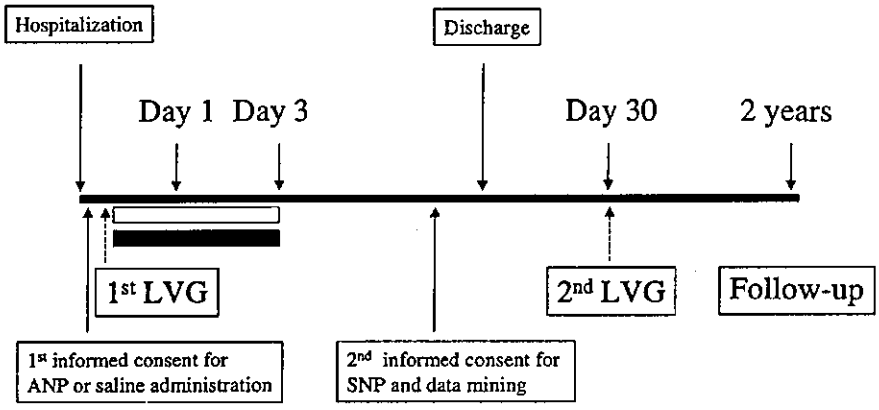

Fig 1. Overview of the J-WIND-ANP protocol. (White box) ANP administration; (Black box) CK measurement.

Table 4 Drug List for Data Mining

Angiotensin converting enzyme inhibiters:
☐ *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*
β-blockers:
☐ *Carvedilol* ☐ *Celiproolol 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* ☐ *Frandol* ☐ *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:

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? although this value did not reach significance because of the small number of patients and large standard deviation. The estimated percent reductions in ΣCK 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 ΣCK in the placebo group. To detect statistically significant differences with 80% power and with α=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![6] 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 α=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 groupsare 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.

References

1. Primary Angioplasty in Myocardial Infarction Study Group (Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al). A comparison of immediate angioplasty with thrombolytic therapy for myocardial infarction. *N Engl J Med* 1993; **328:** 673–679.
2. Sakurai K, Watanabe J, Iwabuchi K, Koseki Y, Kon-No Y, Fukuchi M, et al. Comparison of the efficacy of reperfusion therapies for early mortality from acute myocardial infarction in Japan. *Circ J* 2003; **67:** 209–214.
3. Lamas GA, Flaker GC, Mitchell G, Smith SC Jr, Gersh BJ, Wun CC, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. *Circulation* 1995; **92:** 1101–1109.
4. Verma S, Fedak PW, Weisel RD, Butany J, Rao V, Maitland A, et al. Fundamentals of reperfusion injury for the clinical cardiologist. *Circulation* 2002; **105:** 2332–2336.
5. Jonassen AK, Aasum E, Riemersma RA, Mjos OD, Larsen TS. Glucose-insulin-potassium reduces infarct size when administered during reperfusion. *Cardiovasc Drugs Ther* 2000; **14:** 615–623.
6. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000; **101:** 2154–2159.
7. Cody RJ, Atlas SA, Laragh JH, Kubo SH, Covit AB, Ryman KS, et al. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. J Clin Invest. 1986; **78:** 1362–1374.
8. Emori T, Hirata Y, Imai T, Eguchi S, Kanno K, Marumo F. Cellular mechanism of natriuretic peptides-induced inhibition of endothelin-1 biosynthesis in rat endothelial cells. *Endocrinology* 1993; **133:** 2474–2480.
9. Hayashi M, Tsutamoto T, Wada A, Maeda K, Mabuchi N, Tsutsui T, et al. Intravenous atrial natriuretic peptide prevents left ventricular remodeling in patients with first anterior acute myocardial infarction. *J Am Coll Cardiol* 2001; **37:** 1820–1826.
10. Kuga H, Ogawa K, Oida A, Taguchi I, Nakatsugawa M, Hoshi T, et al. Administration of atrial natriuretic peptide attenuates reperfusion phenomena and preserves left ventricular regional wall motion after direct coronary angioplasty for acute myocardial infarction. *Circ J* 2003; **67:** 443–448.
11. Kikuchi M, Nakamura M, Suzuki T, Sato M, Takino T, Hiramori K. Usefulness of carperitide for the treatment of refractory heart failure due to severe acute myocardial infarction. *Jpn Heart J* 2001; **42:** 271–280.
12. Fukuzawa S, Ozawa S, Inagaki M, Shimada K, Sugioka J, Tateno K, et al. Nicorandil affords cardioprotection in patients with acute myocardial infarction treated with primary percutaneous transluminal coronary angioplasty: Assessment with thallium-201/iodine-123 BMIPP dual SPECT. *J Nucl Cardiol* 2000; **7:** 447–453.
13. Kobayashi Y, Goto Y, Daikoku S, Itoh A, Miyazaki S, Ohshima S, et al. Cardioprotective effect of intravenous nicorandil in patients with successful reperfusion for acute myocardial infarction. *Jpn Circ J* 1998; **62:** 183–189.
14. Doddi S, Marathe A, Ravi SS, Torney DC. Discovery of association rules in medical data. *Med Inform Internet Med* 2001; **26:** 25–33.
15. Bate A, Lindquist M, Edwards IR, Orre R. A data mining approach for signal detection and analysis. *Drug Saf* 2002; **25:** 393–397.
16. Christenson RH, Vollmer RT, Ohman EM, Peck S, Thompson TD, Duh SH, et al. Relation of temporal creatine kinase-MB release and outcome after thrombolytic therapy for acute myocardial infarction: TAMI Study Group. *Am J Cardiol* 2000; **85:** 543–547.
17. Sheehan FH, Schofer J, Mathey DG, Kellett MA, Smith H, Bolson EL, et al. Measurement of regional wall motion from biplane contrast ventriculograms: A comparison of the 30 degree right anterior oblique and 60 degree left anterior oblique projections in patients with acute myocardial infarction. *Circulation* 1986; **74:** 796–804.
18. Deschepper CF, Boutin-Ganache I, Zahabi A, Jiang Z. In search of cardiovascular candidate genes: Interactions between phenotypes and genotypes. *Hypertension* 2002; **39:** 332–336.

Appendix 1

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

Principal Investigator

Masafumi Kitakaze, National Cardiovascular Center.

Steering Committee

Tetsuo Minamio, Research Resident of Japan Foundation for Aging and Health for Medical Frontier Strategy Research by Health and Labor Sciences Research Grants; Kim Jiyoong, National Cardiovascular Center; Masanori Asakura, Research Fellow of the Japan Society for the Promotion of Science for Young Scientists; Yasunori Shintani, Osaka University Graduate School of Medicine; Hiroshi Asanuma, Osaka University Graduate School of Medicine.

Safety and Data Monitoring Committee

Kazuhiro Sase, National Cardiovascular Center, Yukihiro Koretsune, Hideo Kusuoka, National Osaka Hospital, Takashi Washio, Osaka University Graduate School of Technology.

Individual Data Manager

Akiko Ogai, National Cardiovascular Center.

J-WIND Investigators

Principal investigators in the hospitals are indicated with asterisks.

Division of Cardiology, Tokuyama Central Hospital, Tokuyama, Yamaguchi: Takahiro Iwami, *Hiroshi Ogawa; Division of Cardiology, Department of Medicine, National Cardiovascular Center, Suita city, Osaka: Satoshi Yasuda, *Shunichi Miyazaki; Department of Cardiology, Hyogo Brain and Heart Center at Himeji, Himeji city, Hyogo: Junya Shite, *Teishi Kajiya; Division of Cardiology, Shinbeppu Hospital, Beppu city, Ohita: Hidenori Tanaka, *Natsuki Nakamura; Division of Cardiovascular Center, Kumamoto National Hospital, Kumamoto-city, Kumamoto: *Fujimoto Kazuteru; Division of Cardiology, Kawasaki Medical School, Kurashiki city, Okayama: Shuichiro Kaji, *Takashi Akasaka; The Depart-

ment of Internal Medicine, Cardiovascular Division, Hyogo College of Medicine, Nishinomiya city, Hyogo: Motomaru Masutani, *Tadaaki Iwasaki; Division of Cardiology, Osaka Prefectural Hospital, Osaka city, Osaka: Mitsutoshi Asai, *Moritake Hoki; Department of Cardiology, Uwajima City Hospital, Uwajima, Ehime: Jiroh Komatsu, *Kouki Watanabe; Divison of Cardiology, Fukuyama Cardiovascular Hospital, Fukuyama, Hiroshima: Seiichi Haruta, *Hiroki Kohno; Intensive Care Unit, Chiba Hokusoh Hospital, Nippon Medical School, Inba-gun, Chiba: *Noritake Hata; Internal Medicine Second Division, Surugadai Nihon-University Hospital, Chiyoda-ku, Tokyo, Ken Nagao, *Katsuo Kanmatsuse; Department of Cardiology, Akane Foundation Tsuchiya General Hospital, Naka-Ku, Hiroshima: Hironori Ueda, *Yasuhiko Hayashi; The Division of Cardiology, Tohsei National Hospital, *Hiroyuki Yokoyama; Department of Cardiovascular Medicine, Kumamoto University School of Medicine, Kumamoto-city, Kumamoto: Michihiro Yoshimura, *Hisao Ogawa; Cardiovascular Division, Osaka Police Hospital, Osaka city, Osaka: Atsushi Hirayama, *Kazuhisa Kodama; Division of Cardiology, Yokohama City University Medical Center, Yokohama city, Kanagawa: Teruyasu Sugano, *Kazuo Kimura; Cardiovascular Division, Kansai Rosai Hospital, Amagasaki city, Hyogo; Ohnish Toshinari, *Shinsuke Nanto; First Department of Internal Medicine, Nara Medical University, Kashihara city, Nara: Shiro Uemura, *Yoshihiko Saito; Second Department of Internal Medicine, University of Yamanashi, Nakakyoma county, Yamanashi: Ken Umetani,*Kiyotaka Kukiyama

Circ J 2004; **68:** 101 – 106

Rationale and Design of a Large-Scale Trial Using Nicorandil 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 a K-ATP Channel Opener (J-WIND-KATP) ——

Tetsuo Minamino, MD; Kim Jiyoong, MD*; Masanori Asakura, MD**;
Yasunori Shintani, MD†; Hiroshi Asanuma, MD†; Masafumi Kitakaze, MD*;
the J-WIND Investigators

Background The benefits of percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI) are limited by reperfusion injury. In animal models, nicorandil, a hybrid of an ATP-sensitive K^+ (KATP) channel opener and nitrates, reduces infarct size, so the Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by a K-ATP channel opener (J-WIND-KATP) designed a prospective, randomized, multicenter study to evaluate whether nicorandil reduces myocardial infarct size and improves regional wall motion when used as an adjunctive therapy for AMI.

Methods and Results Twenty-six hospitals in Japan are participating in the J-WIND-KATP study. Patients with AMI who are candidates for PCI are randomly allocated to receive either intravenous nicorandil or placebo. The primary end-points are (1) estimated infarct size and (2) left ventricular function. Single nucleotide polymorphisms (SNPs) that may be associated with the function of KATP-channel and the susceptibility of AMI to the drug will be examined. Furthermore, a data mining method will be used to design the optimal combined therapy for post-myocardial infarction (MI) patients.

Conclusions It is intended that J-WIND-KATP will provide important data on the effects of nicorandil as an adjunct to PCI for AMI and that the SNPs information that 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:** 101 – 106)

Key Words: Acute myocardial infarction; Data mining; Nicorandil; 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 nicorandil, a hybrid of an adenosine triphosphate (ATP)-sensitive potassium (K^+-ATP) channel opener and nitrates, is a promising candidate for adjunctive therapy for AMI. In animal models, several studies, including ours, have demonstrated that nicorandil reduces the size of the myocardial size and improves post-ischemic left ventricular function[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 these experimental effects of nicorandil can translate into clinical benefits. Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by a K-ATP channel opener (J-WIND-KATP) is a prospective, randomized, multicenter study designed to evaluate the beneficial effects of nicorandil as an adjunctive therapy for AMI. In the J-WIND-KATP, in addition to examining the effects of nicorandil 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 KATP-channel function or metabolism of nicorandil and the responsiveness of nicorandil therapy will be 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 the J-WIND-KATP, we can genetically

(Received July 8, 2003; revised manuscript received October 21, 2003; accepted November 19, 2003)
*Research Resident of Japan Foundation for Aging and Health for Medical Frontier Strategy Research by Health and Labor Sciences Research Grants; *Cardiovascular Division of Medicine, National Cardiovascular Center, Suita, **Research Fellow of the Japan Society for the Promotion of Science for Young Scientists and †Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Suita, Japan*
Mailing address: Masafumi Kitakaze, MD, PhD, Cardiovascular Division of Medicine, National Cardiovascular Center, Suita 565-8565, Japan. E-mail: kitakaze@hsp.ncvc.go.jp

Table 1 Inclusion Criteria for J-WIND-KATP

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-KATP

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

Table 3 Cessation Criteria for J-WIND-KATP

1. Patient's decision to cease attending the study
2. Prolonged hypotension
3. Difficulty in continuing in 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

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 principle investigator of each participating hospital will be in charge of the written informed consent forms (Appendix 1). The patients registered in the J-WIND-KATP 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 a nicorandil 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 nicorandil group, after a bolus injection of nicorandil (0.067 mg/kg), it is continuously infused intravenously at 1.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 24 h. In the control group, saline is continuously infused at the corresponding dose in the same manner. Accordingly, most patients enrolled in J-WIND-KATP start to receive nicorandil 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

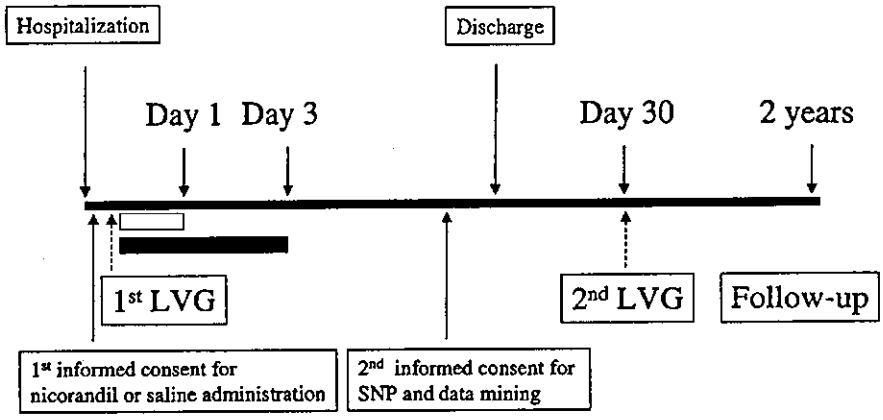

Fig 1. Overview of the J-WIND-KATP protocol. (White box) Nicorandil administration; (Black box) CK measurement.

Table 4 Drug List for Data Mining

Angiotensin converting enzyme inhibiters:
☐ *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*

β-blockers:
☐ *Carvedilol* ☐ *Celiproolol 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* ☐ *Frandol* ☐ *Nitroglycerin*
☐ *Others:* _____ *dose* ____ *mg*

Inotropic agents:
☐ *Pimobendan* ☐ *Digitalis* ☐ *Docarpamine*
☐ *Others:* _____ *dose* ____ *mg*

Adenosine re-uptake inhibitors: *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:

views of left ventriculogram (LVG) are 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-KATP, 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 2 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-infarc-

tion, 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) an association of SNPs of KATP-channel related genes with responsiveness to nicorandil treatment. SNPs of genes that may influence the occurrence of AMI are compared between patients enrolled in the J-WIND-KATP 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-KATP 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 nicorandil decreased the peak CK value by 20% compared with placebo[7] although this value did not reach significance because of the small number of patients and large standard deviation. The estimated percent reductions in ΣCK are 20% in the nicorandil treatment group and the standard deviation will be 5-fold larger than the mean value (>100%). There will be no changes in ΣCK in the placebo group. To detect statistically significant differences with 80% power and with α=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![6] In the J-WIND-KATP, genotype distribution will be analyzed among the patients in the nicorandil treatment group and will be compared between normal subjects and AMI patients, using SNPs of genes that may modulate the functions of the KATP-channel and may affect the metabolism of nicorandil in patients. The association of SNPs of targeted genes with patient responsiveness to nicorandil 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 K-ATP channels-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-KATP. 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 nicorandil treatments, a two-tailed Student's t test for unpaired data will be used. All significance tests will be 2-sided, with type I error rate α=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 nicorandil-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-squared test.

For the analysis of SNPs, genotype distributions is analyzed among the patients in the nicorandil 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-KATP. 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-KATP, 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-KATP 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 nicorandil used in the J-WIND-KATP 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-KATP will provide important data on the effects of nicorandil as an adjunct to PCI for AMI patients. Furthermore, by analyzing the SNPs of genes associated with the responsiveness to nicorandil 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-KATP will allow comprehensive assessments of the potential benefits of nicorandil, 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 the National Cardiovascular Center and Masatsugu Hori at Osaka University Graduate School for their encouragement and support.

References

1. Primary Angioplasty in Myocardial Infarction Study Group (Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, et al). A comparison of immediate angioplasty with thrombolytic therapy for myocardial infarction. *N Engl J Med* 1993; **328:** 673–679.
2. Sakurai K, Watanabe J, Iwabuchi K, Koseki Y, Kon-No Y, Fukuchi M, et al. Comparison of the efficacy of reperfusion therapies for early mortality from acute myocardial infarction in Japan. *Circ J* 2003; **67:** 209–214.
3. Lamas GA, Flaker GC, Mitchell G, Smith SC Jr, Gersh BJ, Wun CC, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. *Circulation* 1995; **92:** 1101–1109.
4. Verma S, Fedak PW, Weisel RD, Butany J, Rao V, Maitland A, et al. Fundamentals of reperfusion injury for the clinical cardiologist. *Circulation* 2002; **105:** 2332–2336.
5. Jonassen AK, Aasum E, Riemersma RA, Mjos OD, Larsen TS. Glucose-insulin-potassium reduces infarct size when administered during reperfusion. *Cardiovasc Drugs Ther* 2000; **14:** 615–623.
6. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000; **101:** 2154–2159.
7. Kitakaze M, Minamino T, Node K, Komamura K, Shinozaki Y, Chujo M, et al. Role of activation of ectosolic 5'-nucleotidase in the cardioprotection mediated by opening of K^+ channels. *Am J Physiol* 1996; **270:** H1744–H1756.
8. Mizumura T, Nithipatikom K, Gross GJ. Infarct size-reducing effect of nicorandil is mediated by the KATP channel but not by its nitrate-like properties in dogs. *Cardiovasc Res* 1996; **32:** 274–285.
9. Sugimoto K, Ito H, Iwakura K, Ikushima M, Kato A, Kimura R, et al. Intravenous nicorandil in conjunction with coronary reperfusion therapy is associated with better clinical and functional outcomes in patients with acute myocardial infarction. *Circ J* 2003; **67:** 295–300.
10. Fukuzawa S, Ozawa S, Inagaki M, Shimada K, Sugioka J, Tateno K, et al. Nicorandil affords cardioprotection in patients with acute myocardial infarction treated with primary percutaneous transluminal coronary angioplasty: Assessment with thallium-201/iodine-123 BMIPP dual SPECT. *J Nucl Cardiol* 2000; **7:** 447–453.
11. Kobayashi Y, Goto Y, Daikoku S, Itoh A, Miyazaki S, Ohshima S, et al. Cardioprotective effect of intravenous nicorandil in patients with successful reperfusion for acute myocardial infarction. *Jpn Circ J* 1998; **62:** 183–189.
12. Doddi S, Marathe A, Ravi SS, Torney DC. Discovery of association rules in medical data. *Med Inform Internet Med* 2001; **26:** 25–33.
13. Bate A, Lindquist M, Edwards IR, Orre R. A data mining approach for signal detection and analysis. *Drug Saf* 2002; **25:** 393–397.
14. Christenson RH, Vollmer RT, Ohman EM, Peck S, Thompson TD, Duh SH, et al. Relation of temporal creatine kinase-MB release and outcome after thrombolytic therapy for acute myocardial infarction: TAMI Study Group. *Am J Cardiol* 2000; **85:** 543–547.
15. Sheehan FH, Schofer J, Mathey DG, Kellett MA, Smith H, Bolson EL, et al. Measurement of regional wall motion from biplane contrast ventriculograms: A comparison of the 30 degree right anterior oblique and 60 degree left anterior oblique projections in patients with acute myocardial infarction. *Circulation* 1986; **74:** 796–804.
16. Deschepper CF, Boutin-Ganache I, Zahabi A, Jiang Z. In search of cardiovascular candidate genes: Interactions between phenotypes and genotypes. Hypertension 2002; **39:** 332–336.

Appendix 1

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

Principle Investigator

Masafumi Kitakaze, National Cardiovascular Center.

Steering Committee

Tetsuo Minamio, Research Resident of Japan Foundation for Aging and Health for Medical Frontier Strategy Research by Health and Labor Sciences Research Grants; Kim Jiyoong, National Cardiovascular Center; Masanori Asakura, Research Fellow of the Japan Society for the Promotion of Science for Young Scientists; Yasunori Shintani, Osaka University Graduate School of Medicine; Hiroshi Asanuma, Osaka University Graduate School of Medicine.

Safety and Data Monitoring Committee

Kazuhiro Sase, National Cardiovascular Center; Yukihiro Koretsune, Hideo Kusuoka, National Osaka Hospital, Takashi Washio, Osaka University Graduate School of Technology.

Individual Data Manager

Akiko Ogai, National Cardiovascular Center.

J-WIND Investigators

Principal investigators in the hospitals are indicated with asterisks. Department of Cardiology, Ehime National Hospital, Onsen-gun, Ehime: Takashi Otani, *Michihito Sekiya; Division of Cardiology, Funabashi, Municipal Medical Center, Funabashi, Chiba: Kazuhiro Shimada, *Shigeru Fukuzawa; Department of Cardiology, Rinku General Medical Center, Izumisano, Osaka: Yuji Yasuga, *Yoshiyuki Nagai; Division of Cardiology, Saiseikai Fukuoka General Hospital, Fukuoka city, Fukuoka: Yutaka Akatuka, *Yusuke Yamamoto; Division of Cardiology, Tokushima Red Cross Hospital, Komatsushima, Tokushima: Takefumi Takahashi, *Yoshikazu Hiasa; Department of Cardiology, Hiroshima City Hospital, Naka-Ku, Hiroshima: Ichiro Inoue, *Masaharu Ishihara; Department of Cardiology, Kyushu Kosei Nenkin Hospital, Kitakyushu city, Fukuoka: Masao Takemoto, *Hideo Yamamoto; Division of Cardiology, Miki City Hospital, Miki, Hyogo: *Kojiro Awano; Department of Cardiology, Kameda Medical Center, Kamogawa city, Chiba: Akihiko Matsumura, *Yuji Hashimoto; Division of Cardiology, St Mary's Hospital, Kurume

city, Fukuoka: Seiki Harada, *Kunihiko Yamamoto; Department of Cardiology, Chiba Emergency Medical Center, Chiba city, Chiba: *Iwao Ishibashi; Department of Cardiology, Musashino Red Cross Hospital, Musashino city, Tokyo: Tohru Obayashi, *Akihiro Niwa; Department of Cardiology, Ogaki Municipal Hospital, Ogaki city, Gifu: Tomohiro Kono, *Takahito Sone; Shizuoka Prefectural General Hospital, Shizuoka city, Shizuoka: Kazuhiko Ohbayashi, *Osamu Doi; Division of Cardiology, Department of Internal Medicine, Kobe City General Hospital, Kobe city, Hyogo: Atsushi Yamamuro, *Kenichi Shiratori; Division of Cardiology, Sakurabashi Watanabe Hospital, Osaka, Osaka: Hiroshi Ito, *Kenshi Fujii; Department of Cardiovascular Medicine, Kyushu University Faculty of Medicine, Higashi-ku, Fukuoka: Yoji Hirakawa, *Kensuke Egashira; Department of Cardiology, Kanazawa Medical University Hospital, Kahoku County, Ishikawa: Shinji Okubo, *Noboru Takekoshi; Department of Cardiology, Kawachi General Hospital, Higashiosaka-city, Osaka: Sadao Yoshida, *Masayoshi Mishima; Department of Cardiology, Cardiovascular Center, Omura Municipal Hospital, Omura city, Nagasaki: *Yoshito Tanioka; Department of Cardiovascular Medicine, Matsuyama Shimin Hospital, Matsuyama city, Ehime: Hiroyuki Fujieda, *Mitsunori Abe; Department of Cardiology, Sasebo Municipal General Hospital, Sasebo city, Nagasaki: Kohsuke Shioguchi, *Toshihiko Yamasa; Center for Cardiovascular Interventions, Chiba University Hospital, Chuo-ku, Chiba: Nobuyuki Komiyama, *Issei Komuro; Cardiovascular Division of Medicine, Nagasaki Municipal Hospital, Nagasaki-city, Nagasaki: Hiroshi Nakashima, *Shin Suzuki; Second Department of Internal Medicine, Tokyo Medical University Hospital, Shinjuku-ku, Tokyo: Nobuhiro Tanaka, *Akira Yamashina; Department of Cardiology, Tokyo Metropolitan Bokuto General Hospital, Sumida-Ku, Tokyo: Toru Iwama, *Ichiro Kubo; Department of Cardiovascular medicine, Hokkaido Cardiovascular Hospital, Sapporo city, Hokkaido; Masaru Yamaki, *Naoki Funayama.

厚生労働科学研究費補助金(循環器疾患等総合研究事業)

分担研究報告書

食後血糖上昇の抑制による心筋梗塞二次予防に関する大規模薬剤介入臨床研究

分担研究者　友池 仁暢　国立循環器病センター 院長

研究要旨
現在わが国における心臓死は全国民死亡原因の第2位を占めている。なかでも慢性心不全患者は増加し続けており、その原因として心筋梗塞後心ポンプ機能低下が重要である。慢性心不全による繰り返す入院、多種類の治療薬の使用は医療費増加につながり、厚生行政上の重要課題となっている。また臨床的見地からも、梗塞後慢性心不全患者のQOLは低く、健康寿命の延長のためにも梗塞後心不全の発症を抑制することは極めて重要な案件である。

今後わが国が迎える超高齢化社会の到来を考慮すると、心筋梗塞の二次予防というアプローチが特に重要となる。心筋梗塞のリスクファクターである生活習慣病のうち、発症およびその予後に最も影響を与える糖尿病は、食後高血糖のみを有する糖尿病予備軍とともに非常な勢いで増加している。血糖値の上昇は酸化ストレスを引き起こすことが知られており、食後の高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることが報告されている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後患者の食後の血糖上昇を抑えることが、心筋梗塞二次予防につながると考え、我々は本研究を立案した。本研究は急性心筋梗塞で入院した症例に対してαグルコシダーゼ阻害薬を投与し、その心血管イベントの抑制効果の有無を全国100施設と共同した多施設大規模臨床試験にて検討する。

かかる大規模多施設臨床研究の成否にはサンプルサイズおよび質の高いデータの確保が重要な要素となる。我々は厚生科研 効果的医療技術の確立推進臨床研究事業 虚血・再潅流における心筋保護に関する大規模無作為薬剤効果比較試験(課題番号H14—心筋—006、JWIND試験)にて、心筋梗塞における急性期の薬剤介入という困難な性格であるにもかかわらず、全国68施設との共同で700例を超えんとする症例の登録を得て解析しつつある実績を有する。心筋梗塞の多施設臨床研究チームとしてネットワークがすでに確立されている我々の研究グループは、そのインフラストラクチャーを活用することにより、本研究の遂行能力を十分有するものと考えられる。

A.研究目的

血糖の上昇は酸化ストレスを引き起こすことが知られており、食後高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることがわかっている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後の症例に対して、αグルコシダーゼ阻害薬により食後の血糖上昇を抑えることが、心筋梗塞二次予防につながると考え我々は本研究を立案した。当該患者数が相当数にのぼる治療法は、当然のことながら検討段階から安全な薬剤の使用が必須である。われわれが考慮しているαグルコシダーゼ阻害薬は、血中には原則取り込まれず、消化管にとどまり糖分の吸収を抑える薬剤であるため、幅広い患者層への適用が可能であると考えられる。

B. 研究方法

<u>食後血糖上昇の抑制による心筋梗塞二次予防に関する大規模薬剤介入臨床研究</u>

[対象]
急性心筋梗塞と診断され、再灌流療法をうけた20才以上の症例

[除外基準]
αグルコシダーゼ阻害薬がすでに投与されている症例
低血糖発作の既往のある症例
その他、重篤な肝障害、腎障害や同意の得られない症例、不適当と考えられる症例

[方法]
エントリー時にαグルコシダーゼ阻害薬が投与されていない症例を無作為割付により2群にわけて、αグルコシダーゼ阻害薬投与(ボグリボース、1回0.2mg 1日3回毎食直前)群と偽薬投与群に割り付

ける。以後3年間フォローアップし心血管イベント、心不全への進展、心筋リモデリングおよび糖尿病の発症につき2群間で比較検討する。またエントリー時の顕性糖尿病の有無で層別解析をする。
フォローアップ期間は6ヶ月ごとにデータ登録を行い、心血管イベントおよび糖尿病の状況(空腹時血糖、HbA1C)、内服状況を調査していく。

[目標症例数]
4000症例(コントロール群2000症例、αグルコシダーゼ阻害薬群2000症例)

[参加予定施設]
全国100施設
国立循環器病センター、駿河台日本大学病院、りんくう総合医療センター市立泉佐野病院、宇和島市立宇和島病院、新別府病院など厚生科研 課題番号H14—心筋—006(JWIND試験)参加68施設に加え、計100施設での共同研究を計画している。

[中央予定施設]
国立循環器病センター

[評価項目]
プライマリーエンドポイント
心血管イベント(死亡、心疾患による入院、再梗塞、心不全、再インターベンション、CABG)
セカンダリーエンドポイント
死亡率
インターベンション後再狭窄
心筋リモデリング(心エコー、核医学検査、BNP)
慢性心不全への移行の抑制(心不全による入院、NYHA)
脳血管障害の発症
糖尿病の発症

[割り付け方法]
インターネットを利用した中央割付法

[サブスタディ]
データマイニング
フォローアップの際に、他の内服薬もすべて検討し、治療法最適化をデータマイニング法にて検討する。

SNPを用いた薬剤効果の検討
現在医療費の高騰から、テーラーメイド医療の重要性が強く訴えられている。
αグルコシダーゼ阻害薬の効果がみられた群とない群において各種動脈硬化関連遺伝子、心筋梗塞関連遺伝子、糖尿病関連遺伝子のSNPを用いて検討を行う。

[動物実験による検討]
糖尿病マウスを利用した、長期間高血糖状態がマウス心筋代謝に与える影響の検討
耐糖能異常の梗塞後心筋に与える影響を検討するため、KKAyなどの糖尿病マウスに心筋梗塞を作成し、高血糖状態に長期間さらされることによりいかなる遺伝子発現変化をきたすかをaffimetrix社製のmicro chipを利用して解析する。またαグルコシダーゼ阻害薬等の薬剤による遺伝子発現変化を検討し、また高血糖及びその是正による心筋代謝への影響を検討する。

マウス心筋梗塞モデル、およびイヌ心筋梗塞モデルにおける食後高血糖抑制による心不全予防効果の検討
糖尿病のない野生型マウス、およびイヌに心筋梗塞を作成し、αグルコシダーゼ阻害薬(boglibose)を経口で投与し、心エコーなどを用いて心機能を検討する。

平成16年度は、参加予定施設とキックオフミーティングを行いプロトコルの確定をすると共にインターネット登録用のホームページを立ち上げた。中央施設である国立循環器病センターの倫理審査委員会を通過し予定通りエントリーが開始された。また、イヌ心不全モデルにおいて糖代謝に関連する遺伝子が変化しており、ヒト心不全症例での検討でも同様のことが見付かった。

(倫理面への配慮)
以下の点を明記し、倫理委員会の承認手続きを経て研究を開始した。拡散か施設でも同様の手続きを開始している。
(1)学研究及び医療行為の対象となる個人の人権の擁護
本研究は遺伝子情報を扱わず臨床情報のみの解析であるが、臨床データの収集は「連結匿名化」を行った上で中央解析施設(国立循環器病センター)に集積し、解析時には個人特定に繋がるデータとは切り離した状態での解析を行う。

(2)医学研究及び医療行為の対象となる個人への利益と不利益

本研究で使用される薬剤は臨床の現場で日常使われている薬剤であり、開発途中のいわゆる治験薬とは根本的に異なる。本研究ではコントロール目標を立て厳密にコントロールするので、より細やかな治療を受けられる可能性がある。また検査項目に関して一般の診療に必要な物に限っており新たな採血等の必要がなく対象となる個人への負担は少ない。個人情報の保護に努めれば個人への不利益は少ないものと考えられる。

(3)医学的貢献度

我が国における心不全による死亡は全死因の第二位を占めており、その抑止は社会的急務となっている。特に心筋梗塞後の心機能低下に起因する慢性心不全については、5年生存率が50%以下と低いことから、その改善が急がれている。心筋梗塞後の心機能低下は再梗塞によりその危険性が増大する。心筋梗塞再発予防における大規模薬剤介入を念頭に置いた本研究は、医学的貢献度も非常に高いと考える。

(4)医学研究及び医療行為の対象となる個人に理解を求め同意を得る方法

患者さん用説明文書を用いて、研究遂行者の担当者が説明し、別紙の同意文書により同意を得る。

(5)動物を用いた実験について

動物実験は施設の倫理規定に基づき審査に通過した実験のみを行い、マウス等動物の生命を最大限尊重し、効率的に実験を進める。

C.研究結果

現在わが国において、心臓死は全国民死亡原因の第2位を占めている。なかでも慢性心不全患者は増加し続けており、その原因としては心筋梗塞後の心機能低下が重要である。くり返す入院、多種類の治療薬の使用は医療費増加につながり、厚生行政上の重要課題である。また臨床的見地からも、梗塞後心不全患者のQOLは低く、健康寿命の延長のためにも梗塞後の心不全発症を抑制することは極めて重要な案件である。

くり返す心筋梗塞後の心機能低下に対して、二次予防および心筋リモデリング抑制というアプローチがあげられる。加齢そのものが発症のリスクファクターであるため、今後わが国が迎える超高齢化社会の到来にあたり、心筋梗塞二次予防の重要性が増している。一方で心筋梗塞のリスクファクターである生活習慣病のうち、その発症・予後に最も影響を与えるとされる糖尿病およびその予備軍は、生活習慣の変化、高齢化をうけて非常な勢いで増加している。したがって今後わが国の心筋梗塞二次予防において、耐糖能異常への新たな対処の必要性が高まっている。

血糖の上昇は酸化ストレスを引き起こすことが知られており、食後高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることがわかっている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後の症例に対して、αグルコシダーゼ阻害薬により食後の血糖上昇を抑えることが、心筋梗塞二次予防につながると考え我々は本研究を立案した。当該患者数が相当数にのぼる治療法は、当然のことながら検討段階から安全な薬剤の使用が必須である。われわれが考慮しているαグルコシダーゼ阻害薬は、血中には原則取り込まれず、消化管にとどまり糖分の吸収を抑える薬剤であるため、幅広い患者層への適用が可能であると考えられる。

当該研究期間3年の研究計画

1年目　研究体制の整備、症例エントリーの開始、動物実験による検討

当該年度は、参加予定施設を含めたキックオフミーティングを開催しプロトコルの確定を行った。また、インターネットを用いた登録のためホームページを立ち上げ、予定通りエントリーを開始した。また、実験動物を使った評価系において耐糖能異常と心不全の関連について検討した。

2年目　症例のエントリー、エントリーされた症例の観察、動物実験による検討

3年目　エントリーされた症例の観察、データ解析

D.考察

心機能と生体の糖利用は密接な関係にあることが基礎医学の成果として明らかになりつつある。本研究は大規模臨床研究にて、抗高血糖薬の投与により心筋梗塞二次予防が可能であるかを臨床的に検討するものであり、以下の結果が期待される。

1. 心筋梗塞の二次予防により慢性心不全患者の増加を抑制できれば、厚生行政面においては大幅な医療費抑制効果が期待され、また医療面においては患者のQOLの著明な改善、健康寿命の延長が期待できる。
2. 包括医療制度の導入により急性心筋梗塞を含めた心血管イベントの発症数の減少は、そのまま医療費の抑制につながる。

E.結論
糖利用の正常化は、新しい心血管疾患の治療法
になりうると考えられた。

F.健康危険情報
特記なし

G.研究発表
1. 論文発表
特記なし

2. 学会発表
特記なし

H.知的財産権の出願・登録情報(予定を含む)
1. 特許取得
特記なし

2. 実用新案登録
特記なし

3. その他
特記なし

厚生労働科学研究費補助金(循環器疾患等総合研究事業)

分担研究報告書

食後血糖上昇の抑制による心筋梗塞二次予防に関する大規模薬剤介入臨床研究

分担研究者　宮武 邦夫　国立循環器病センター 副院長

研究要旨
現在わが国における心臓死は全国民死亡原因の第2位を占めている。なかでも慢性心不全患者は増加し続けており、その原因として心筋梗塞後心ポンプ機能低下が重要である。慢性心不全による繰り返す入院、多種類の治療薬の使用は医療費増加につながり、厚生行政上の重要課題となっている。また臨床的見地からも、梗塞後慢性心不全患者のQOLは低く、健康寿命の延長のためにも梗塞後心不全の発症を抑制することは極めて重要な案件である。

今後わが国が迎える超高齢化社会の到来を考慮すると、心筋梗塞の二次予防というアプローチが特に重要となる。心筋梗塞のリスクファクターである生活習慣病のうち、発症およびその予後に最も影響を与える糖尿病は、食後高血糖のみを有する糖尿病予備軍とともに非常な勢いで増加している。血糖値の上昇は酸化ストレスを引き起こすことが知られており、食後の高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることが報告されている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後患者の食後の血糖上昇を抑えることが、心筋梗塞二次予防につながると考え、我々は本研究を立案した。本研究は急性心筋梗塞で入院した症例に対してαグルコシダーゼ阻害薬を投与し、その心血管イベントの抑制効果の有無を全国100施設と共同した多施設大規模臨床試験にて検討する。

かかる大規模多施設臨床研究の成否にはサンプルサイズおよび質の高いデータの確保が重要な要素となる。我々は厚生科研 効果的医療技術の確立推進臨床研究事業 虚血・再潅流における心筋保護に関する大規模無作為薬剤効果比較試験(課題番号H14—心筋—006、JWIND試験)にて、心筋梗塞における急性期の薬剤介入という困難な性格であるにもかかわらず、全国68施設との共同で700例を超えんとする症例の登録を得て解析しつつある実績を有する。心筋梗塞の多施設臨床研究チームとしてネットワークがすでに確立されている我々の研究グループは、そのインフラストラクチャーを活用することにより、本研究の遂行能力を十分有するものと考えられる。

A.研究目的

血糖の上昇は酸化ストレスを引き起こすことが知られており、食後高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることがわかっている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後の症例に対して、αグルコシダーゼ阻害薬により食後の血糖上昇を抑えることが、心筋梗塞二次予防につながると考え我々は本研究を立案した。当該患者数が相当数にのぼる治療法は、当然のことながら検討段階から安全な薬剤の使用が必須である。われわれが考慮しているαグルコシダーゼ阻害薬は、血中には原則取り込まれず、消化管にとどまり糖分の吸収を抑える薬剤であるため、幅広い患者層への適用が可能であると考えられる。

B. 研究方法

<u>食後血糖上昇の抑制による心筋梗塞二次予防に関する大規模薬剤介入臨床研究</u>

[対象]
急性心筋梗塞と診断され、再灌流療法をうけた20才以上の症例

[除外基準]
αグルコシダーゼ阻害薬がすでに投与されている症例
低血糖発作の既往のある症例
その他、重篤な肝障害、腎障害や同意の得られない症例、不適当と考えられる症例

[方法]
エントリー時にαグルコシダーゼ阻害薬が投与されていない症例を無作為割付により2群にわけて、αグルコシダーゼ阻害薬投与(ボグリボース、1回0.2mg 1日3回毎食直前)群と偽薬投与群に割り付

ける。以後3年間フォローアップし心血管イベント、心不全への進展、心筋リモデリングおよび糖尿病の発症につき2群間で比較検討する。またエントリー時の顕性糖尿病の有無で層別解析をする。
フォローアップ期間は6ヶ月ごとにデータ登録を行い、心血管イベントおよび糖尿病の状況(空腹時血糖、HbA1C)、内服状況を調査していく。

[目標症例数]
4000症例(コントロール群2000症例、αグルコシダーゼ阻害薬群2000症例)

[参加予定施設]
全国100施設
国立循環器病センター、駿河台日本大学病院、りんくう総合医療センター市立泉佐野病院、宇和島市立宇和島病院、新別府病院など厚生科研 課題番号H14—心筋—006(JWIND試験)参加68施設に加え、計100施設での共同研究を計画している。

[中央予定施設]
国立循環器病センター

[評価項目]
プライマリーエンドポイント
心血管イベント(死亡、心疾患による入院、再梗塞、心不全、再インターベンション、CABG)
セカンダリーエンドポイント
死亡率
インターベンション後再狭窄
心筋リモデリング(心エコー、核医学検査、BNP)
慢性心不全への移行の抑制(心不全による入院、NYHA)
脳血管障害の発症
糖尿病の発症

[割り付け方法]
インターネットを利用した中央割付法

[サブスタディ]
データマイニング
フォローアップの際に、他の内服薬もすべて検討し、治療法最適化をデータマイニング法にて検討する。

SNPを用いた薬剤効果の検討
現在医療費の高騰から、テーラーメイド医療の重要性が強く訴えられている。
αグルコシダーゼ阻害薬の効果がみられた群とない群において各種動脈硬化関連遺伝子、心筋梗塞関連遺伝子、糖尿病関連遺伝子のSNPを用いて検討を行う。

[動物実験による検討]
糖尿病マウスを利用した、長期間高血糖状態がマウス心筋代謝に与える影響の検討
耐糖能異常の梗塞後心筋に与える影響を検討するため、KKAyなどの糖尿病マウスに心筋梗塞を作成し、高血糖状態に長期間さらされることによりいかなる遺伝子発現変化をきたすかをaffimetrix社製のmicro chipを利用して解析する。またαグルコシダーゼ阻害薬等の薬剤による遺伝子発現変化を検討し、また高血糖及びその是正による心筋代謝への影響を検討する。

マウス心筋梗塞モデル、およびイヌ心筋梗塞モデルにおける食後高血糖抑制による心不全予防効果の検討
糖尿病のない野生型マウス、およびイヌに心筋梗塞を作成し、αグルコシダーゼ阻害薬(boglibose)を経口で投与し、心エコーなどを用いて心機能を検討する。

平成16年度は、参加予定施設とキックオフミーティングを行いプロトコルの確定をすると共にインターネット登録用のホームページを立ち上げた。中央施設である国立循環器病センターの倫理審査委員会を通過し予定通りエントリーが開始された。また、イヌ心不全モデルにおいて糖代謝に関連する遺伝子が変化しており、ヒト心不全症例での検討でも同様のことが見付かった。

(倫理面への配慮)
以下の点を明記し、倫理委員会の承認手続きを経て研究を開始した。拡散か施設でも同様の手続きを開始している。
(1)研究及び医療行為の対象となる個人の人権の擁護
本研究は遺伝子情報を扱わず臨床情報のみの解析であるが、臨床データの収集は「連結匿名化」を行った上で中央解析施設(国立循環器病センター)に集積し、解析時には個人特定に繋がるデータとは切り離した状態での解析を行う。

(2)医学研究及び医療行為の対象となる個人への利益と不利益

本研究で使用される薬剤は臨床の現場で日常使われている薬剤であり、開発途中のいわゆる治験薬とは根本的に異なる。本研究ではコントロール目標を立て厳密にコントロールするので、より細やかな治療を受けられる可能性がある。また検査項目に関して一般の診療に必要な物に限っており新たな採血等の必要がなく対象となる個人への負担は少ない。個人情報の保護に努めれば個人への不利益は少ないものと考えられる。

(3)医学的貢献度
我が国における心不全による死亡は全死因の第二位を占めており、その抑止は社会的急務となっている。特に心筋梗塞後の心機能低下に起因する慢性心不全については、5年生存率が50%以下と低いことから、その改善が急がれている。心筋梗塞後の心機能低下は再梗塞によりその危険性が増大する。心筋梗塞再発予防における大規模薬剤介入を念頭に置いた本研究は、医学的貢献度も非常に高いと考える。

(4)医学研究及び医療行為の対象となる個人に理解を求め同意を得る方法
患者さん用説明文書を用いて、研究遂行者の担当者が説明し、別紙の同意文書により同意を得る。

(5)動物を用いた実験について
動物実験は施設の倫理規定に基づき審査に通過した実験のみを行い、マウス等動物の生命を最大限尊重し、効率的に実験を進める。

C.研究結果
現在わが国において、心臓死は全国民死亡原因の第2位を占めている。なかでも慢性心不全患者は増加し続けており、その原因としては心筋梗塞後の心機能低下が重要である。くり返す入院、多種類の治療薬の使用は医療費増加につながり、**厚生行政上の重要課題**である。また臨床的見地からも、梗塞後心不全患者のQOLは低く、健康寿命の延長のためにも梗塞後の心不全発症を抑制することは極めて重要な案件である。

くり返す心筋梗塞後の心機能低下に対して、二次予防および心筋リモデリング抑制というアプローチがあげられる。加齢そのものが発症のリスクファクターであるため、今後わが国が迎える超高齢化社会の到来にあたり、心筋梗塞二次予防の重要性が増している。一方で心筋梗塞のリスクファクターである生活習慣病のうち、その発症・予後に最も影響を与えるとされる**糖尿病およびその予備軍**は、生活習慣の変化、高齢化をうけて非常な勢いで増加している。したがって今後わが国の心筋梗塞二次予防において、耐糖能異常への新たな対処の必要性が高まっている。

血糖の上昇は**酸化ストレス**を引き起こすことが知られており、食後高血糖のみがすでに大血管障害のリスクとなり、心筋梗塞の発症リスクを高めることがわかっている(Donahue RP, et al. Diabetes 36: 689-692,1987)。そこで心筋梗塞後の症例に対して、αグルコシダーゼ阻害薬により食後の血糖上昇を抑えることが、**心筋梗塞二次予防**につながると考え我々は本研究を立案した。当該患者数が相当数にのぼる治療法は、当然のことながら検討段階から安全な薬剤の使用が必須である。われわれが考慮しているαグルコシダーゼ阻害薬は、血中には原則取り込まれず、消化管にとどまり糖分の吸収を抑える薬剤であるため、幅広い患者層への適用が可能であると考えられる。

当該研究期間3年の研究計画
1年目　研究体制の整備、症例エントリーの開始、動物実験による検討
当該年度は、参加予定施設を含めたキックオフミーティングを開催しプロトコルの確定を行った。また、インターネットを用いた登録のためホームページを立ち上げ、予定通りエントリーを開始した。また、実験動物を使った評価系において耐糖能異常と心不全の関連について検討した。
2年目　症例のエントリー、エントリーされた症例の観察、動物実験による検討
3年目　エントリーされた症例の観察、データ解析

D.考察
心機能と生体の糖利用は密接な関係にあることが基礎医学の成果として明らかになりつつある。本研究は大規模臨床研究にて、抗高血糖薬の投与により心筋梗塞二次予防が可能であるかを臨床的に検討するものであり、以下の結果が期待される。
1. 心筋梗塞の二次予防により慢性心不全患者の増加を抑制できれば、厚生行政面においては大幅な医療費抑制効果が期待され、また医療面においては患者のQOLの著明な改善、健康寿命の延長が期待できる。
2. 包括医療制度の導入により急性心筋梗塞を含めた心血管イベントの発症数の減少は、そのまま医療費の抑制につながる。

E.結論
糖利用の正常化は、新しい心血管疾患の治療法になりうると考えられた。

F.健康危険情報
特記なし

G.研究発表
1. 論文発表
特記なし

2. 学会発表
特記なし

H.知的財産権の出願・登録情報（予定を含む）
1. 特許取得
特記なし

2. 実用新案登録
特記なし

3. その他
特記なし