報道されていれば，全米で100人以上の命が救えたはずだ」と非難が起こったのである。

この事件は，情報の曖昧さとコミュニケーション，そして意思決定が複雑に絡み合い，慎重な対応を要求するという問題提示を含んでいる。そしてここにインフォームド・コンセントがからんでくることにより，さらに微妙な問題が生じてくるのである。

情報の流通とCumulative Meta Analysis

図1はNEJMに1992年に報告された論文から引用したものであるが（Lau J, et al. N Engl J Med. 1992 Jul 23; 327(4): 248-54），最近よく教科書に載るようになった例である。

急性心筋梗塞に対するstreptokinaseの有効性を検討した試験が1959年から行われているが，最終的にこの問題に決着がついたのは，GISSI-1というイタリアで行われた大規模なトライアルの結果からである。1万1000人を対象にした大規模臨床試験で，ポジティヴなデータが出た。しかしそれでも十分ではなかったので，1988年に1万7000人を対象にしたISIS-2という試験を行った。ここで15％ぐらいのrisk redctionが証明され，streptokinaseが心筋梗塞に対して有効な治療であるということを世の中が認知するようになった。この知識が教科書に載るまでに，1959年に行われた最初の臨床試験から数えて30数年かかったわけである。もしCumulative Meta Analysisという手法ですべての臨床試験が登録され逐次解析されていたら，1970年の段階で決着がついていたことになり，この情報が適切に患者に流されていたら，1万1000人や1万7000人を対象にした二つの大規模臨床試験はおそらくは実施不可能ではなかったか，というのがこの著者たちの結論である。

情報がどこまで提示されているかによって，実はインフォームド・コンセントのあり方も変わる。ということは，臨床試験の根幹まで変わってしまうという事例である。

わが国でのマスコミ報道の事例から

プラバスタチン（メバロチン）は三共が創った新薬であるが，これによる脂質低下が心筋梗塞を減らすか，という仮説はスコットランドで行われた大規模臨床試験WOSCOPSで証明され，1995年のNEJMに

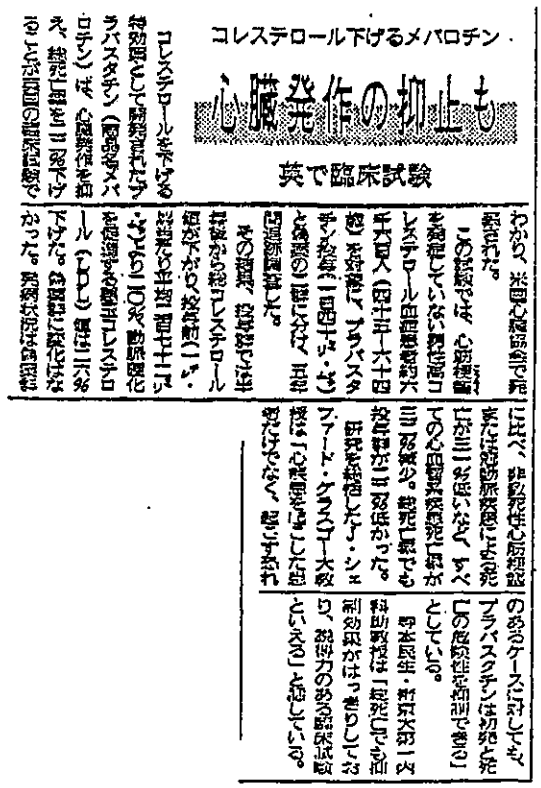
コレステロール下げるメバロチン
心臓発作の抑止も
英で臨床試験

図2
（読売新聞1995年11月22日より）

論文が掲載されている。これも「Ingelfingerの原則」に従って情報開示され，11月の米国心臓病学会の翌日に新聞報道がいっせいになされた。記事はすべて用意されており解禁日をもって流されたわけである。

しかし，このときわれわれは8000例を目標として，メバロチンの有効性を日本人で検証するための臨床試験の登録を行っていた。われわれはこの情報を1週間前に入手していたが，もしこれが報道されたら，患者の同意撤回がいっせいに起こり試験が中止になるのでは危惧した。三共としても最善を尽くすということで，ぴりぴりとした緊張感のなか，マスコミ二十数社を集めてプレスリリースを行ったが，読売新聞の夕刊に小さな記事が出たのみで（図2），WOSCOPSの結果を伝えたマスコミはほとんどなかったのである。患者からの同意撤回もほとんどなかった。

日本のマスコミは副作用については敏感で過剰なまでの報道を行うが，効いたということ，それがどういう意味があるかということについてはかなり無頓着である。幸いこの臨床試験は，その後倫理委員会

が検討を重ね，日本人に対する情報が十分ではないから，WOSCOPSのデータがあったとしても継続すべきである，という結論が出されて進行された。現在8214例のフォローアップがすべて終わり解析を待つ段階である。もしあのとき，大新聞が大々的に1面で報道していたらどうなっていただろうか。これもまたコミュニケーションの怖さを考えさせられたひとつの事例である。

おわりに

「麦飯を食べたらコレステロールが下がった。したがって動脈硬化が改善する」等といった情報が新聞に載ることがある。これらの情報は比較のない1群のデザインであり，エビデンスレベルからするとほとんどゼロである。また，最近，インフルエンザ脳症に解熱剤であるボルタレンを使うと死亡率が上昇するという報道があった。正確な研究データは「オッズが10倍になった」のである。ところが新聞には「薬によって死亡が10倍になった」と出ている。オッズ比とリスク比を混同した例である。オッズ比とは，確率と1から確率を引いたものの比で，これが10倍になったのである。基本的な疫学用語であるが，情報発信側が科学的な専門用語を知らないためしばしば誤解して使われている。先の麦飯のように，最近のダイエットブームを反映して，何々を食べるとやせる，といったあやしげな情報が氾濫しているが，さすがにこれではいけないということで，医師や専門家の立場から「さまざまな健康情報から真実を見きわめよう」という記事が一般雑誌にも載るようになってきている。

このように，国民は健康，保健，医療に関する情報を欲しがっているが，それが正しく選択され，適切なタイミングで，受け手を考えて流されているかというと，そうではないというのが現実である。JMCAでは，11月に行われるシンポジウムと公開講座を，“医学論文等のメディカルライティング”と“一般向け医療情報伝達”の二つの側面から計画しており，そのワーキンググループを発足させることにした。また協会をNPO化し，速やかにホームページを立ち上げ，必要な情報を適宜会員に発信できるようにしたいと考えている。

Original Article

Renoprotective Effect of Losartan in Comparison to Amlodipine in Patients with Chronic Kidney Disease and Hypertension—a Report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) Study

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A 12-month, multicenter (57 clinical institutions), randomized, open-labeled trial was undertaken to compare the efficacy of the angiotensin II receptor antagonist losartan and the calcium channel blocker amlodipine in patients with proteinuric chronic kidney disease (CKD) and hypertension. A total of 117 patients (79, chronic glomerulonephritis; 14, diabetic nephropathy; 24, other CKD) were randomly allocated into two treatment groups. Losartan and amlodipine exerted the same efficacy for blood pressure (BP) control; however, losartan significantly reduced the 24-h urinary protein excretion at months 3, 6, and 12, with the reduction of 20.7%, 35.2%, 35.8%, whereas amlodipine did not change the amount of proteinuria over the 12-month study period. When patients were stratified into groups according to the level of BP control at 3 months, the reduction in urinary protein excretion by losartan was evident in the group for which a BP of <140/90 mmHg was achieved, as well as in the group for which the goal BP (<130/85 mmHg) for treatment of CKD was not achieved. When patients were stratified according to baseline urinary protein excretion, those with ≥2 g/day showed a reduction in proteinuria by losartan of 23.3%, 39.4%, and 47.9% at months 3, 6, and 12, and those with <2 g/day showed a reduction of 18.5% and 31.2% at months 3 and 6, respectively. No fatal adverse

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events were experienced in either drug group. We conclude that losartan reduced proteinuria in patients with CKD and hypertension. This positive effect may contribute to the renal protective benefit of losartan, and is beyond the magnitude of BP control. (*Hypertens Res* 2004; 27: 21–30)

***Key Words*: losartan, angiotensin, proteinuria, hypertension, renoprotection**

Introduction

On the basis of understanding the role of angiotensin II in circulation and renal functions, the relevance of intervention of the renin-angiotensin system (RAS) for therapy of hypertension and kidney diseases has so far been extensively discussed (*1*, *2*). High blood pressure (BP) strongly affects the structure and functions of nephrons, and inversely, impaired renal function elevates the systemic BP level in patients with kidney diseases. Angiotensin converting enzyme (ACE) inhibitors are now one of the most frequently used drugs for hypertension, and a number of evidences are available with regard to the effect of ACE inhibition to ameliorate kidney diseases, especially proteinuria as a symptom (*3*). Indeed, in many clinical studies dealing with kidney diseases, proteinuria has been adopted as a surrogate endpoint, because proteinuria is not merely a marker of permselectivity of the glomerular membrane, but is toxic to the kidney *per se*, and plays a key role in the progression of kidney diseases, eventually leading to end-stage renal disease (ESRD) (*4–7*).

With reference to the effect of ACE inhibitors, the use of angiotensin II receptor antagonists for the treatment of kidney diseases has also been discussed. The RENAAL study, an international multicenter clinical trial of the angiotensin II receptor antagonist losartan, was published in 2001 (*8*). This trial studied the effect of losartan in patients with type 2 diabetic nephropathy. The results clearly demonstrated that losartan retarded the elevation of serum creatinine and decreased the rate of onset of ESRD. On the other hand, the effects of intervention of the actions of angiotensin II in patients with non-diabetic chronic kidney disease (CKD) and hypertension has been still a subject of debate with regard to relation to BP lowering effect. Any pharmacotherapy to lower BP may be effective for protection of renal functions; however, whether blockade of angiotensin II receptors confers renal protection in excess of that due to BP control has not been clearly answered. There is thus need of accumulation of evidences of comparative study with other classes of antihypertensive drugs in patients with CKD and hypertension. For this reason, we have performed a 12-month study comparing the effects of the angiotensin II receptor antagonist losartan and the calcium channel blocker amlodipine. A portion of the results were previously disclosed as an interim report at 3 months (*9*) with the full analysis set (FAS) (*10*). We here report our final results based on the final selection of patients by the Coordinating Committee. Our findings show that, although losartan and amlodipine exerted the same degree of BP control, only losartan induced a significant reduction in urinary protein excretion over the 12-month observation period.

Methods

This study was a 12-month, multicenter, randomized, open-labeled, clinical trial designed to compare the effect of the angiotensin II receptor antagonist losartan and the calcium channel blocker amlodipine to reduce proteinuria in patients with CKD and hypertension. Fifty-seven affiliated clinics in Japan contributed to this study. The overall design of the study has been described previously in an interim report presented at 3 months (*9*). Males and female outpatients, aged 20–74 years, who had CKD and hypertension and who met the following criteria during the 8-week pretreatment screening period were eligible for the study:

1) CKD: serum creatinine (Scr) levels of $1.5 \leq Scr < 3.0$ mg/dl in males of body weight (BW) ≥ 60 kg, and of $1.3 \leq Scr < 3.0$ mg/dl in females, or males of BW < 60 kg.

2) Hypertension: systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg as measured in a sitting position at least two separate times at their visits to clinics.

3) Proteinuria: urinary protein excretion of ≥ 0.5 g/day.

The overview of study design is shown in Fig. 1. The randomization method was modified by dynamic balancing for Scr, the 24-h urinary protein excretion that was measured at the time of registration, and presence or absence of diabetic nephropathy, so that patients were allocated to the two groups avoiding significant difference of baseline characteristics in average. Patients of the two groups received either losartan 25 mg as a starting dose to up to 100 mg once daily, or amlodipine 2.5 mg as a starting dose to up to 5 mg once daily, respectively. However, in cases in which a patient's compliance was judged by investigator(s) to be sufficiently good for the administration of a higher dose, either 50 mg of losartan or 5 mg of amlodipine was adopted as a starting dose.

The target BP was $< 130/85$ mmHg, and patients were not allowed combination therapy with other antihypertensive agents during the first 3 months. However, after 3 months, if a BP of $< 130/85$ mmHg was not achieved, antihypertensive combination therapy with α-blockers, β-blockers, α/β-blockers, diuretics (excepting potassium-sparing diuretics), and other calcium channel blockers were considered as appropriate. Guidance was given to patients to maintain their usual diet, especially for those under dietary restrictions. The study protocol was reviewed and approved by the Institutional Review Boards of all clinics contributing to the study. Written informed consent was obtained from all enrolled pa-

Table 1. Baseline Characteristics of Patients Enrolled in the Study

	Losartan group	Amlodipine group	*p* value
N	58	59	
Age (years)	55.7±13.6	57.5±11.9	NS*
Male/female	36/22	41/18	NS†
BMI (kg/m²)	23.9±3.7	22.9±3.2	NS*
Systolic BP (mmHg)	156.5±12.2	155.4±13.5	NS*
Diastolic BP (mmHg)	94.0±9.2	93.5±8.6	NS*
Serum creatinine (mg/dl)	2.04±0.48	1.97±0.52	NS*
Urinary protein (g/day)	2.85±2.65	2.50±2.07	NS*
Serum albumin (g/dl)	3.79±0.48	3.80±0.47	NS*
Diagnoses (No. of patients)			
Chronic glomerulonephritis	38 (11#)	41 (12#)	
Diabetic nephropathy	7	7	
Hypertensive nephrosclerosis	11	9	
Tubulointerstitial nephritis	1	0	
Polycystic kidney disease	1	0	
Renal amyloidosis	0	1	
Castleman's disease	0	1	

Mean±SD. * Unpaired *t*-test; † Fisher's exact test. # IgA nephropathy. BMI, body mass index; BP, blood pressure.

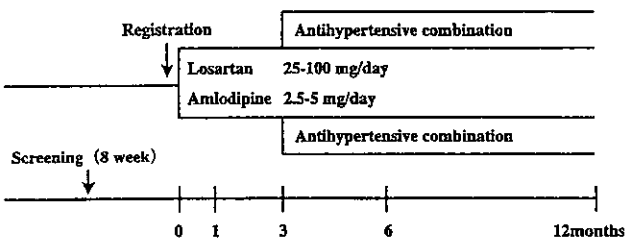

Fig. 1. *Study design for treatment of patients with proteinuric CKD and hypertension. Antihypertensive combination therapy was allowed after the first 3 months, if necessary. For this alternation, the target goal BP setting was <130/85 mmHg.*

tients.

Exclusion criteria were as follows:

1) DBP≥120 mmHg.
2) Renovascular hypertension or endocrine hypertension.
3) BP control treatment with antihypertensive agent(s).
4) Patients in whom antianxiety drugs could not be discontinued.
5) Pregnancy, possibility of pregnancy, or in a period of lactation.
6) Patients that the chief investigator judged not to be eligible.

BP was measured at patients' visit to the clinic with the patient in a sitting position.

A 24-h urine collection was performed from 8:00 AM of the day before to 8:00 AM of the day of the clinic visit, and was used to obtain the 24-h urine volume, urinary protein excretion, urinary creatinine level, and the amount of sodium excretion. The creatinine clearance (Ccr) was calculated as $Ccr = Ucr \times V/Scr \times 1.73/A$, where Ccr is the creatinine clearance (ml/min), Ucr is the urinary creatine (mg/dl), V is the urine volume (ml/min), Scr is the serum creatine (mg/dl), and A is the body surface area. The rate of renal impairment as a function of time was expressed with a reciprocal slope of Scr (1/Scr).

Protein intake was estimated by measurement of urea nitrogen plus protein concentration using the following formula: Protein intake (g/day)=[urinary urea nitrogen (g/day)+0.031(g)×BW(kg)]×6.25+urinary protein excretion (g/day) (*11*). Sodium chloride (NaCl) intake was measured by NaCl concentrations in the collected urine using the following formula: NaCl intake (g/day)=urinary sodium excretion (mEq/day)/17.

All values were expressed as the mean±SD. The baseline characteristics of the enrolled patients were tested for comparability between the losartan group and the amlodipine group using unpaired *t*-test or Fisher's exact test. The differences in changes in SBP and DBP between the two groups were tested by repeated-measures analysis of variance with treatment effect, period effect, and the interaction between treatment and period effect. Changes in urinary protein excretion, Scr, and Ccr within each group were analyzed by paired *t*-test. Unpaired *t*-test was used to compare the percent changes of urinary protein excretion, Scr, and Ccr between the losartan group and the amlodipine group. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

In all patients enrolled during the term from December 1999

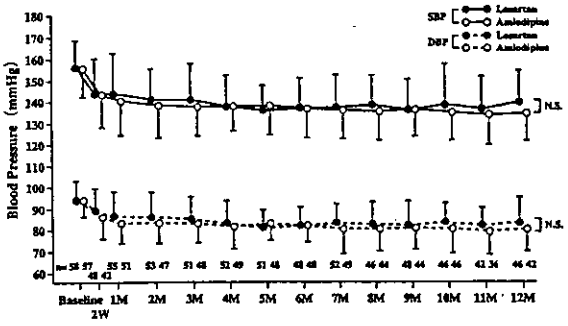

Fig. 2. *SBP and DBP changes (mmHg) throughout 12 months in groups treated with losartan and amlodipine. Circles and bars indicate the mean and SD. SBP and DBP were not significantly different between the losartan and amlodipine groups.*

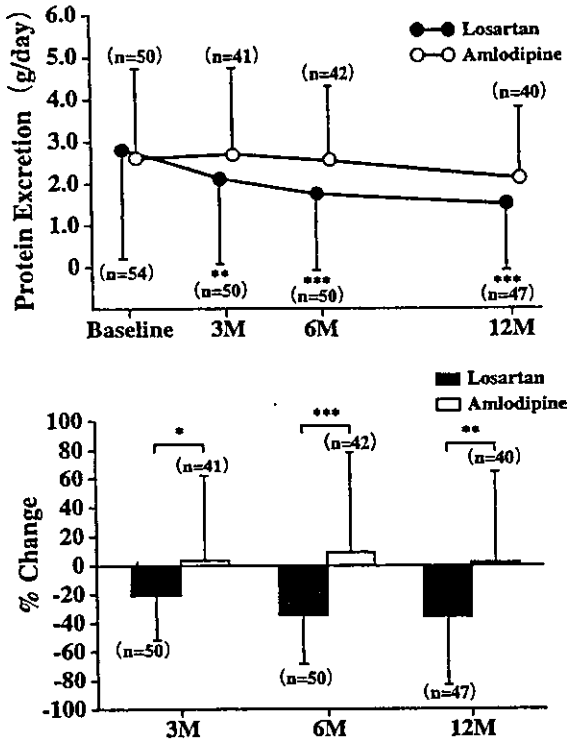

Fig. 3. *Changes in 24-h urinary protein excretion (upper panel) and respective percent changes (lower panel) from baseline. Circles and bars indicate the mean and SD.* * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

to March 2002, 117 patients (58 for losartan and 59 for amlodipine) were eligible, as their baseline characteristics are shown in Table 1. A large number of patients were diagnosed with chronic glomerulonephritis, including IgA nephropathy. Patients with diabetic nephropathy and hypertensive nephrosclerosis were also included. The characteristics of the two treatment groups were similar. Forty-seven patients in the losartan group and 40 patients in the amlodipine group completed the 12-month study for measurement of urinary protein endpoint. The dietary compliance assessment of 24-h urinary urea nitrogen plus proteins and sodium showed that, there was no significant difference in total protein and NaCl intake between the two drug treatment groups at baseline and no change from baseline to month 3, as reported previously (*9*). At month 12, again, there was no change from baseline and therefore no difference between the losartan group and the amlodipine group in protein intake or NaCl intake (protein [g/day]: losartan, 50.7±19.7; amlodipine, 53.5±17.0; NaCl [g/day]: losartan, 8.0±3.8; amlodipine, 9.6±3.5).

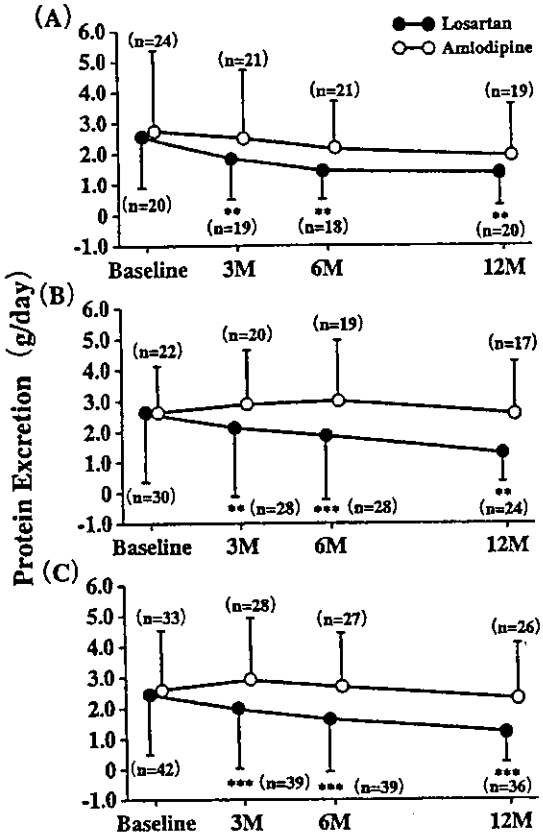

Fig. 4. *Changes in urinary protein excretion in patients stratified in response to BP control measured at month 3. (A) BP<140/90 mmHg. (B) BP≥140/90 mmHg. (C) BP≥130/85 mmHg. Note that patients in group C are included in either the group A or B because of respective BP ranges, as a consequence. Circles and bars indicate the mean and SD.* ** $p<0.01$, *** $p<0.001$.

The BP-lowering effect, in both systole (SBP) and diastole (DBP), was similar with losartan and amlodipine. Figure 2 shows changes in SBP and DBP measured at week 2 and at every month. In the losartan group, SBP was reduced from 156.5±12.2 mmHg at baseline to 139.5±14.8 mmHg at month 12 (−11.3±9.2%), and DBP from 94.0±9.2 mmHg at baseline to 83.0±11.7 mmHg at month 12 (−12.2±10.8%), and in the amlodipine group, the reduction in SBP

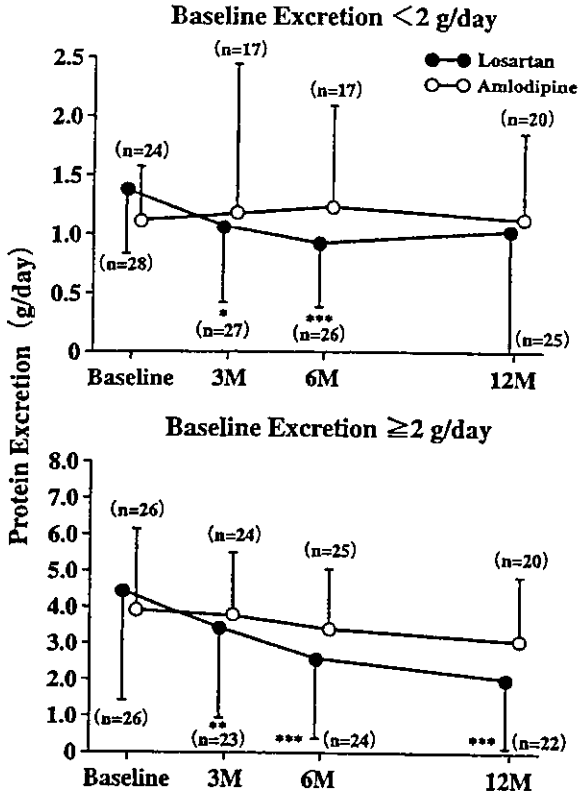

Fig. 5. *Changes in urinary protein excretion from baseline in patients stratified into two groups showing proteinuria of <2 g/day (upper panel) and ≥2 g/day (lower panel) as measured at baseline. Circles and bars indicate the mean and SD.* * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

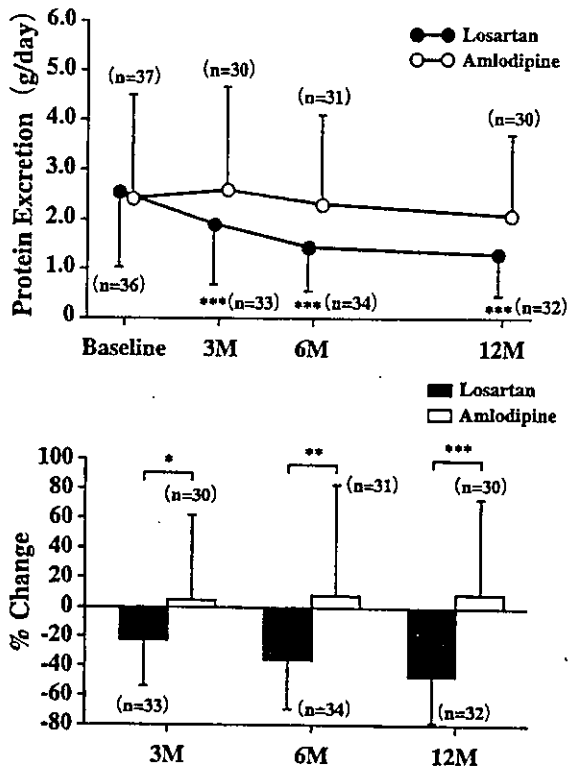

Fig. 6. *Changes in urinary protein excretion (upper panel) and respective percent changes (lower panel) in patients with chronic glomerulonephritis. Circles and bars indicate the mean and SD.* * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

was from 155.7±13.6 mmHg at baseline to 134.3±13.1 mmHg at month 12 (−12.7±10.0%), and that of DBP was from 94.1±7.9 mmHg at baseline to 79.7±10.1 mmHg at month 12 (−15.1±12.5%), respectively.

However, urinary protein excretion was significantly reduced only in the losartan group. The upper panel of Fig. 3 shows the change in urinary protein excretion and the lower panel shows the percent change from the respective baselines. The apparent changes in percent were −20.7%, −35.2%, and −35.8% at months 3, 6, and 12, respectively. We then analyzed the relationship between BP control and reduction of proteinuria in patients treated with losartan.

The responsiveness to the drug was assessed by BP measured at month 3. In this analysis, patients whose BP was controlled to <140/90 mmHg as well as those whose BP was not controlled at month 3 showed a statistically significant reduction in urinary protein excretion from baseline at each of months 3, 6, and 12. Although the JNC-VI guidelines recommend a BP goal of <130/85 mmHg for hypertensive patients with CKD (*12*), patients in whom this goal was not achieved still showed a statistically significant reduction in urinary protein excretion by losartan (Fig. 4). In the losartan group with a BP of <130/85 mmHg, there was an apparent reduction in urinary protein excretion, but without statistical significance.

Although at baseline there was no statistically significant difference between treatment groups in the ratio of males to females (Table 1), the number of female patients in the amlodipine group decreased during the study. However, in the losartan group, changes in proteinuria were almost comparable between males and females: −21.0% ($n=31$) and −20.2% ($n=19$) at month 3, −35.5% ($n=31$) and −34.6% ($n=19$) at month 6, and −35.2% ($n=29$) and −36.9% ($n=18$) at month 12 in males and females, respectively. Likewise, although no effect was observed with amlodipine, changes in the amount of proteinuria in males and females were +7.1% (n=31) and −8.0% ($n=10$) at month 3, +13.6% ($n=30$) and −4.6% ($n=12$) at month 6, and −1.5% ($n=30$) and +10.6% ($n=10$) at month 12, respectively.

In order to examine whether the magnitude of proteinuria affected the result of treatments with losartan and amlodipine, we stratified patients into two subgroups: those with proteinuria <1 g/day and those with proteinuria ≥1 g/day at baseline. In these subgroups, the change in urinary protein excretion from baseline was not significantly different between the losartan group and the amlodipine group. We next stratified patients with proteinuria levels of <2 g/day and

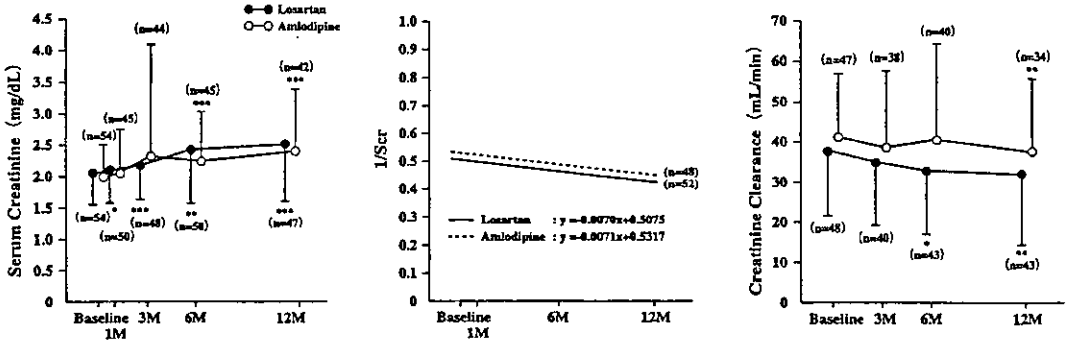

Fig. 7. *Changes in Scr (left panel), 1/Scr (middle panel), and creatinine clearance (right panel) in patients treated with losartan for Scr and 1/Scr. Circles and bars indicate the mean and SD.* * $p<0.05$, ** $p<0.01$, *** $p<0.001$. *There was no difference for the slope of 1/Scr between the losartan and amlodipine group.*

≥2 g/day at baseline. As shown in Fig. 5, the reduction in urinary protein excretion was evident in losartan groups of both <2 g/day and ≥2 g/day. Again, amlodipine did not significantly reduce urinary protein excretion in both groups of <2 g/day and ≥2 g/day.

With respect to the diagnosis of patients, 38 patients in the losartan group and 41 in the amlodipine group had chronic glomerulonephritis, and 7 in the losartan group and 7 in the amlodipine group had diabetic nephropathy. Analysis of the patients with diabetic nephropathy revealed an apparent decrease from baseline in urinary protein excretion in the two treatment groups, with no statistically significant difference between the groups (data not shown). Analysis of the subgroup with chronic glomerulonephritis exhibited a statistically significant reduction in proteinuria in the losartan group at months 3, 6, and 12. Because amlodipine did not reduce proteinuria in patients with chronic glomerulonephritis, there was a prominent difference in the percent reduction in urinary protein excretion from baseline between the two treatment groups (Fig. 6).

Changes in Ccr and Scr and the slope of 1/Scr did not differ between the two treatment groups. Scr slightly increased from the baseline to month 3 in both groups. Ccr showed a tendency of decline (Fig. 7).

Adverse events considered to be possibly related to the study were reported for increases in aspartate aminotransferase (AST; GOT) (2 cases), alanine aminotransferase (ALT; GPT) (1 case) and γ-GTP (4 cases). These changes were mild and the incidence was almost the same between the losartan group and the amlodipine group. An increase in serum uric acid (2 cases) was reported in the amlodipine group, but was not observed in the losartan group. Hyperkalemia ranging from 5.1 to 6.9 mEq/l was reported in the losartan group (3 cases) and in the amlodipine group (2 cases). Two cases of dizziness and 1 case of transient ischemic attack were reported in the losartan and amlodipine groups. No fatal adverse events were observed in either group during the 12-month study.

Discussion

The present study demonstrated that, in patients with proteinuric CKD and hypertension, losartan effectively reduced proteinuria while amlodipine did not. It is noteworthy that the potency of BP-lowering of losartan and amlodipine was same throughout the entire 12-month study period. Allocation of patients resulted in an almost comparable male to female ratio between the treatment groups at baseline. However, more number of female patients decreased in the amlodipine group than in the losartan group as the study progressed. Consequently, at month 12, in the losartan group, the male/female ratio was 29/18, while in the amlodipine group it was 30/10. Although the losartan group included a greater number of female patients than the amlodipine group at months 3, 6, and 12, the percent reduction in urinary protein excretion in males was comparable to that in females in the losartan group. Therefore, it was unlikely that a sex hormone such as estrogen played a role in the vascular protection in this study. The fact that a large majority of female patients in the losartan group at baseline were aged (22 females: 54–59 year-old, 4; in their 60's, 9; in her 70's, 1) may warrant this discussion, because female patients of mid-50's or older were probably undergoing menopause.

In the present study, we first stratified patients into 3 subgroups with regard to BP reduction measured at month 3. The first 3 months was a meaningful period because no other drugs was added on either losartan or amlodipine during this period. Losartan reduced both BP and proteinuria. However, it was also true that not all patients responded to losartan to reach the goal BP of <130/85 mmHg that was recommended by the JNC-VI (*12*). In fact, the goal BP was achieved in only 8 patients in the losartan group and 13 patients in the amlodipine group. It was expected that patients who reached the goal BP of <130/85 mmHg would show a prominent decrease in urinary protein excretion. However, there was no significant change in urinary protein excretion from baseline in either the losartan group or the amlodipine group, al-

though in the losartan group urinary protein tended to decrease. The reason for this finding is unclear; however, since the number of patients in each group was very small, this might be the reason why we failed to demonstrate statistical significance, especially in the losartan group. Nonetheless, even in patients who did not accomplish the BP goal, reduction of proteinuria was evident. Likewise, patients who achieved a BP of $<140/90$ mmHg represented the anti-proteinuric effect of losartan. A striking evidence was that patients who did not accomplish the level of BP $<140/90$ mmHg also showed the reduction in proteinuria, the degree of which did not largely differ from those in the group of BP $<140/90$ mmHg.

It must not be a conclusion that, in patients with CKD and hypertension, it is sufficient to pursue a reduction in proteinuria without a corresponding reduction in BP. It should be emphasized that BP control is still an important strategy in treating patients with CKD and hypertension, as the JNC-VI recommends. Our results can only be taken to indicate that losartan may still be effective to reduce proteinuria, even if BP can not reach the BP goal of the JNC-VI guidelines (*12*). In this aspect, losartan should be used in clinical practice under the condition of exerting anti-hypertensive effect. The goal BP of $<130/80$ mmHg for patients with CKD which was currently recommended by JNC-VII guideline (*13*) should also be taken into account. Thus, the use of losartan will bring better outcomes for patients with CKD and hypertension with concomitant BP control.

Although we failed to find a difference in anti-proteinuric effect between losartan and amlodipine when patients were stratified with the baseline proteinuria of <1 g/day and ≥ 1 g/day, further stratification with levels of <2 g/day and ≥ 2 g/day clearly demonstrated the anti-proteinuric effect of losartan at all assay points in the group of ≥ 2 g/day. These results suggest that losartan was effective to reduce severe proteinuria of probably glomerular origin. The effect was still observable in the group of <2 g/day at months 3 and 6, but was not statistically significant at month 12, probably due to a wide range of standard deviation from the mean value. Very recently, Tojo *et al.* (*14*) reported that, in streptozotocin-induced diabetic rats, intervention of actions of angiotensin II by either an ACE inhibitor or an angiotensin II antagonist restored albumin reabsorption in the proximal tubules without changing blood glucose *via* restoration of the expression of megalin, a glycoprotein responsible for reabsorption of proteins in the proximal tubules, resulting in the reduction in urinary protein excretion. The authors suggested that expression of megalin is suppressed in the proximal tubules when the kidney is impaired for tubular dysfunction. This evidence may explain, at least in part, our results on the effect of losartan on proteinuria, a part of which may be of tubular origin.

While the RENAAL study (*8*) was conducted in patients with type 2 diabetes, a large majority of the patients enrolled in the present study had chronic glomerulonephritis including cases of immunoglobulin A (IgA) nephropathy. In these patients, losartan effectively reduced urinary protein excretion. Chronic glomerulonephritis involves many factors in its etiology, and the complicated proteinuria is not solely a result of hyperfiltration of glomeruli. Rather, remodeling of the glomerulus must be considered. Since amlodipine did not affect the protein excretion in such patients, the present result is of particular interest in considering the direct actions of angiotensin II on the structure and functions of glomeruli. Patients with diabetic nephropathy in the losartan group and the amlodipine group were 7 and 5 on the day of start and only 5 and 4 patients completed the study, respectively. Because of this limited number of diabetic patients, there was no statistically significant change in urinary protein excretion in either drug treatment group, although the magnitude of the mean reduction of urinary protein ranged from -30% to -50%. We therefore cannot conclude from these results that these drugs have no anti-proteinuric effect in patients with diabetic nephropathy.

With respect to the pharmacotherapy of patients with CKD, the therapeutic benefit of interfering with the actions of angiotensin II has been extensively documented with ACE inhibitors over the last decade. The breakthrough evidence that direct blockade of angiotensin II receptors protects the kidney in patients with type 2 diabetic nephropathy was provided by the RENAAL study (*8*) with losartan, and the IDNT study with irbesartan (*15*).

Recent publications provided evidences that the angiotensin II receptor antagonist candesartan was effective in Japanese patients with type-2 diabetic nephropathy, with a dose as low as 4 mg/day to prevent aggravation of proteinuria (*16*), or reduce urinary protein excretion by combination therapy with amlodipine (*17*), supporting previous evidences on losartan and irbesartan for diabetic nephropathy. The results of our present study provide the additional information useful in clinical practice, that losartan is effective not only for patients with type 2 diabetic nephropathy, but also those with a variety of types of CKD. Nakao *et al.* (*18*) recently studied the effect of combination therapy and monotherapy with losartan and the ACE inhibitor trandolapril in patients with non-diabetic renal disease. They demonstrated that losartan as well as trandolapril effectively lowered urinary protein excretion, although the combination of these two drugs exerted a more favorable effect on proteinuria. Taken together, the antiproteinuric effect of losartan may play a major role in its renoprotective effect.

The therapeutic benefit of losartan for kidney diseases in comparison to other antihypertensive drugs is still not fully explained. As is indicated in the JNC-VI (*12*) and JNC-VII (*13*) guidelines and several clinical reports, aggressive blood pressure control is mostly important. On the other hand, many clinical trials have demonstrated that blood pressure control is not the only factor pertinent for renoprotection; rather, ACE inhibitors and angiotensin II receptor antagonists provide additional benefit in patients with kidney dis-

eases.

The RAS is now well understood to be involved in the pathogenesis of renal impairment independent of its vasoconstrictive actions, inducing disturbance of glomerular and tubular functions. The direct actions of angiotensin II in the kidney include an increase in tubular sodium reabsorption and an influence on glomerular filtration rate (GFR), but morphopathological changes such as accumulation of extracellular matrix and mesangial cell proliferation and hypertrophy (*19*, *20*) are of more importance for pathogenesis of renal impairment. These concepts clearly constitute the theory of usefulness of blocking the actions of angiotensin II in kidney diseases. Although the UK Prospective Diabetes Study (UKPDS) (*21*) concluded that the effects of ACE inhibitor captopril and the β-blocker atenolol were similar in reducing the risk of macrovascular and microvascular complications related to type 2 diabetes, the African-American Study of Kidney Disease and Hypertension (AASK) Study (*22*), which compared the effects of the ACE inhibitor ramipril, the calcium channel blocker amlodipine, and the β-blocker metoprolol on the progression of hypertensive renal disease in African-Americans, showed that ramipril induced a slower decline in GFR and a lower risk of clinical end points compared to amlodipine.

The mechanism and mode of action of losartan and amlodipine to explain the exertion of different effect of renoprotection are not thoroughly explained and are controversial. Documents are available to explain the renoprotective efficacy of calcium channel blockers, including amlodipine. However, whether calcium channel blockers exert unique antiproteinuric effects is still controversial. In the AASK Study (*22*), proteinuria was not decreased with amlodipine. The Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetes (J-MIND) study (*23*) reported that nifedipine retard and enalapril had a similar effect on nephropathy in hypertensive type 2 diabetic Japanese patients, but albumin excretion rate was not reduced with either drug despite the effective BP lowering. Kumagai *et al.* (*24*) reported the comparative evaluation of amlodipine with ACE inhibitors enalapril or captopril for renoprotective effect in hypertensive patients with renal dysfunction. They concluded that the effect of 1-year treatment with amlodipine on renal function was likely the same as that of ACE inhibitors. They also showed that urinary protein excretion tended to be reduced by either ACE inhibitor or amlodipine, but without statistical significance. These evidences suggest that, while a strong argument has been made for proteinuria as a risk factor for progression of renal disease (*25*), there is still a discrepancy between renoprotection as a final goal and urinary protein excretion as an important clinical sign for renal dysfunction.

There is thus a strong body of evidence suggesting that the pathways by which angiotensin II aggravates renal functions are mediated by angiotensin II type 1 (AT_1) receptors. Calcium channel blockers act to dilate the microvasculature, improving regional circulation by regulating the voltage-dependent calcium channels. The blockade of angiotensin II receptors results in a reduction in renal perfusion pressure in addition to dilation of the efferent arterioles to a greater extent than the afferent arterioles because of their different manner of constriction in response to angiotensin II, and thus angiotensin II antagonists reduce the glomerular filtration pressure to same extent. On the other hand, the action of angiotensin II is not solely to constrict macrovascular and microvascular trees, but a variety of cellular actions are evident. A number of reports have described roles of angiotensin II through AT_1 receptors to produce extracellular matrix as well as to stimulate proliferation and/or hypertrophy of many types of cells, *via* the direct stimulation of mitogen-activated protein kinase (MAPK), transforming growth factor (TGF-β), nuclear factor (NF-κB), induction of proto-oncogenes, and so on (*19*, *20*, *26*). Thus, although there is still no confirmatory theory, wider biological functions of angiotensin II may explain the diversity of renoprotective activity of the two drugs without depending on their BP lowering efficacy. The precise mechanism of the action of these drugs should be further investigated.

In the present study, there was no change in Ccr either in the losartan or amlodipine groups. Andersen *et al.* (*27*) conducted a 2-month, randomized, double-blind cross-over clinical trial to evaluate the effect of losartan and the ACE inhibitor enalapril in patients with type 1 diabetic nephropathy, and reported that angiotensin II blockade reduced urinary protein excretion without changing GFR. In the RENAAL study (*8*), the risk of a doubling of the serum creatinine concentration in the losartan treatment group and the placebo group was almost the same until 12 months from initiation of the study, although the reduction in urinary protein excretion was observed in the losartan treatment group within 6 months. The IDNT study (*15*) with irbesartan also reported no difference in the change in serum creatinine in comparison to placebo and amlodipine within 12 months. Thus, it is likely that effects on proteinuria and on Ccr differ in response to blockade of angiotensin II receptors, although the reason is not explained. The present study was completed at 12 months. It might be expected that longer-term treatment of the patients with CKD and hypertension with losartan would have more beneficial effects on renal functions such as improvement of GFR in patients beyond the effect to reduce proteinuria.

In conclusion, a term of total 12 months treatments of Japanese patients with proteinuric CKD and hypertension with losartan reduced proteinuria more effectively than amlodipine, although BP lowering effect was not different between the two drug-treated groups. Since the effect was beyond the blood pressure control, losartan is effective in patients with CKD manifesting proteinuria and hypertension.

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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).

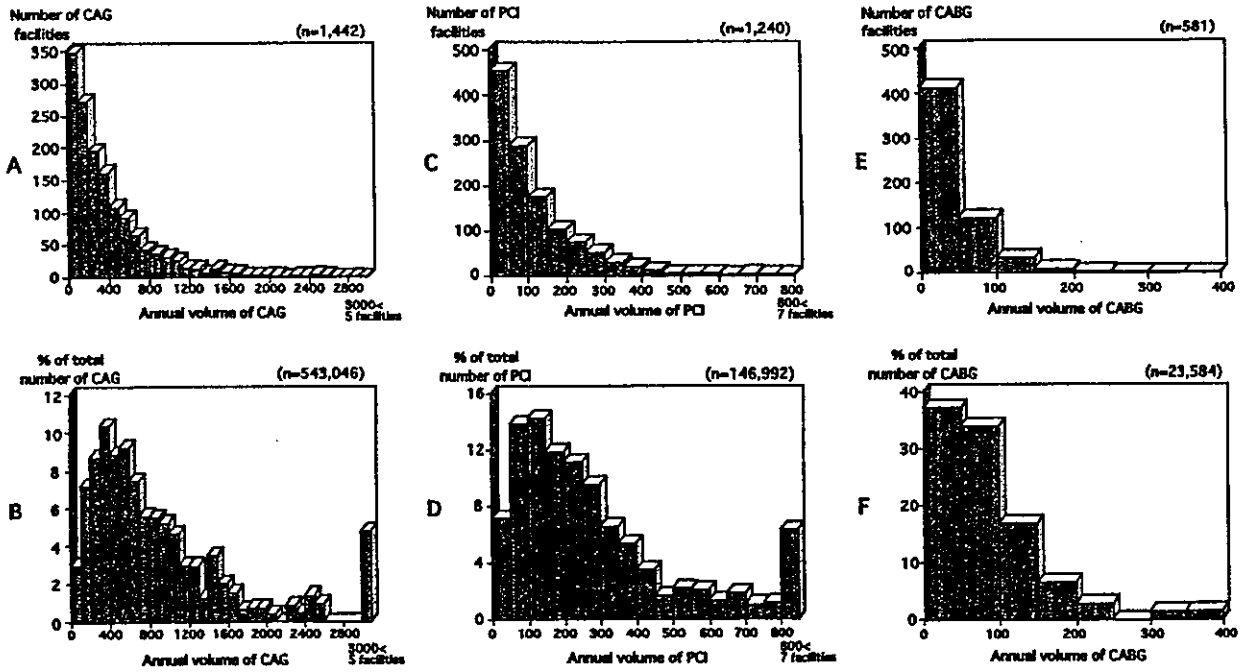

Fig 1. Annual volume of coronary arteriography (CAG), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) performed per facility, and the numbers of these facilities or % of these total numbers.

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

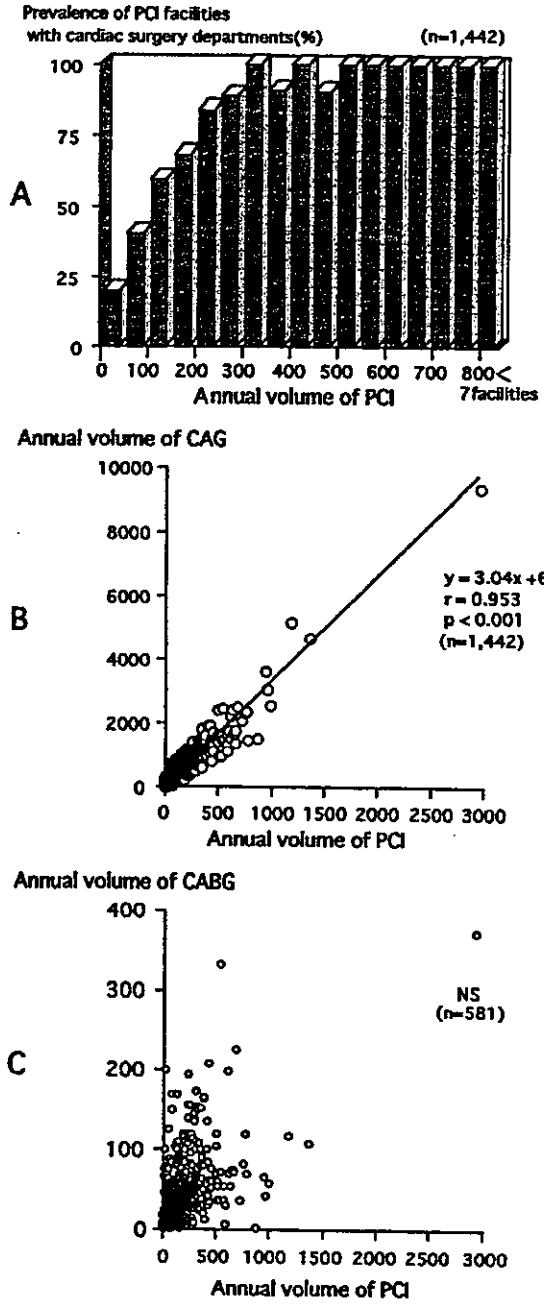

Fig 2. Annual volume of percutaneous coronary intervention (PCI) performed and other parameters. CAG, coronary arteriography; CABG, coronary artery bypass grafting.

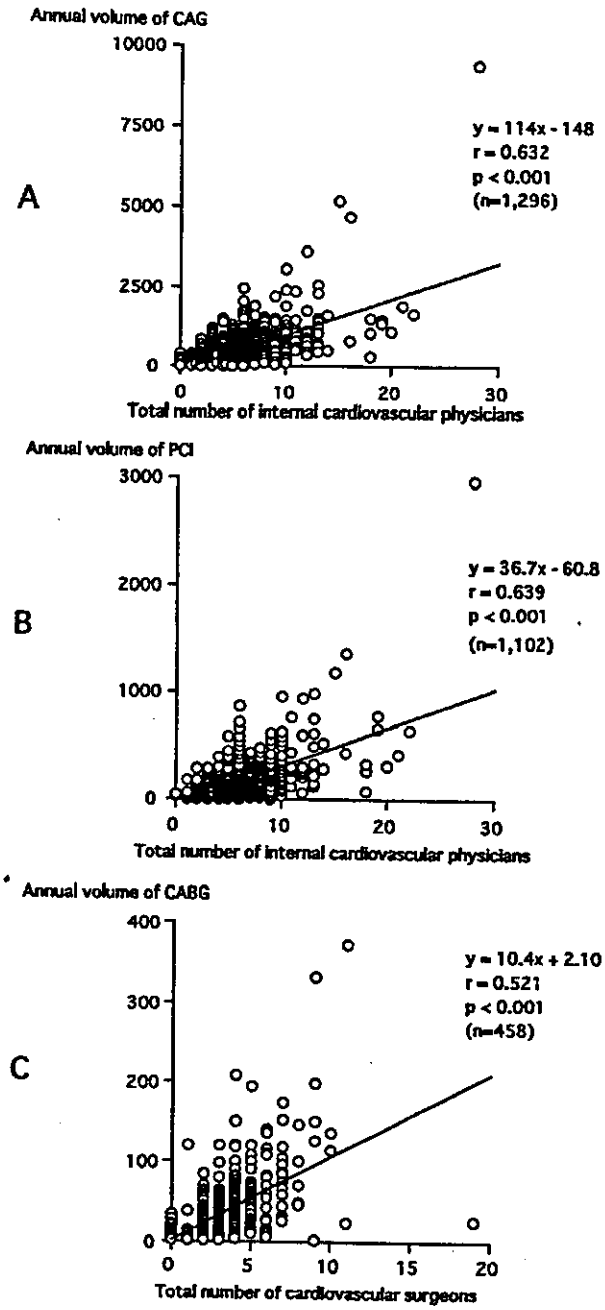

Fig 3. Numbers of cardiologists and cardiovascular surgeons and other parameters. CAG, coronary arteriography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

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.

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Appendix 1

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Data Collection Center: Japan Clinical Research Assist Center (JCRAC, Tokyo): Mr Kenichi Yamamoto, Mr Shiro Maesaki, and Mr Yasuhiro Okawa.

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

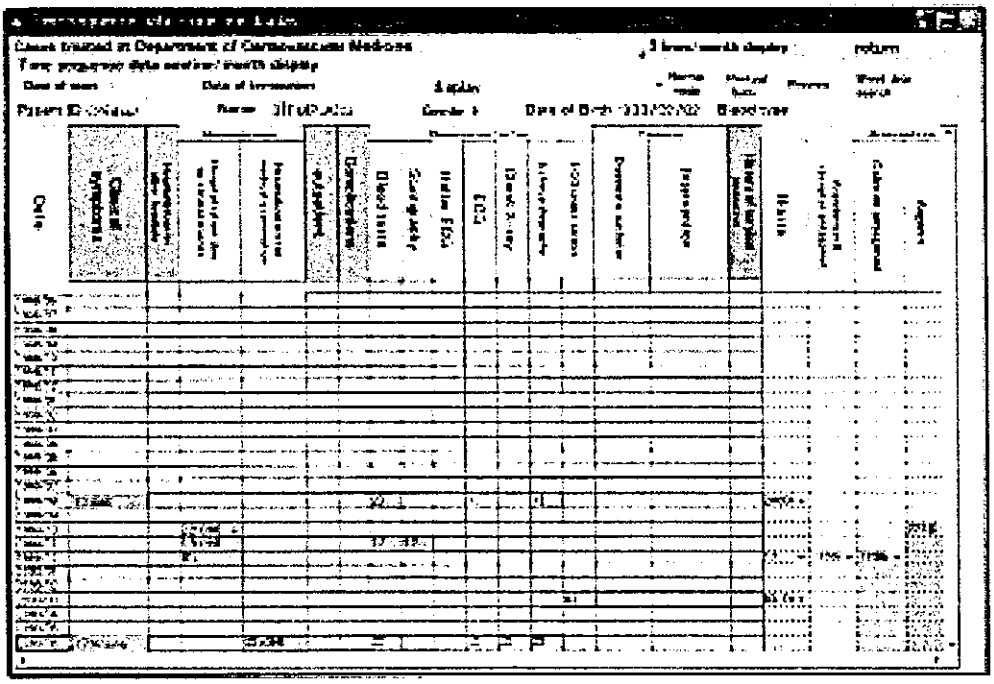

Figure 1. Presentation in time sequence of a patient's clinical history.