designed so that one can refer to detailed data for each item in Figure 2. The presentation style which enables making a diagnosis on the spot such as this may save time in grasping the clinical history of a patient in an actual clinical situation and is highly useful. Further, in the case of an emergency, this could be an effective supportive tool for treating patients without delay.

In addition, Figure 3 shows an example of investigation of variation in total cholesterol. Here, we show an image of the investigation of the results of the first

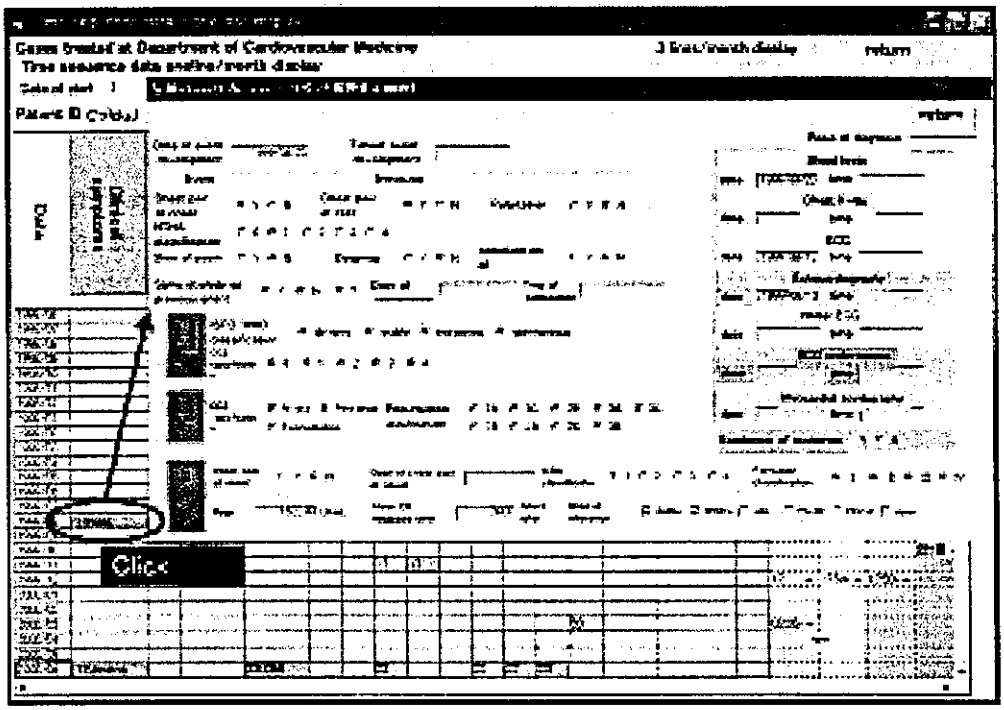

Figure 2. Details of each clinical item.

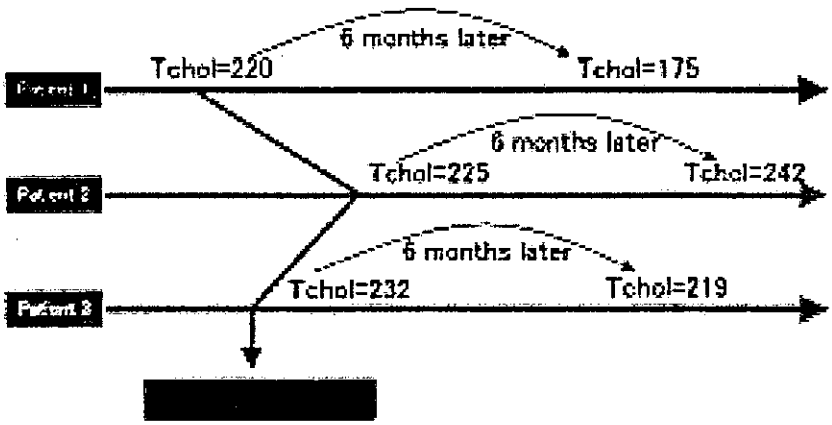

Figure 3. Investigation of variation in total cholesterol.

laboratory blood test of total cholesterol (Tchol) in three patients and the variation in Tchol six months later in the same three patients. By arranging side by side the starting points of the three patients which are actually different, one can conduct epidemiological surveys such as prospective and transversal studies.

Also, it is possible to conduct an investigation following up a certain specific lesion in a coronary artery for progression, regression, restenosis, and so on as time passes. Further, we have developed a function to show the degree of stenosis in each lesion in time sequence, which enables one to readily investigate the progression, regression, and restenosis of coronary atherosclerosis in each lesion.

In this way, it is possible to investigate and analyze the data accumulated based on day-to-day clinical information in time sequence. Utilizing the RCN System, one can always peruse in real-time the results, similar to those obtained in a clinical research study, which would require enrollment of a great number of patients, a large amount of money, and follow-up over a long period of time.

Technique to extract clinical findings by data analysis: Based on the RCN System mentioned in the previous section, we are going to describe a method for extracting medical findings. In this study, we have developed and describe a comprehensive data analysis technique called data mining and an analytical system to extract, process, and present the data in accordance to the purpose.

Data mining is a technology which has become generally accepted and used in recent years and by setting up a simple criterion this technique can efficiently search for a rule satisfying the criterion in a vast amount of data[1,2] Table I shows an example of the results of analysis by data mining. Table I deals with "a patient with myocardial infarction (MI)" and shows premises when an evaluation standard with high degrees of certainty and support and a high odds ratio is selected. By utilizing such comprehensive data analysis, one can not only confirm clinical findings obtained based on a rule of thumb, but also extract findings completely unknown so far.

Figure 4 shows an example of a screen indicating the results in analytical function and automatic graph making function of the RCN System. One of the characteristics of the RCN System lies in its function enabling one to grasp trends in the data visually, including medical findings obtained by data mining. This is useful as a function to extract/process the data by the simple operation of selecting conditions, and present the results of the search graphically. Graphic presentation helps one to display trends in the data and the differences between groups and could greatly assist one in making clinical decisions.

Utilizing the technique to extract clinical findings by data mining and an analytical system contribute greatly to the establishment of a totally new diagnostic method or clinical guidelines.

Table I. Example of Data Analysis by Data Mining

Premise	Conclusion	Certainty	Support	Odds ratio
Gene X1 = A/C Gene Y1 = A/A Male	MI (+)	0.8163	0.1646	4.7281
Gene X2 = A/A Gene Y2 = A/A Familial IHD (-) Male	MI (+)	0.8438	0.1588	4.6703
Gene X3 = C/C Gene Y3 = defect Male	MI (+)	0.875	0.1657	6.3194

Certainty means a ratio of data securing the conclusion to those satisfying the premise. Support means a ratio of data satisfying both premises and conclusion to all of the data. Odds ratio means how many times more readily the data satisfying the premises can secure the conclusion when compared with the data which does not satisfy the premises. For example, in the rule in the first line of Table I a male patient with gene type X1 being A/C, hetero type, and gene type Y1 being A/A, homo type develops MI with a probability of 81.63 % (certainty: 0.8163) and such a rule occurs in 16.46 % of the total number of patients (support: 0.1646). Also, this shows that a male patient with gene X1 being A/C, hetero type and gene Y1 being A/A, homo type tends to develop MI 4.7281 times as frequently as those who have different gene type (odds ratio: 4.7281).

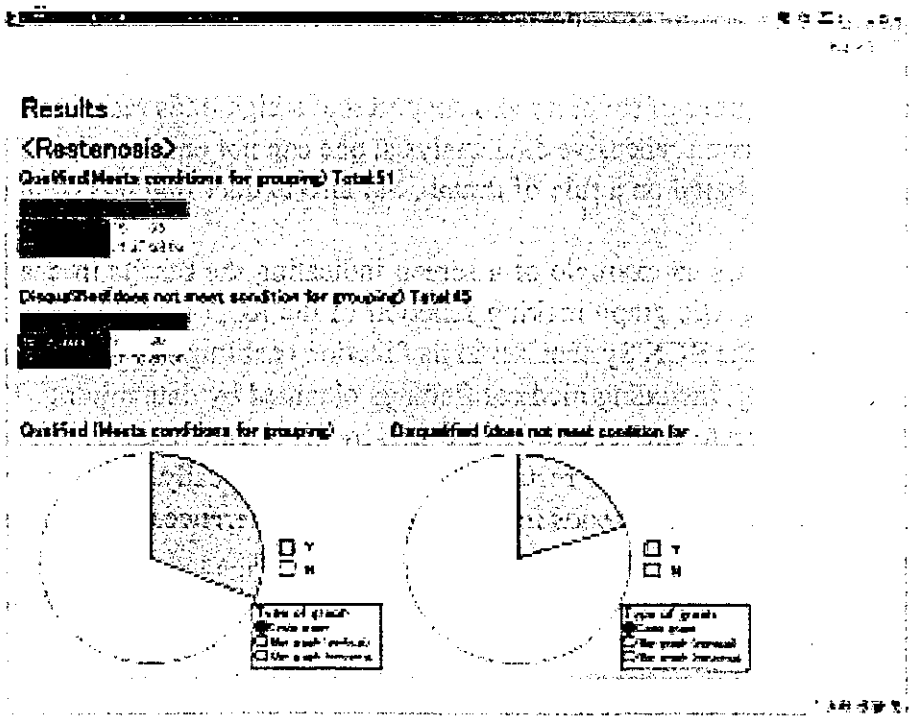

Figure 4. Example of graphic image of the analytical system of case data. Here, the patients are divided into two groups, one developing diabetes and the other no diabetes. The ratio of the patients who develop restenosis after recanalization of coronary artery is shown.

RESULTS

Biochemistry markers useful in diagnosis of coronary artery diseases without left ventricular dysfunction: In cases other than cardiac failure, we have studied atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) which are known as markers indicating the severity of cardiac failure or prognosis of the patients. When limiting the cases to those with normal contraction ability of the left ventricle, we have obtained the finding showing that ANP and BNP are correlated with the severity of coronary artery diseases. As shown in Figures 5A and 5B, the higher the values of ANP and BNP, the greater the number of lesions in the coronary artery tends to be. We will continue to collect and analyze more data.

Factors regulating restenosis in coronary angioplasty: The ratio of patients with inadequately controlled diabetes who develop restenosis after coronary arterial intervention tends to be high compared with other patients.[3] Table II shows the relation between the existence of diabetes, HbAlC, and restenosis. In the case of patients with diabetes whose HbAlC values are higher than 7.0, we have obtained the result that, compared with other cases, they have a higher ratio of restenosis after recanalization of a coronary artery.

Further, in our data, when pioglitazone, a drug for the treatment of diabetes, is used, there was a tendency toward a lower rate of restenosis after coronary intervention treatment, compared with other drugs. Table III shows the relation between drugs for the treatment of diabetes and restenosis rate.

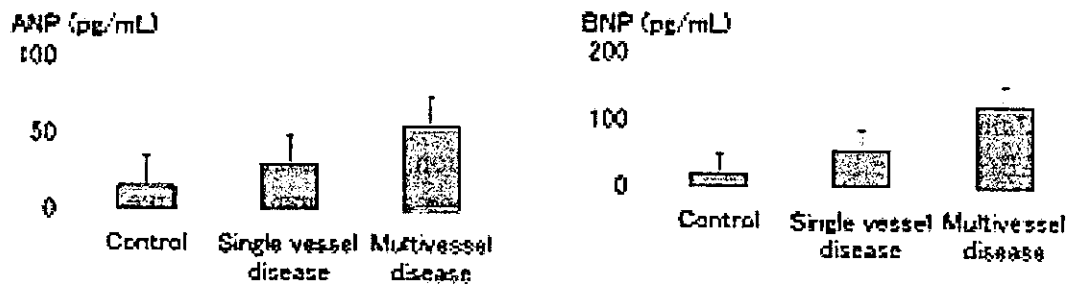

Figure 5. **A:** Correlation between plasma ANP level and the severity of coronary artery diseases. **B:** Correlation between plasma BNP level and the severity of coronary artery diseases.

Table II. Relation Between Existence of Diabetes, HbAlC, and Restenosis Rate

	With diabetes	Without diabetes
HbA1C 7.0 or more	39.2 (%)	27.5 (%)
HbA1C less than 7.0	29.6 (%)	-

Table III. Relation Between Drugs for the Treatment of Diabetes and Restenosis Rate

Drugs	Rate of restenosis
Sulfonylurea	33.6 (%)
Glucosidase inhibitor	29.7 (%)
Pioglitazone	25.0 (%)
Insulin	36.5 (%)

For three drugs except pioglitazone, restenosis after recanalization occurs at a rate of approximately 30% or higher, while in the cases where pioglitazone is prescribed, the rate is as low as 25%.

Table IV. Relation Between Ile823Met Polymorphism and Various Factors

	Ile/Ile	Ile/Met+Met/Met	Statistics
HDL-C	44.9 ± 11.5	49.0 ± 15.1	$P = 0.04$
BMI	23.5 ± 3.7	23.1 ± 3.3	NS
Tchol	180.9 ± 31.8	183.5 ± 36.4	NS
TG	125.7 ± 65.1	129.4 ± 87.9	NS
LDL-C	115.1 ± 32.7	114.9 ± 37.9	NS
Smoking	59 (61.5)	115 (68.0)	NS
Hypertension	65 (67.7)	120 (71.0)	NS
Diabetes	20 (20.8)	46.0 (27.2)	NS

It becomes clear that patients with Ile823Met including Met have an HDL concentration significantly higher than those without Met[5]. No significant difference was observed in other factors such as obesity (BMI), total plasma cholesterol (Tchol), tryglycerides (TG), bad cholesterol (LDL-C), smoking, hypertension, and diabetes.

Ile823met and lipid concentration: It is reported that Ile823Met polymorphism of the ABCA1 gene has an effect on the concentration of good cholesterol (HDL-C).[4] Taking into consideration differences in race and eating habits, we have investigated what results would be obtained in Japanese people. Table IV shows the relation between Ile823Met polymorphism and various factors in patients receiving no administration of the drug for the treatment of hyperlipidemia.

Genetic markers for coronary artery diseases: We have selected approximately 50 genes which have something to do with arterial sclerosis and investigated the possible influence of polymorphism of such genes on the occurrence of coronary artery diseases, especially myocardial infarction. Analysis of the Gensini Score, known as an index for arterial sclerosis in coronary arteries, and background factors such as the presence of hypertension, obesity, and diabetes, and the existence of coronary arterial sclerosis lesions is ongoing and we are planning to report the results shortly.

DISCUSSION

The aims of this study were to contribute to clinical practice from the approach of having clinical information in electronic form by IT, describe a universal technique to extract clinical findings by constructing an RCN System, and demonstrate the effectiveness of such a system by describing the clinical findings obtained so far.

The clinical findings obtained so far include:

- Biochemical markers (ANP, BNP) having a correlation with the severity of coronary diseases in patients with normal cardiac function
- That the existence of diabetes and drugs for the treatment of diabetes influence the restenosis rate after recanalization of a coronary artery
- That the ABCA1 gene has an effect on lipid concentration, which is a risk factor for heart diseases
- Analysis of genetic polymorphism to find out specific sequence(s) which may have an influence on the onset of coronary diseases, myocardial infarction, and severity of coronary arterial sclerosis.

Based on these results, one can see that preparation of establishment of prompt extraction of useful clinical findings and useful diagnosing method is steadily carried out.

At this point in time, we are at the stage where the construction of a clinical database and extraction of clinical findings by data analysis by local health care institutions have been completed. From the view of spreading social technology, any development to be made from now on is extremely important. By cooperating with health care institutions all over Japan, the collection and analysis of more extensive clinical data or medical check up data will become possible. As a result, the sharing of clinical data amang all health care institutions in Japan will become possible. By this, physicians can promptly grasp their patients' clinical history and background and treat them immediately and effectively. Patients can visit any health care institution in Japan and receive appropriate health care services without being subjected to duplication of testing.

Nationwide linking of databases accompanying the exchange of data does not present significant difficulty thanks to widespread internet and broadband circuits. While the challenge of implementing an effective security system required for the handling of clinical data should be met by all means, the sharing of clinical information data between health care institutions all over Japan should be feasible. One can expect that clinical findings and completely new diagnostic methods obtained by accumulation and analysis of vast amounts of clinical data by network linking with health care institutions throughout Japan will be shared by all of the health care institutions in Japan.

Also, up until now we have constructed the system concentrating on cardiovascular disease related items. Our next challenge is to widely promote the RCN System without emphasis on any particular disease or clinical department. Further, it is not necessary to limit the application of this system to health care institutions and it is possible to establish links to other industries, such as the pharmaceutical and insurance industries. For the pharmaceutical industry, information as to what type of patient receives what drug and whether there are any side effects would be valuable in the development of pharmaceutical products. For the insurance industry, information concerning the risk of onset of diseases subject to insurance payment as well as the risk of death could be used in setting insurance rates, etc.

In this study, we have sought to contribute to the establishment of clinical guidelines and realize the sharing of clinical information by "one case history per one patient" system. We hope that in the end our attempt will greatly contribute to the realization of a safe and at the same time precise and efficient health care system in Japan.

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A part of this study was performed under contract to the New Energy and Industrial Technology Development Organization (NEDO). The authors are grateful for the assistance received from many people during this study. The authors particularly thank people at Hitachi Corporation for providing us with valuable advice and instruction on system design, data analysis, data mining, etc.

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SCIENTIFIC LETTER

Circulating malondialdehyde modified LDL is a biochemical risk marker for coronary artery disease

T Amaki, T Suzuki, F Nakamura, D Hayashi, Y Imai, H Morita, K Fukino, T Nojiri, S Kitano, N Hibi, T Yamazaki, R Nagai

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Oxidatively modified low density lipoprotein (OxLDL) plays an important role in the development of atherosclerosis as its uptake by macrophages and smooth muscle cells leads to formation of foam cells which is a critical step in the evolution of the pathological state.[1 2] Circulating OxLDL concentrations may therefore reflect the state of pathological atherosclerosis, and be a possible biochemical risk marker for coronary artery disease (CAD). Numerous efforts have been directed at detecting OxLDL concentrations in the circulation for this reason, but technical difficulties have hampered detection of minute amounts of OxLDL. To overcome these limitations, we focused on circulating malondialdehyde modified LDL (MDA-LDL), a chemical modification thought to reflect naturally occurring oxidation of LDL,[3 4] and developed a sensitive immunoassay of circulating MDA-LDL concentrations. The diagnostic performance of MDA-LDL in CAD was compared against known lipid markers. This comparison revealed, for the first time, that MDA-LDL is superior, thus suggesting that MDA-LDL may be a promising tool for the biochemical detection of CAD.

METHODS

Consenting patients with CAD defined as having greater than 75% stenosis in one or more arteries on coronary angiography were enrolled, as were normal control subjects which included patients with normal coronary angiograms, and subjects who were admitted for regular health examinations and had: (1) no history of CAD; (2) normal renal function; (3) normal ECG and chest *x* ray.

Blood was drawn under fasting conditions and centrifuged within four hours. Stabilising reagent containing sucrose and EDTA was added and samples were stored at −20°C until the time of assay, which was within 28 days. MDA-LDL concentrations were measured by a sandwich enzyme linked immunosorbent assay (ELISA) procedure using an anti-MDA-LDL monoclonal antibody as the capture antibody and an anti-human apolipoprotein B monoclonal antibody labelled by β galactosidase as previously described with slight modifications.[5] The assay specifications were as follows: the measuring range of the assay was from 12.5–400 U/l; within run reproducibility, as a measure of analytical precision, showed a coefficient of variance of 5.6%; recovery, as a measure of analytical accuracy and defined as the observed versus expected value when concentrated MDA-LDL was added to patient serum, was 98%. One unit per litre of MDA-LDL was defined as the absorbance obtained with the standard at a concentration of 1 mg/l. Circulating concentrations of total cholesterol (normal reference 150–219 mg/dl), LDL cholesterol (70–139 mg/dl), high density lipoprotein (HDL) cholesterol (41–96 mg/dl), triglyceride (50–149 mg/dl), and apoprotein B (66–109 mg/dl) were also measured.

Statistical analysis was done using the unpaired *t* test for analysis of two groups and the Kruskal-Wallis test for effects of age. Data are shown as mean (SD) and a probability value of $p < 0.05$ was considered significant.

RESULTS

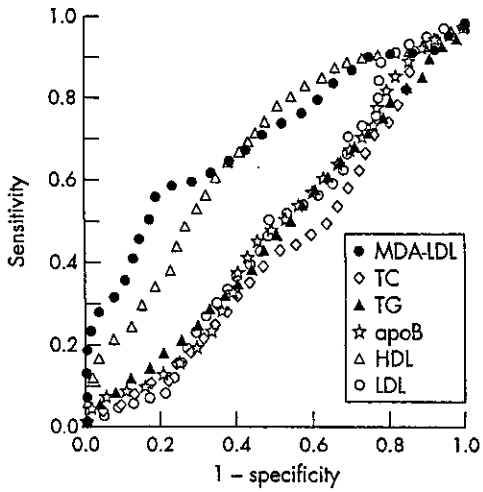
Fifty three patients with CAD (43 males and 10 females, aged 65.3 (9.4) years) and 57 normal controls (46 males and 11 females, aged 50.4 (13.1) years) were enrolled. Comparison of baseline characteristics (fig 1A) showed similar total cholesterol, LDL, triglyceride and apoprotein B concentrations between groups, but higher age and lower HDL cholesterol concentrations in CAD patients. MDA-LDL concentrations were notably raised in CAD patients (CAD 104.8 (42.9) U/l *v* control subjects 76.0 (23.3) U/l, $p < 0.0001$). Lack of association of MDA-LDL concentrations with age either for patients or controls ruled out age dependent effects (data not shown). Higher MDA-LDL concentrations were seen in severe CAD as manifested by the greater number of diseased vessels (single vessel disease (SVD) 102.6 (39.5) U/l, n = 21; two vessel disease (2VD) 95.6 (38.8) U/l, n = 24; three vessel disease (3VD) 138.1 (52.0) U/l, n = 8; $p = 0.02$ for SVD *v* 3VD and for 2VD *v* 3VD). Analysis according to degree of stenosis showed a tendency for total occlusion lesions to show slightly higher concentrations although not significantly higher (⩽ 75% stenosis, 103.4 (46.3) U/l, n = 10; ⩽ 90%, 85.0 (27.0) U/l, n = 9; ⩽ 99%, 89.2 (18.8) U/l, n = 4; 100%, 120.1 (56.7) U/l, n = 17). Of the CAD patients, nine patients had acute coronary syndromes (ACS) such as acute myocardial infarction and unstable angina, and all remaining patients had stable CAD (that is stable angina, post-intervention re-study, post-bypass angiogram). There was no significant difference in MDA-LDL concentrations between ACS and stable CAD patients suggesting that unstable plaque pathology does not affect concentrations. Of 27 patients with hyperlipidaemia, 22 received statins for more than three months; this did not affect the findings. MDA-LDL concentrations were elevated in CAD patients not receiving statins (CAD patients without statins 101.5 (42.7) U/l, n = 31; control 76.0 (23.3) U/l, n = 57, $p = 0.0005$). There was also no difference in MDA-LDL concentrations between the 22 patients receiving statins from the other CAD patients (patients receiving statins 109.3 (43.8) U/l, n = 22; other CAD patients 101.5 (42.7) U/l, n = 31, $p = 0.52$). Furthermore, MDA-LDL concentrations in patients with CAD did not differ from control patients regardless of history of diabetes mellitus, hypertension or smoking habit.

Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; MDA, malondialdehyde-modified; Ox, oxidative; SVD, single vessel disease; 2VD, two vessel disease; 3VD, three vessel disease.

A

	CAD	Controls	P
n	53	57	
Age, y	65.3 (9.4)	50.4 (13.1)	<0.001
Men, n (%)	43 (81%)	46 (81%)	0.954
Hypertension, %	81.1	24.6	<0.001
Diabetes mellitus, %	34	1.8	<0.001
Smoking, %	60.4	36.8	0.014
MDA-LDL (U/l)	104.8 (42.9)	76.0 (23.3)	<0.0001
Total cholesterol (mg/dl)	186.3 (29.5)	198.1 (38.2)	0.0738
LDL (mg/dl)	115.3 (23.2)	121.6 (33.6)	0.2614
HDL (mg/dl)	46.6 (12.2)	54.3 (14.9)	0.0039
Triglyceride (mg/dl)	108.2 (56.0)	123.5 (71.8)	0.2213
apoB (mg/dl)	95.9 (20.9)	97.6 (26.9)	0.715

B



C

Item	Cut-off	Sensitivity	Specificity	PPV	NPV
MDA-LDL	85.6 U/l	0.64	0.65	0.63	0.66
Total cholesterol	193 mg/dl	0.43	0.49	0.44	0.48
LDL	113 mg/dl	0.47	0.47	0.45	0.49
HDL	49 mg/dl	0.68	0.60	0.61	0.67
Triglyceride	102 mg/dl	0.47	0.49	0.46	0.50
apoB	97 mg/dl	0.45	0.53	0.47	0.51

PPV = positive predictive value, NPV = negative predictive value

Figure 1 (A) Baseline characteristics of participants. (B) Receiver operating characteristics (ROC) curve analysis of MDA-LDL and other lipid markers in patients with CAD. (C) Sensitivity, specificity, and positive and negative predictive values are shown.

Diagnostic implications of MDA-LDL concentrations against other lipid markers were assessed by receiver operating characteristics curve analysis. The analysis demonstrated MDA-LDL to show superior performance against the other parameters in our study population (fig 1B). MDA-LDL concentrations at a cut-off level of 85.6 U/l showed a sensitivity and specificity of 64% and 65%, respectively (area under the curve 0.72). Odds ratio showed a 3.3-fold likelihood for patients with raised MDA-LDL concentrations to have coronary artery disease. The other lipid parameters showed the following diagnostic performance (as shown in order of highest area under the curve): HDL cholesterol (0.67), apoprotein B (0.49), LDL cholesterol (0.45), triglyeride (0.45), and total cholesterol (0.40). Sensitivity, specificity as well as positive and negative predictive values are shown (fig 1C). Therefore, MDA-LDL was the most superior lipid marker of those tested in this study.

DISCUSSION

Our study shows increased serum concentrations of MDA-LDL in patients with CAD. MDA-LDL is an independent risk factor of CAD as there was no association with other risk factors such as hypertension, hyperlipidaemia, smoking habit, or sex. MDA-LDL concentrations are higher in patients with severe disease, such as multi-vessel disease, which shows that not only are MDA-LDL concentrations raised in patients with CAD but also that the concentrations reflect the severity of the pathogenic state. Receiver operating characteristic curve analysis showed superior performance of association between MDA-LDL and CAD as compared to other lipid markers, which is the first comparison to our knowledge. The conclusions of our study are limited given the small patient study population, but suggest that MDA-LDL is a promising lipid parameter to assess the risk of CAD.

Limitations of the present study include: (1) biased populations which analysed very sick patients versus very healthy patients; (2) the new measure was performed in a single centre laboratory; (3) the blood sampling protocol was ideal which may overestimate the clinical utility.

Future questions which remain to be answered are the prognostic and therapeutic roles of MDA-LDL concentrations in CAD. Will patients with higher concentrations of

MDA-LDL be prone to CAD in later life? Will MDA-LDL concentrations be a therapeutic parameter to assess risk for CAD (for example, lipid lowering)? These questions will need to be clarified in future studies before MDA-LDL concentration can become established as a powerful diagnostic lipid parameter of CAD.

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IMAGES IN CARDIOLOGY

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Magnetic resonance angiography of pseudocoarctation

A 40 year old woman presented with an abnormal chest radiograph without any symptoms. She had no history of hypertension. On examination she had a regular pulse and normal range of blood pressure measured at each extremity. The chest radiograph revealed a large mass with features suggesting an aortic anomaly including peripheral linear calcification and a tubular and tortuous opacity, the outline of which was smoothly continuous to the descending thoracic aorta (panel A). Conventional *x* ray aortography failed because the catheter inserted via the right femoral artery could not pass over the tortuous aortic arch in order to get the tip located proximal to the arch for contrast injection. The patient underwent contrast enhanced, magnetic resonance angiography. Three dimensional reconstructed images demonstrated an extremely elongated and approximately three-turned, helical, aortic arch with multiple saccular aneurysms in the anteroposterior (panel B) and oblique lateral (panel C) views. The more caudal origin of the left subclavian artery was clearly depicted in the posterior view of the three dimensional image (arrow in panel C). This congenital anomaly consisting of redundancy of the aortic arch without any significant obstruction has been known as pseudocoarctation. Surgical intervention was considered but rejected because of the absence of symptoms, complications, any evidence of risk of rupture, and associated cardiac abnormalities related to pseudocoarctation in this patient.

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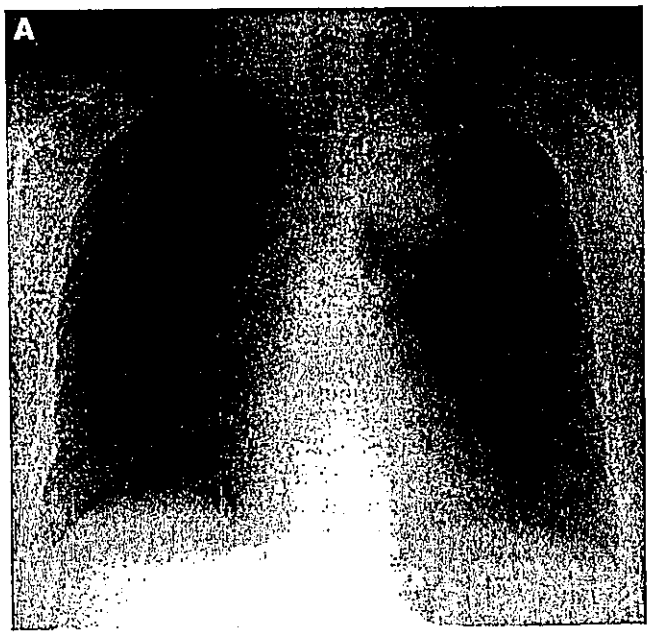

Clinical Studies

Design and Rationale of the Japanese Coronary Artery Disease (JCAD) Study

A Large-scale, Multicentered Prospective Cohort Study

JCAD study Investigators and Operation Secretariat headed by
Doubun HAYASHI,[1] MD, *and* Tsutomu YAMAZAKI,[2] MD

SUMMARY

Since there is in sufficient evidence on patients with coronary artery disease in Japan, the Japanese Coronary Artery Disease (JCAD) Study, in which 217 institutions participate, was designed to collect basic data based on evidence-based medicine (EBM). In this study, cardiac catheterization is performed on all cases to select study subjects confirmed as having CAD diagnosed based on the criteria that he or she has stenosis in at least one branch of a coronary artery to the extent of 75% or higher according to the AHA classification. Data including background information, risk factors, clinical management, and medication are to be collected over the web. The follow-up arm of the study consists of following each subject for three years to obtain data on the long-term prognosis of patients with CAD while the other arm is for enrolling new subjects every six months who will be followed for six months only for the purpose of determining the latest trend in patients. The two arms of the study have been ongoing since April 2000. As of September 30, 2003, 15,506 subjects have been enrolled in the follow-up arm and the follow-up data have been entered in the database. The authors plan to report data showing any correlation between incidence rate, focusing mainly on cerebrocardiovascular events, and other factors such as the management of risk factors, and type and dosage of medications obtained in the largest cohort ever studied in Japan of patients with a coronary artery lesion confirmed by cardiac catheterization. (Jpn Heart J 2004; 45: 895-911)

Key words: Coronary artery disease, Coronary risk factors, Japanese prospective cohort, Major cardiovascular event (MACE), Pharmacological treatment, Registration via Web

DYNAMIC statistics of the Japanese population in 1999[1)] show that the number of deaths from heart disease amounts to 151,079 a year, which corresponds to 15.4% of all deaths, and is second to only those from malignant neoplasms. Considering that coronary artery disease (CAD) is responsible for the majority of deaths from heart disease, seeking an approach to the trends in patients with CAD

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and the coronary risk factors behind it is one of the most important tasks for clinicians.

In European countries as well as in the USA, the frequency of occurrence of CAD has traditionally been high and many cohort studies such as the Framingham Study[2] have been conducted. These studies have shown that the combination of various factors including smoking, hypertension, diabetes and hypercholesterolemia is responsible for the onset of CAD. Based on these findings, many related societies and organizations have issued various guidelines,[3-6] aiming at helping people properly manage known risk factors, and these have resulted in a certain level of success. In Japan too, several important cohort studies such as the Hisayama Study,[7] Hiroshima-Nagasaki Study,[8] and J-LIT[9] were published. Based on the findings of these studies, various guidelines were prepared and attempts have been made to apply these guidelines to day-to-day clinical practice. However, the guidelines were, in fact, prepared by importing European and American guidelines without substantial modification due to the shortage in absolute quantity of data accumulated in Japan as a whole which determines treatment. Further, taking into account the report[10] that according to the data obtained so far in Japan, the mortality of CAD is one-third to one-fifth as much as that in Europe and the USA, for both physicians and patients, it may not be easy to comply with the Japanese guidelines prepared by referring to European and America guidelines.

However, as Japanese people continue to increasingly adopt a Western lifestyle, it is believed the incidence of CAD will increase in Japan in the near future as it has in Europe and the USA. It is conceivable that before long Japanese clinicians will find themselves in an environment demanding they focus more on the prevention and treatment of CAD. Therefore, it is a matter of urgent necessity to construct an original database that will serve as the basis of clinical practice which incorporates disease structures peculiar to Japan, including the facts that there are more cases of cerebrovascular disease than those of CAD, and that the incidence of hypertension is overwhelmingly higher than other diseases.

This study was planned to offer guidance for the preparation of treatment guideline(s) for Japanese patients, by way of investigating the current status of medical treatment and management of risk factors in CAD patients, and grasping the correlation between background factors and the occurrence of cerebrocardiovascular events. To be more specific, this is a large-scale, multicentered prospective cohort study (observational study) aiming at a total enrollment of approximately 20,000 subjects. Fifty-five advisors and administrators were selected from major regional hospitals performing many cardiac catheterization procedures. In total, 217 institutions have participated in the study.

PURPOSE

The JCAD Study aims at offering fundamental data which can contribute to evidence-based medicine (EBM) for the treatment and management of patients with CAD by investigating sequentially how CAD patients are treated and how their risk factors are managed in Japan, and further, by gaining information on the incidence of major cerebrocardiovascular events.

STUDY DESIGN AND SUBJECTS

This study has two concurrently ongoing arms, one following the same subjects for three years with a follow-up examination every six months (Follow-up Study), the other enrolling new subjects every six months with a follow-up period of six months (Trend Study) (see Figure 1). For both the Follow-up and Trend Studies, at the time of performing cardiac catheterization during the enrollment period, patients having significant stenosis of at least 75% according to the AHA classification in one or more branches of a coronary artery and whose clinical information six months later is available to investigators were continuously enrolled until the target number of cases allocated to each institution was achieved. Subjects were enrolled regardless of age or sex. Subjects whose cerebrocardiovascular event, including death was confirmed within six months of enrollment were included in the study, even though their clinical information six months later was not available.

Follow-up Study (to follow the same subjects for three years. Simultaneously serves as the first enrollment of the Trend Study:

i) Age/sex: no preference.

ii) To enroll all the subjects who have received cardiac catheterization during a one-year period from April 2000 through March 2003 and who meet all of the following three conditions:

(1) Subjects who have significant stenosis of at least 75% according to the AHA classification in a coronary artery at the time of cardiac catheterization;

(2) Subjects who are retained as outpatients of the same institution six months after cardiac catheterization; and

(3) Subjects who are not retained as outpatients of the institution but whose cardiac event (including death) is confirmed within six months of cardiac catheterization.

Trend Study (to enroll subjects every six months who are not enrolled in the Follow-up Study to follow them for six months only.):

i) Age/sex: no preference.

ii) To enroll subjects who have undergone cardiac catheterization during the following period. Other criteria are the same as for the Follow-up Study.

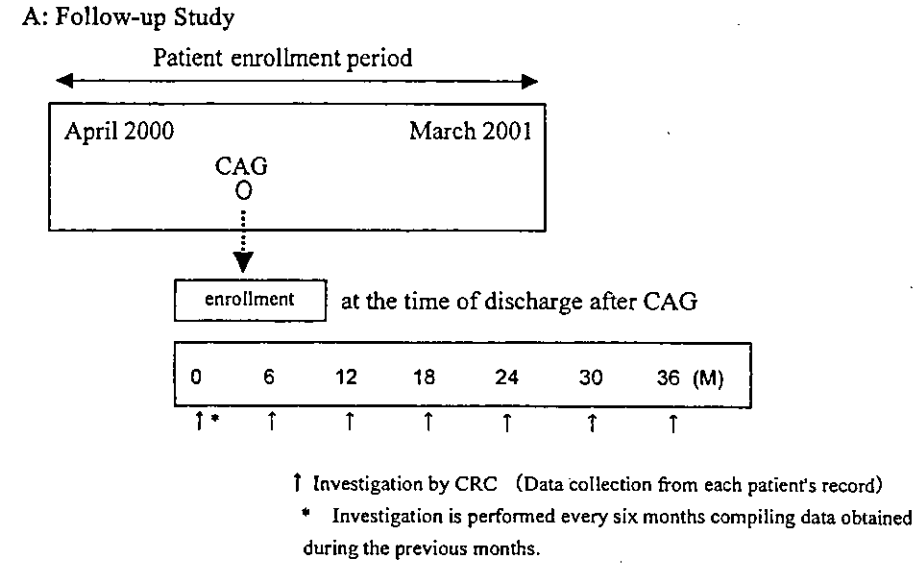

Figure 1. Schematic represetation of the Follow-up (A) and Trend (B) Studies.

METHOD, PROTECTION OF PRIVACY, AND ETHICS

An enrollment system was established within the University Hospital Medical Information Network (UMIN) and subjects were enrolled through the web by participating institutions located throughout Japan. For security purposes, an ID

and password used exclusively by a responsible investigator at each institution and a cryptocommunication system (SSL128bit) were employed. To protect subject privacy, only the system manager was allowed access to case card numbers and birth dates which identify the individual patients. Other participants, including the secretariat and administrators of the study, were denied access to such information. Access to individual patient data was givin only to the attending physician in charge of each patient. Further, in principle, case records were to be prepared by physicians themselves or by a Clinical Research Coordinator (CRC) being overseen by physicians. In addition, each physician was to confirm whether the data had been entered correctly.

Table I. JCAD Study Items to be Investigated (A: Follow-up Study, B: Trend Study)

A: Follow-up Study (Following-up each patient for 3 years)

	CAG*	6M	12M	18M	24M	30M	36M
Background	○						
CHD diagnosis	○						
Coronary imaging & treatment	○						
Patient's medical history	○						
CHD risk factors	○	○	○	○	○	○	○
Medication	○	○	○	○	○	○	○
Lifestyle improvement therapy Y/N	○	○	○	○	○	○	○
Event	○ (observation throughout the study period)						

The investigation items have to be determined on the date defined above or before/after one month from the date.

B: Trend Study (enrolling new patients every six months, following the patients only for six months thereafter)

	CAG*	6M
Background	○	
CHD diagnosis	○	
Coronary imaging & treatment	○	
Patient's medical history	○	
CHD risk factors	○	○
Medication	○	○
Lifestyle improvement therapy Y/N	○	○
Event	○	○

The investigation items have to be determined on the date defined above or before/after one month from the date.
* At the time of CAG: values obtained on the latest date before discharge (during hospitalization for check-up) have to be entered.

1) Clinical Research Review Board

In principle, the Clinical Research Review Board of each participating institution reviews and approves the study protocol and other documents, and evaluates the study on an ongoing basis.

2) Informed Consent

In principle, each attending physician explains the study to each candidate patient and obtains his or her voluntary written informed consent prior to enrollment.

3) Confidentiality of Data

In reporting the data collected, the physician, CRC, staff members of the Study Secretariat, and others use a case card number or subject number (designated by UMIN after enrollment).

PARAMETERS TO BE DETERMINED

For the subjects who were enrolled after cardiac catheterization, data on medications administered before cardiac catheterization, risk factors, and results of the catheterization procedure, diagnosis at the time of catheterization procedure, previous disease (treatment), if any, site of stenosis, extent of stenosis, treatment performed after catheterization procedure (percutaneous transluminal angioplasty, coronary artery bypass, etc.) were recorded. Further information regarding how coronary risk factors such as hyperlipidemia, impaired glucose tolerance, hypertension, smoking, and drinking are managed, as well as laboratory data obtained at that time regarding total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low density lipoprotein cholesterol (LDL-C; Friedewald formula), fasting blood glucose (FBG), HbAlc, blood pressure, body mass index (BMI), uric acid (UA), lipoprotein small a (Lp (a)), C-reactive protein (CRP), and cardiac failure, if any, were collected at enrollment and every six months thereafter. In the case of acute disease such as myocardial infarction, hematological data obtained during a stable phase were recorded. These data were to be entered every six months (see Table I).

With the endpoint being all cerebrocardiovascular events, in case such an event should occur after enrollment, a description of the event, treatment, and outcome were recorded any time such an event occurred. "Event" is defined as the case where the subject develops a new cerebrocardiovascular disease or experiences a recurrence of such a disease after the cardiac catheterization procedure or treatment performed following such a procedure. If there are no symptoms of ischemia and restenosis is confirmed by regular cardiac catheterization, such a case is to be excluded from "event".

ANALYSES

In the Follow-up and Trend Studies, enrolled cases will be analyzed by the "intention-to-treat" method. The following analyses are planned for each of the studies:

Follow-up study: How the risk factors each CAD patient with stenosis of 75% according to the AHA classification has are managed during the three-year period and how such management influences the endpoint are to be analyzed. The chi-square test is used for qualitative data, while the *t*-test is used for quantitative data in the case of a comparison between two groups. In the case of comparison among three or more groups such data are subjected to variance analysis, and if there is any significant difference, Scheffe's post hoc analysis is also to be performed. The χ^2 test is used for any change in risk factors, while changes in parameters are to be evaluated by variance analysis and then subjected to Scheffe's multiple comparison. Relation between the endpoint and the presence (or absence) of any risk factors, such as treatment after cardiac catheterization procedure, medication administered, risk factor parameter, and expenses incurred (in treatment, drugs, etc.) are to be analyzed by multivariate studies based on Cox's proportional hazard model. Further, multiple regression analysis based on these factors is to be performed in an attempt to construct a linear model to forecast the occurrence of cardiovascular events.

Trend study: The trend in the selection of treatment for CAD patients in Japan for each six-month period is to be investigated and how the difference in the selection of treatment correlates with the endpoint is to be studied. The risk factors for each subject and the changes in parameters are to be studied using the same analytical methods as in the Follow-up Study. Analysis of events is to be performed in the same manner as in the Follow-up Study. In addition, relative risk is to be calculated for every six-month period, and how the occurrence of cardiovascular events is influenced by the presence (or absence) of any of the risk factors, medication administered, and changes in risk factor parameters is to be studied.

FUTURE SCHEDULE

Enrollment began in April 2000 and the initial enrollment of 15,506 cases for the Follow-up Study ended on September 30, 2003. In the Follow-up Study, the patient enrollment procedure was completed by the end of March, 2004 and the data entry period will expire as of the end of September 2004. In April 2005, how risk factors and treatment given to each patient correlate with the recurrence

rate of CAD will be reported based on the Follow-up Study and background factors of Japanese CAD patients, while how they are treated and the change in the recurrence rate of short-term cerebrocardiovascular events will be reported based on the Trend Study.

Subsequently, various subanalyses, including analysis by sex, existence of concomitant coronary risk factors, treatment following the cardiac catheterization procedure, and a cost versus benefit study will be performed and the results will be reported at a later date.

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