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Assessment of Coronary Intervention in Japan From the Japanese Coronary Intervention Study (JCIS) Group

— Comparison Between 1997 and 2000 —

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Background The first nationwide survey of the situation in Japan (the 1997 SJ) regarding percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) was conducted by the Japanese Coronary Intervention Study (JCIS) group and the results of the second nationwide, continuous survey of Japan in 2000 (the 2000 SJ) are presented here.

Methods and Results A questionnaire was collected from 8,268 facilities (99.93%). In the 2000 SJ, the total number of coronary arteriography (CAG) performed was 543,046 (428 CAGs per 10^5 population). The estimated ratio of CAG to patients with coronary artery disease (CAD) in Japan is approximately 1.4-fold that in the US. Total numbers of PCI and CABG performed were 146,992 and 23,584, and increased to 134% and 130%, respectively, over the 3 years. PCI facilities with an annual number of PCIs performed of more than 100 were 40.2%, and the respective CABG facilities were 8.3%. The ratio of PCI to CABG was 6.23 in the 2000 SJ, and was several times higher than the ratio in Western countries.

Conclusion The situation in Japan regarding the number of CAG, PCI, and CABG procedures performed is very different from that in Western countries. This provides important information for diagnosis, treatment and guidelines for Japanese patients with CAD. (*Circ J* 2004; **68:** 181–185)

Key Words: Annual number; Coronary intervention; Japan

Coronary artery disease (CAD) is a serious and common disease that seriously influences the prognosis and quality of life of patients. Coronary intervention for CAD is classified into percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG). The indications of PCI have widened with the development of new devices and techniques, and the outcome of treatment has improved[1,2] Thus, PCI is increasingly used throughout the world[3–5] although it is an invasive and expensive therapy and still has some serious problems in terms of complications and/or restenosis. The first nationwide survey of of PCI and CABG in Japan (the 1997 SJ) was conducted in 1998 by the Japanese Coronary Intervention Study (JCIS) group with the support of 7 Japanese societies of cardiology, including the Japanese Circulation Society, the Japanese Society of Interventional Cardiology, the Japanese College of Cardiology, the Japanese Coronary Association, the Japanese Association for Thoracic Surgery, the Japanese Society for Cardiovascular Surgery, and the Japanese Association for Cerebro-cardiovascular Disease Control[6,7] To define whether PCI and CABG have increased since then, we investigated the first continuous survey of Japan in 2000 (the 2000 SJ) in 2002. In addition, the number of coronary arteriography procedures (CAG) performed in Japan was investigated. This is the first such investigation in Japan, and the relationship between CAG and PCI or CABG was analyzed in the present study.

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Methods

For the 2000 SJ, a questionnaire was dispatched by letter or fax to the departments of internal medicine, cardiology and cardiovascular surgery of 8,274 hospitals throughout Japan. Basic data such as the names and addresses etc of hospitals all over Japan were obtained from the Japanese hospital database of Japan Medical Press Inc (Tokyo, Japan).

We narrowed the questionnaire down to the following 5 questions as the minimum information required, in order to increase the collection rate: (1) number of cases of CAG performed from January 1 to December 31, 2000; (2) the number of cases of PCI performed from January 1 to December 31, 2000; (3) the number of cardiologists; (4) the number of cases of CABG performed from January 1 to December 31, 2000; and (5) the number of cardiovscular surgeons. Note that items (2)–(5) in the 2000 SJ are the same as those in the 1997 SJ, but that item (1) is a new question.

These data were collected in the Second Department of Internal Medicine, Gifu University Graduate School of Medicine, and were analyzed by a host computer at the Japan Clinical Research Assist Center (JCRAC, Tokyo, Japan).

This study was approved by the local ethics committee on human research (Gifu University, Japan).

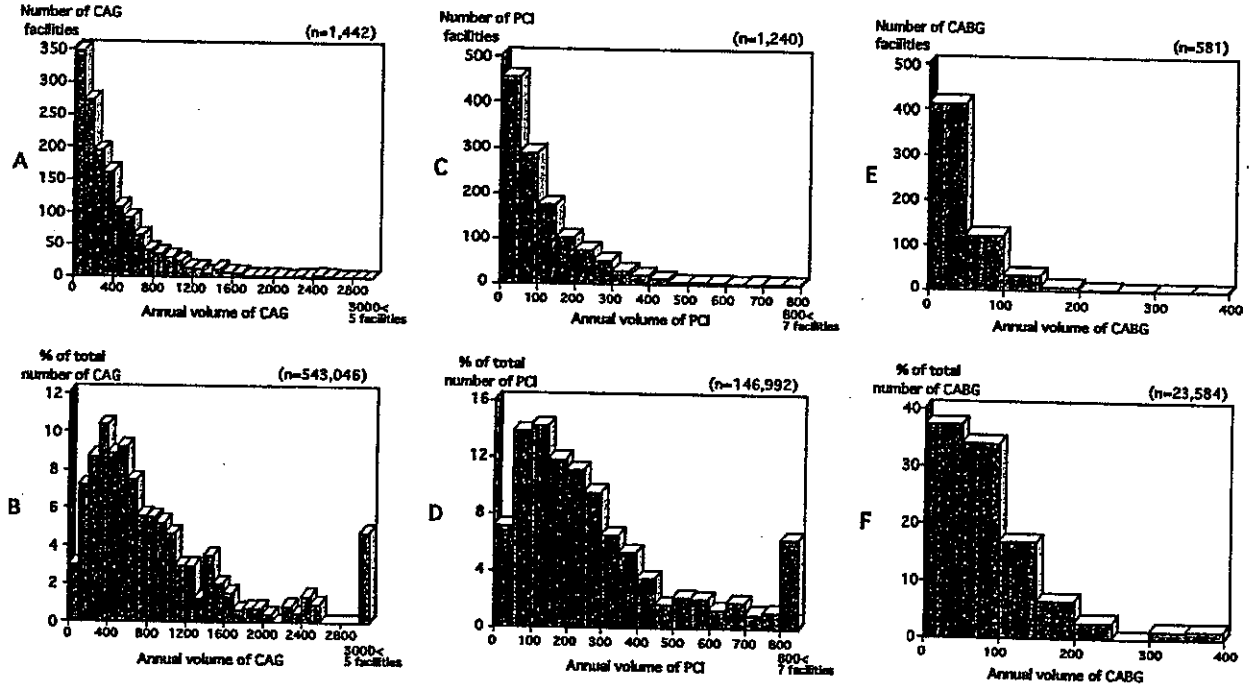

Fig 1. Annual volume of coronary arteriography (CAG), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) performed per facility, and the numbers of these facilities or % of these total numbers.

Table 1 Changes in the Numbers of Coronary Interventions and Facilities During the 3 Years, 1997–2000

	PCI		CABG	
	1997	*2000*	*1997*	*2000*
Total numbers of coronary interventions	*109,788 [113,279]*	*146,992*	*18,121 [18,697]*	*23,584*
Total icrease	*+37,204 [+33,713]*		*+5,463 [+4,887]*	
Rate of increase	*+134% [+130%]*		*+130% [+126%]*	
No. of facilities	*1,023 [1,056]*	*1,240 (+121% [+117%])*	*486 [501]*	*581 (+120% [+116%])*
Mean number per facility	*107*	*119 (+111%)*	*37*	*41 (+111%)*
Facilities in which PCI or CABG was performed in both 1997 and 2000				
No. of facilities	*967*		*427*	
No. of coronary interventions	*106,967*	*131,131*	*16,740*	*18,728*
Increase in number of coronary interventions	*+24,164 (+123%)*		*+1,988 (+112%)*	
Mean number per facility	*111*	*136 (+123%)*	*39*	*44 (+113%)*
Contribution ratio to the total increase in number	*65.0%*		*36.4%*	
Facilities in which PCI or CABG was discontinued during 1997–2000				
No. of facilities	*52*		*51*	
No. of coronary interventions	*1,702*	–	*1,042*	–
Mean number per facility	*33*	–	*20*	–
Facilities in which PCI or CABG was newly started during 1997–2000				
No. of facilities		*273*		*154*
No. of coronary interventions		*13,040*		*3,475*
Mean number per facility		*48*		*23*
Ratio to the total number in 2000		*8.9%*		*14.7%*
Contribution ratio to the total increase in number	*35.0%*		*63.6%*	

[ ] Numbers assuming that the collection rates of 96.85% in 1997 and 99.93% in 2000 are equivalent in both years.
( ) rate of increase in 2000.
PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Results

In the 2000 SJ, we obtained complete answers from 8,268 of 8,274 hospitals (collection rate: 99.93%). The percentage was similar to that of the 1997 SJ (7,993 of 8,253 hospitals: 96.85%).

Number of CAG Performed in Japan

CAG was performed in 1,442 facilities of 8,274 hospitals (17.4%), and the total number performed was 543,046. The mean number of CAG performed per CAG facility was 377 (minimum: 1, maximum: 9,369). Thus, the number of

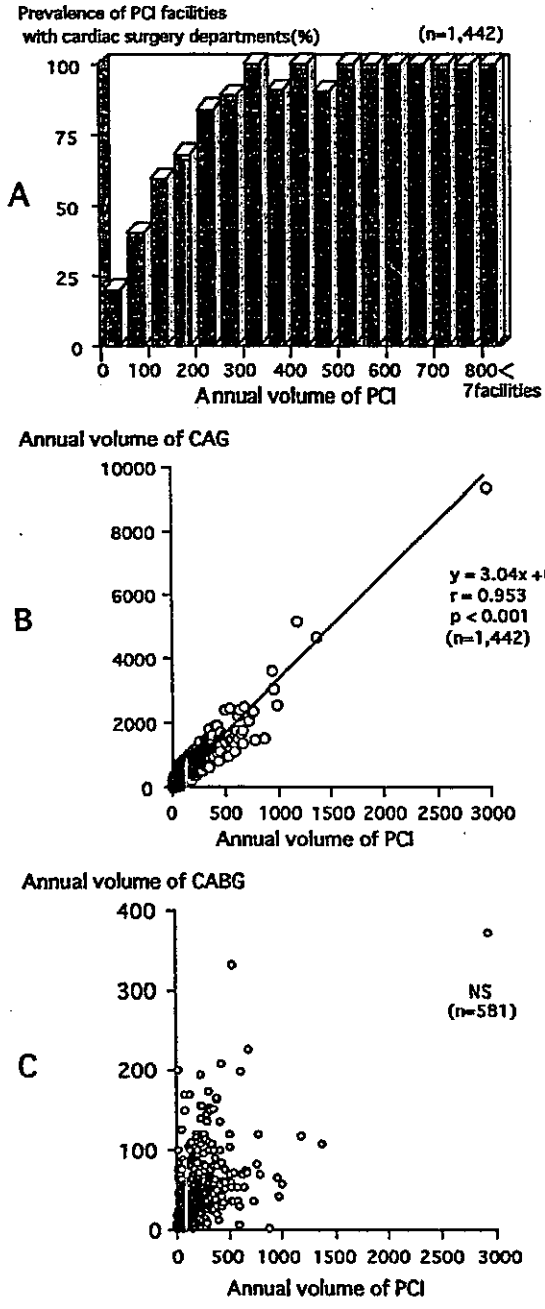

Fig 2. Annual volume of percutaneous coronary intervention (PCI) performed and other parameters. CAG, coronary arteriography; CABG, coronary artery bypass grafting.

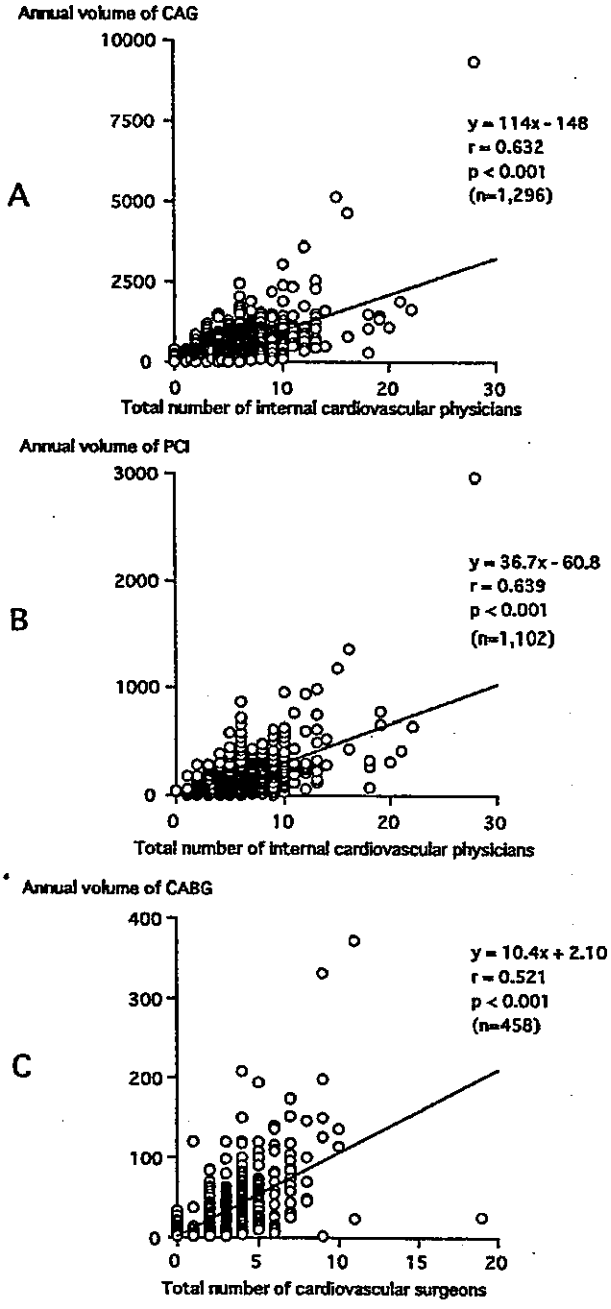

Fig 3. Numbers of cardiologists and cardiovascular surgeons and other parameters. CAG, coronary arteriography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

CAGs performed was 428 patients per 10^5 population in Japan.

The percentage of CAG facilities with an annual number of CAG below 100 was 24.1% (347 facilities), that below 200 was 42.9% (560 facilities), and that over 800 was 11.9% (252 facilities) (Fig 1-A). Only 3.0% of the total CAGs were performed in CAG facilities with an annual number of CAG below 100, 10.1% in those below 200, and 40.0% in those over 800 (Fig 1-B).

Number of PCI Performed in Japan

PCI was performed in 1,240 facilities of 8,274 hospitals (15.0%) (1,023 facilities in the 1997 SJ), and the total number of PCI performed was 146,992 in the 2000 SJ (109,788 in the 1997 SJ). PCI increased to 134% (corrected % by questionnaire collection rate of 2000: 130%) over the 3 years (Table 1). The number of facilities in which PCI was newly performed in 2000 was 273, and the total PCI performed in those facilities was 13,040 (8.9% of the total number in 2000). The mean number of PCI performed per PCI facility was 119 in the 2000 SJ (minimum: 1, maximum: 2,967) (107 in the 1997 SJ). Thus, the number of PCIs performed was 116 patients per 10^5 population in the 2000 SJ, and 90 in the 1997 SJ.

Table 2 Comparison of Coronary Interventions in the US and Japan in 2000

	US		Japan	
	Annual number	*Number per 10^5 population*	*Annual number*	*Number per 10^5 population*
CAG	*1,318,000*	*468*	*543,046*	*428*
PCI	*561,000*	*199*	*146,992*	*116*
CABG	*519,000*	*184*	*23,584*	*19*

CAG, coronary arteriography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

The percentage of PCI facilities with an annual number of PCI below 50 was 36.7% (41.6% in the 1997 SJ), that below 100 was 59.8% (64.8% in the 1997 SJ), and that below 200 was 82.0% (84.5% in the 1997 SJ) (Fig 1-C).

Some 7.1% of the total PCI number (8.9% in the 1997 SJ) was performed in PCI facilities with an annual number of PCI below 50, 20.9% in those below 100 (24.0% in the 1997 SJ), 46.9% in those below 200 (49.6% in the 1997 SJ), and 20.7% in those over 400 (21.6% in the 1997 SJ) (Fig 1-D).

Number of CABG Performed in Japan

CABG was performed in 581 facilities of 8,274 hospitals (7.0%) (486 facilities in the 1997 SJ), and the total number of CABG performed was 23,584 (18,121 in the 1997 SJ). CABG increased to 130% (corrected % by questionnaire collection rate of 2000: 126%) over the 3 years (Table 1). The number of facilities in which CABG was newly performed in 2000 was 154, and the total CABG number performed in those facilities was 3,475 (14.7% of the total number in 2000). The mean number of CABG performed per CABG facility was 41 in the 2000 SJ (minimum: 1, maximum: 371) (37 in the 1997 SJ). Thus, the number of CABGs performed was 19 patients per 10^5 population in the 2000 SJ, and 14 in the 1997 SJ.

The percentage of CABG facilities with an annual number of CABG below 50 was 70.9% (76.1% in the 1997 SJ), and that below 100 was 91.7% (95.1% in the 1997 SJ) (Fig 1-E).

Some 37.2% of the total CABG number (44.7% in the 1997 SJ) was performed in CABG facilities with an annual number of CABG below 50, and 71.2% in those below 100 (79.8% in the 1997 SJ) (Fig 1-F).

PCI facilities with cardiac surgery departments in the same hospital accounted for 19.6% of PCI facilities with an annual number of PCI below 50 (28.4% in the 1997 SJ), 40.0% of those between 50 and 100 (42.6% in the 1997 SJ), 63.8% in those between 100 and 200 (70.6% in the 1997 SJ), and 91.5% in those over 200 (89.7% in the 1997 SJ) (Fig 2-A). Therefore, 72.2% of the total PCI number was performed in PCI facilities equipped with a cardiovascular surgery department.

Correlations Between the Annual Numbers of CAG and PCI or CABG

There was a strong significant correlation between the annual numbers of CAG and PCI performed at each facility ($r=0.953$, $p<0.0001$) in the 2000 SJ (Fig 2-B). The ratio of CAG to PCI was 3.3, and this rate was almost the same among all institutions. On the other hand, there was no significant correlation between PCI and CABG in the 2000 SJ (Fig 2-C).

Ratio of PCI to CABG

The ratio of the total number of PCI performed to that of CABG performed was 6.23 in the 2000 SJ and was similar to that (6.21) of the 1997 SJ. The number of hospitals with a ratio between 0 and 3 was 175 (30.6%), that between 3 and 5 was 114 (19.9%), that between 5 and 8 was 129 (22.6%), and that over 8 was 155 (27.1%). The percentages were similar to those of the 1997 SJ.

Numbers of Cardiologists and Cardiovascular Surgeons in the 2000 SJ

In the 2000 SJ, the total number of cardiologists was 11,232, and that of cardiovascular surgeons was 2,999, and the ratio was 3.7. The 8,769 cardiologists (78.1%) were working at 1,442 CAG facilities, and 8,190 (72.9%) in 1,240 PCI facilities. The mean number of cardiologists per CAG and PCI facility, excluding University hospitals, was 4.5 and 4.8, respectively. There were significant correlations between the number of cardiologists and the annual numbers of CAG or PCI performed (Fig 3-A,-B).

The 2,719 cardiovascular surgeons (90.7%) were working at 581 CABG facilities. The mean number of cardiovascular surgeons per facility excluding the University hospitals was 3.5. There was a significant correlation between the annual number of CABG performed and the number of cardiovascular surgeons (Fig 3-C).

Discussion

Annual Number of CAG Performed in Japan

CAG was performed in 428 patients per 10^5 population in the 2000 SJ. In the US, CAG was performed in 468 patients per 10^5 population in 2000, which was almost equal to Japan (Table 2). There were 12,900,000 patients with coronary heart disease (4,584 patients per 10^5 population) in the US[8] but in Japan precise data on the prevalence of coronary heart disease, based on a nationwide survey, are not available. According to the 5th basic investigation of cardiovascular disease in 2000 by the Japanese Ministry of Health, Labour and Welfare, patients with coronary heart disease accounted for 3.2% of 8,369 Japanese (see Internet Web: http://www.mhlw.go.jp/toukei/saikin/hw/kenkow/jyunkan/jyunkan00/). It is estimated that the number of patients with coronary heart disease is 4,060,000 (3,199 patients per 10^5 population); that is, the ratio of CAG to patients with CAD in Japan is estimated to be approximately 1.4-fold that in the US.

The increase in CAG for patients with CAD in Japan may be related to differences in the indications for CAG and the health insurance system: (1) Japanese doctors may have a tendency to choose CAG in order to clarify the presence or absence of a significant stenosis of the coronary arteries or bypass grafts, and to clarify the presence or absence of restenosis at the PCI site after 3–6 months, even

if the patient is asymptomatic; and (2) the national health insurance system of the Japanese Government bears 70–80% of the costs of CAG for all citizens equally.

Comparison Between 1997 and 2000 of Coronary Interventions

The total number of PCI and CABG performed increased to 130% for PCI and 126% for CABG over the 3 years in Japan, compared with an increase to only 104% for PCI and decrease to 94% for CABG in the US over 2 years (1998–2000)[8]

As shown in Table 1, the total numbers of PCI and CABG in the facilities in which PCI or CABG was performed in both 1997 and 2000 increased to 123% and 113%, respectively. The contribution ratios of the increase to the total increase in the number of PCI and CABG were 65.0% and 36.4%, respectively. The number of facilities in which PCI or CABG was newly performed in 2000 was 273 and 154, respectively, and the total PCI and CABGs performed at those facilities were 13,040 and 3,475, respectively. The contribution ratios of the increase in the new facilities to the total increase in the number of PCI and CABG were 35.0% and 63.6%, respectively (Table 1).

Thus, approximately two-thirds of the increase in the total numbers of PCI and CABG during the intervening 3 years has been the increase in the number of PCI performed per facility and the increase in the number of new CABG facilities. We speculate that these increases in Japan may be related to increased application of PCI and CABG because of the development of new techniques and devices, such as stents. However, similar increases in the numbers of PCI and CABG were not seen in the US during the same period. Therefore, the increases can not be explained purely because of the developments in PCI and CABG techniques. Also, the ratio of increase for the 3 years is too large to explain from the increase in the number of patients with coronary heart disease in Japan. Thus, the increases may be related to other special factors in Japan such as the present Japanese medical economy. Further investigations are required in the future.

The present study demonstrated that the percentage of PCI facilities perfoming an annual number of PCI less than 50 decreased from 41.6% in the 1997 SJ to 36.7% in the 2000 SJ, and that the percentage of CABG facilities perfoming an annual number of CABG less than 50 decreased from 76.1% in the 1997 SJ to 70.9% in the 2000 SJ. The Japanese Ministry of Health, Labour and Welfare, and the ACC/AHA guidelines in the US, recommend that PCI facilities perform at least 100 (or 200 in the US) procedures annually. Therefore, these decreases may be associated with better, more skilful care of patients with CAD, although this has still to be clarified.

The ratio of PCI to CABG in the 2000 SJ, as well as in the 1997 SJ, was several times higher than that of Western countries (Table 2) and although there was a strong significant correlation between the numbers of CAG and PCI performed, there was no significant correlation between the annual numbers of PCI and CABG performed. To analyze these problems, the indications for PCI and CABG in Japan and Western countries should be compared and we intend to do so.

Conclusion

The situation in Japan regarding CAG, PCI and CABG is considerably different from that of Western countries.

Acknowledgments

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Appendix 1

Japanese Coronary Intervention Study (JCIS) Investigators

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Development of a Pioneering Clinical Support System Utilizing Information Technology

Clinical Informatics and Genome Analysis

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SUMMARY

Nowadays, evidence-based medicine has entered the mainstream of clinical judgement and the human genome has been completely decoded. Even the concept of individually designed medicine, that is, tailor-made medicine, is now being discussed. Due to their complexity, however, management methods for clinical information have yet to be established. We have conducted a study on a universal technique which enables one to select or produce by employing information processing technology clinical findings from various clinical information generated in vast quantity in day-to-day clinical practice, and to share such information and/or the results of analysis between two or more institutions. In this study, clinically useful findings have been successfully obtained by systematizing actual clinical information and genomic information obtained by an appropriate collecting and management method of information with due consideration to ethical issues. We report here these medical achievements as well as technological ones which will play a role in propagating such medical achievements. (Jpn Heart J 2004; 45: 315-324)

Key words: RCN System, Database system, Clinical informatics, Data mining, Information technology, Genome analysis, Evidence-based medicine, Tailor-made medicine

AS its population ages, major diseases in Japan have shifted from acute types of disease such as infections to chronic types such as life-style related diseases. Meanwhile, the government has recently implemented in some institutions a Prospective Payment System in which the government reimburses remuneration at a predetermined amount and health care reform with the major purpose being reorganiation of the health care system from an economical point of view is already in place. As a result, medical institutions are now required to safely and effi-

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ciently offer patients with chronic diseases more effective health care services than those currently available in order to cope with this reform.

However, in responding to social demands such as this, there are various issues which are difficult to solve completely only by precautions against human error or allocation of appropriate human resources. Therefore, the first step to solve such issues seems to be the preparation of fundamental information that is readily available prior to actual clinical treatment and the formation of a foundation upon which evidence-based medicine (EBM) is practiced. Since clinical research activity in Japan to evaluate clinical efficacy and safety is not up to the levels in Europe and the US, health care is mainly offered according to the clinical guidelines depending on the clinical data compiled in these countries. However, it must be noted that there are many differences arising from race, incidence of certain diseases, living environment, enzymatic activities for metabolizing drugs, and so on, and there is more and more need to collect fundamental clinical information and analyze clinical data obtained in Japanese subjects.

With the view of resolving these issues, much is expected recently in the realization of effective as well as efficient and safe health care brought about by systematizing clinical information. But in a majority of the cases, the attempt to select useful medical findings from clinical information is being made by individual clinical studies. It is considered that developing a technique to share such individual clinical information between health care institutions all over Japan widely accepted and practiced will in the end greatly contribute to the realization of a safe and at the same time effective health care system.

The objective of this study was to establish a universal technique with which to extract medical findings and to systematize diagnostic procedures by applying pioneering information technology (IT), with the aim of resolving the above-mentioned problems. In other words, we have constructed a clinical information management system with the following functions, in order to offer safe healthcare services, to realize efficient and effective healthcare, to improve the level of healthcare in general and further to overcome economical problems, all by implementing IT in the management of fundamental clinical information:

- Having clinical information in an electronic format (database construction)
- Comprehensive data analysis with data mining as the main function
- Real-time network linking of clinical information

Further, since this system will be utilized to assist in making a diagnosis in a clinical setting based on the vast amount of fundamental data accumulated in real-time, we have named this system the "Real-time Clinical Navigator System" (hereinafter referred to as "RCN System").

METHODS

Clinical information database: In this study, we have converted to electronic data a vast amount of information obtainable in day-to-day clinical activity, that is, various types of clinical information such as events ("death", "acute myocardial infarction", "cardiac failure", "stroke", etc.), laboratory findings ("Tchol", HbAlC", "heart rate", etc.) or prescriptions ("drug for treatment of angina pectoris", "antithrombotic drug", "anticoagulant", etc.) and constructed its database. In collecting such data, we proceeded through the informed consent procedure with each individual patient after we had obtained approval from the ethics committee of the University of Tokyo Faculty of Medicine. We only inputted clinical data and carried out genomic analysis for those patients who provided informed consent.

One of the major features of the RCN System interface is to store data in the form of a so-called chronological table, such as that used in historical science, with the passage of time in mind. There are the following two advantages in data storage methods according to the passage of time:

- It is possible to refer to the clinical information of a patient in time sequence.
- It is easy to establish the starting point in a prospective or retrospective investigation.

To be more specific, presenting a patient's clinical information in a time sequence such as a chronological table enables one to look at the patient's clinical history visually. Figure 1 shows the screen displaying a time sequence. Also, it is

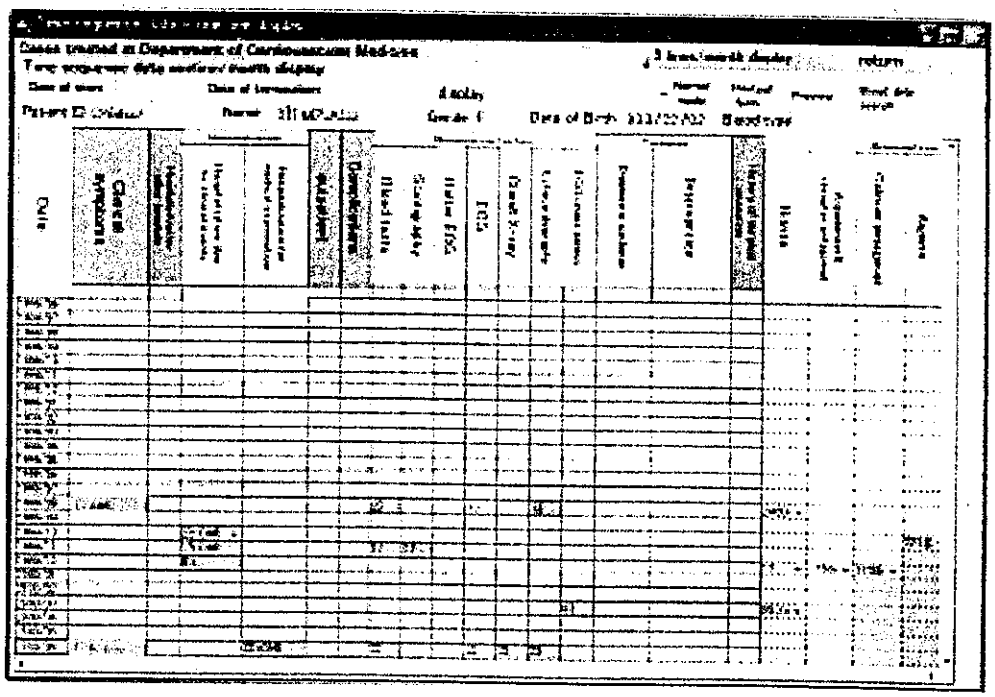

Figure 1. Presentation in time sequence of a patient's clinical history.

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

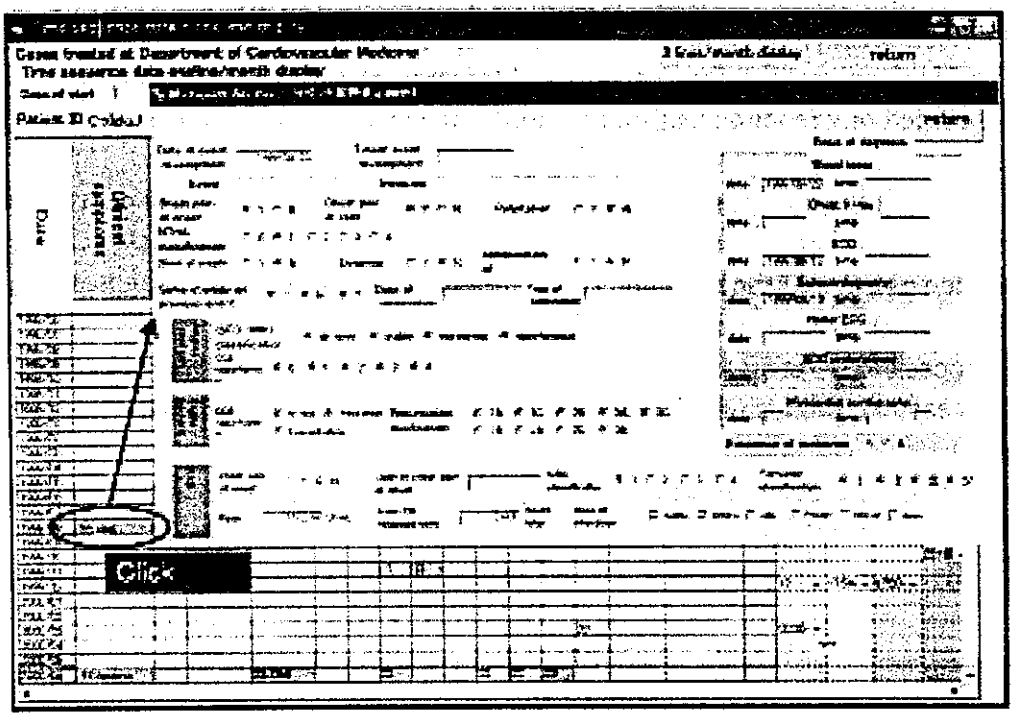

Figure 2. Details of each clinical item.

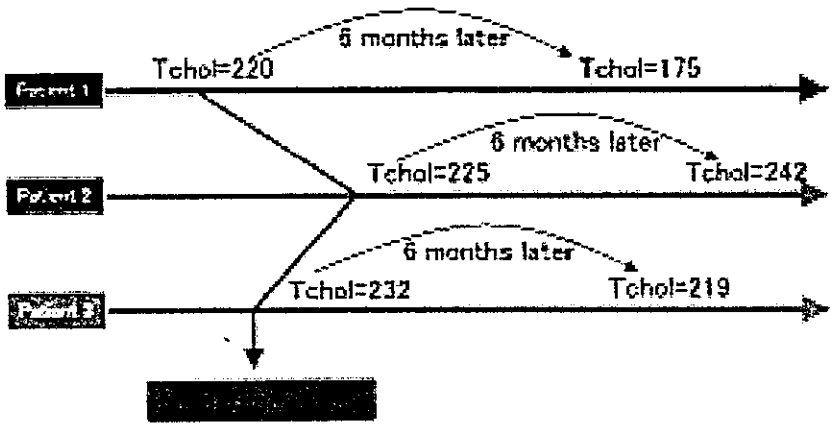

Figure 3. Investigation of variation in total cholesterol.

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).

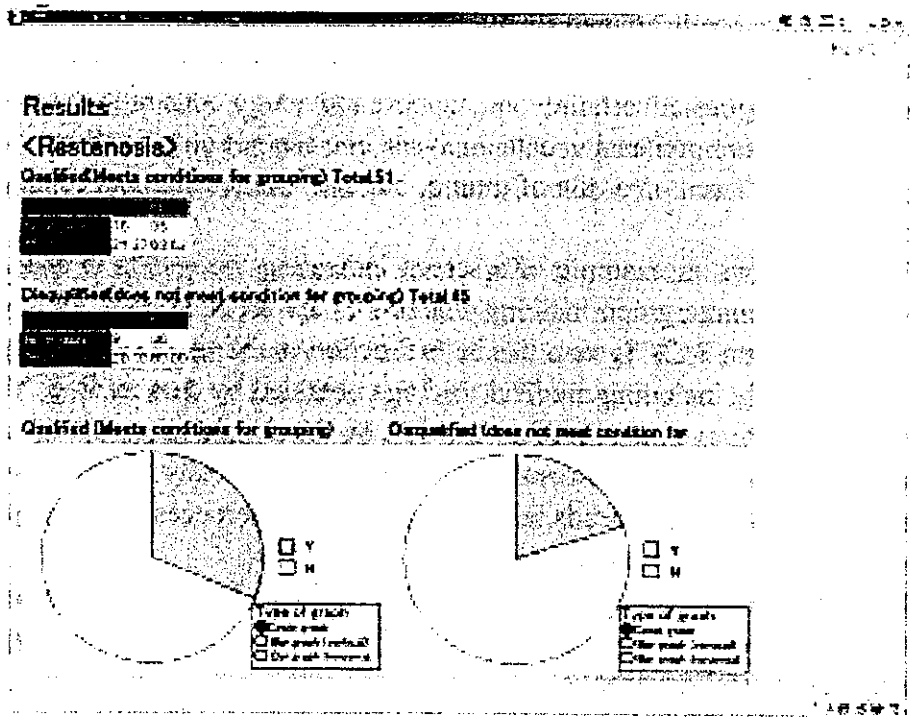

Figure 4. Example of graphic image of the analytical system of case data. Here, the patients are divided into two groups, one developing diabetes and the other no diabetes. The ratio of the patients who develop restenosis after recanalization of coronary artery is shown.

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.

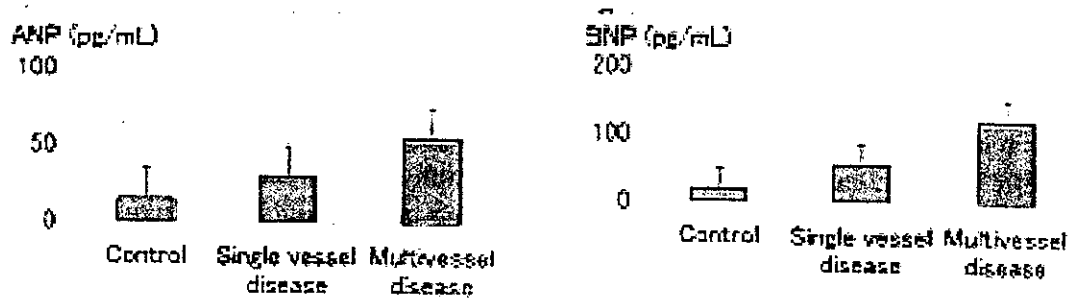

Figure 5. **A:** Correlation between plasma ANP level and the severity of coronary artery diseases. **B:** Correlation between plasma BNP level and the severity of coronary artery diseases.

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 ABCAl 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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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

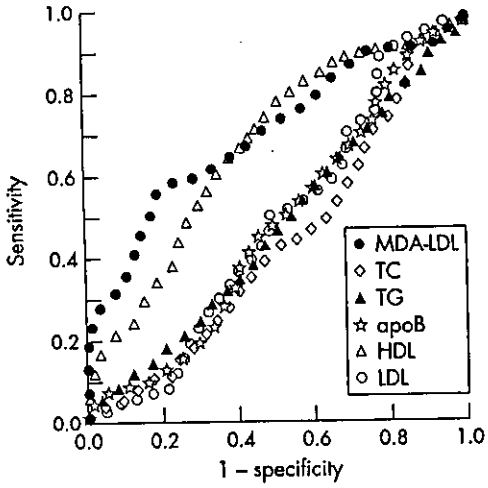
Fifty three patients with CAD (43 males and 10 females, aged 65.3 (9.4) years) and 57 normal controls (46 males and 11 females, aged 50.4 (13.1) years) were enrolled. Comparison of baseline characteristics (fig 1A) showed similar total cholesterol, LDL, triglyceride and apoprotein B concentrations between 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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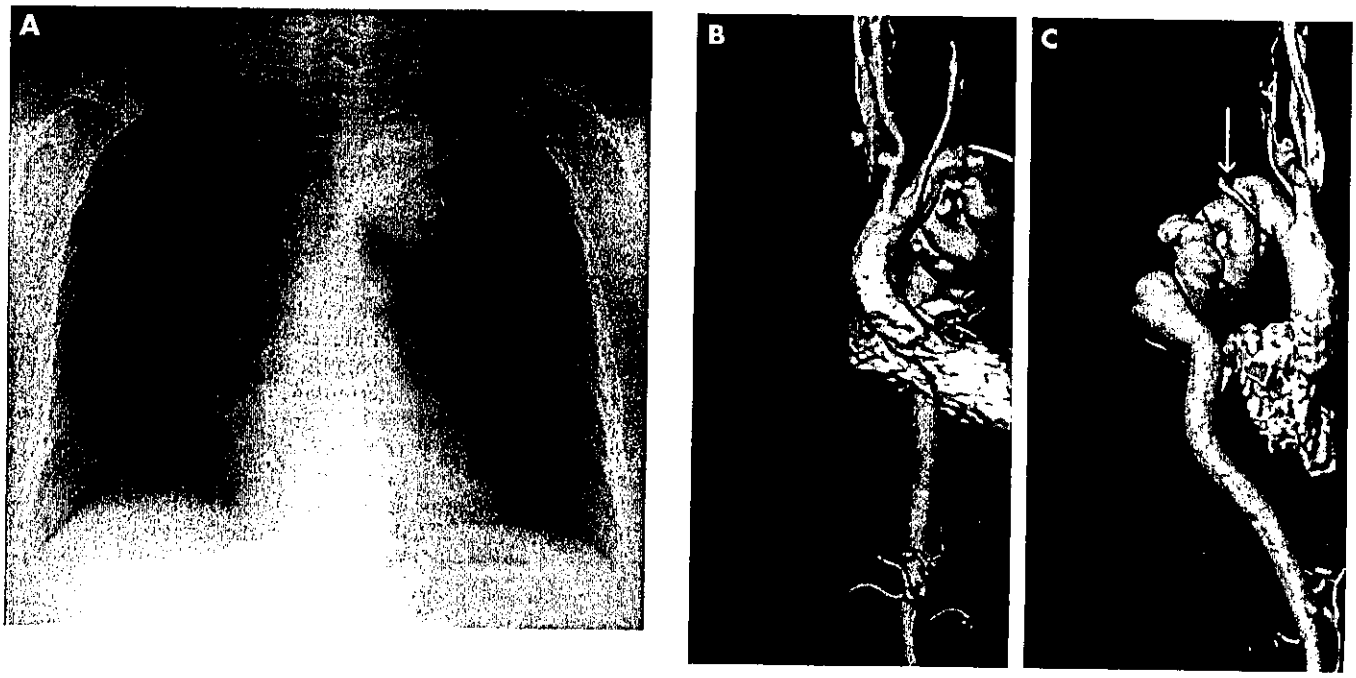

Design and Rationale of the Japanese Coronary Artery Disease (JCAD) Study

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.