3. これらの研究に参加することでどのような恩恵がありますか？

脳卒中の再発を防ぐうえで、プラバスタチンを飲むことがよいかどうかははっきりしていません。かえって他の薬と同様に副作用の心配もあります。私たちは研究期間を通じてスタチン群、非スタチン群、両群全ての方の健康状態を注意深く見守り、新たな病気の発生や薬の安全性を監視します。同時に、この研究や他の研究を通して得られた、健康に関する新たな情報を提供致します。高感度CRP 検査および頸動脈エコー検査は、その結果をあなた自身にお知らせすることができます。また、私たちは研究期間中、この研究や他の研究を通して得られたあなたの健康に関する新たな情報を提供します。そのため、スタチン群、非スタチン群のどちらになった場合でも、この研究に参加しない場合と少なくとも同等の恩恵を受けられると私たちは考えています。また、この研究から得られた結果は、将来あなたと同じ病気で苦しんでおられる多くの方々の治療にも活かされます。私たちは、この研究が脳卒中の再発予防に新たな治療指針をもたらすことを期待しています。

4. これらの研究に参加することでどのような危険がありますか？

プラバスタチンはわが国でも大変多くの患者さんが服用している薬であり、重大な副作用が少ない薬です。ただし、これまでの経験により約3%の方に発疹や下痢、胃不快感などの副作用が報告されています。また、横紋筋融解症、肝障害、黄疸、血小板減少などの重大な副作用の報告がまれにありますが、その頻度は明らかではありません。ちなみに、海外の研究では、この薬による横紋筋融解症は9895 例中1 例もありませんでした。万一、副作用が生じた際には適切に処置し、重度のものが生じた場合には薬を中止して適切な処置を講じます。高感度CRP 濃度の測定は、定期的な血液検査項目に追加するだけですので、採血回数が増えることも無く、危険性はありません。また、頸動脈エコーの超音波検査は非侵襲的検査であり、危険性はありません。

5. 他の治療法にはどんなものがありますか？

脳梗塞の再発予防に有効な手段として、高血圧や糖尿病の治療、抗血小板薬の服用、頸動脈内膜剥離術などがあげられます。担当医が必要と判断したときは、研究中であっても、スタチン群、非スタチン群ともにそれらの治療を受けることができます。

6. プライバシーは守られますか？

この研究に関する情報はカルテに記録され、その一部は臨床研究情報センターのコンピューターに記録されます。また、あなたであることを特定できないようにした上で、研究成果を学会や医学雑誌などに報告する場合があります。しかし、いずれの場合にもあなたのプライバシーは厳重に保護され、個人的な情報が外部に漏れる心配はありません。

7. この研究に参加する義務はありますか？

この研究へ参加するかどうかはあなたの自由であり、参加しない場合にも不利益を受けることはありません。また、参加に同意された場合でも、不利益を受けることなくそれを取り消すことができます。しかし、研究の途中で参加を取り消す場合にはそれを担当医に伝えて下さい。

8. 詳しい研究内容を知ることができますか？

ご希望があれば、他の患者さんのプライバシーやこの研究の独創性に支障がない範囲で研究の実施計画書などをお見せします。

9. 医療費はどのようになりますか？

この研究は製薬会社が費用を負担する「治験」ではなく、脳卒中の制圧を心より願う私たち医師が、健康保険の範囲内で行うものです。また、頸動脈超音波検査を含め、行われる全ての検査は通常の脳卒中診療に必要なものと考えられます。従って、この研究に参加していただいた場合にも特別な謝礼は無く、医療費は通常どおり保険診療によるご負担になります。ただし、高感度 CRP 濃度の測定に必要な費用は研究費から支出されますので、患者様のご負担はありません。

10. 健康被害が発生した場合の補償はありますか？

この研究で使われる薬は既に市販され、通常の診療で広く使われているものです。従って、定められた量を指示どおり服用したにもかかわらず、重篤な健康被害が発生した場合には「医薬品副作用被害救済制度」による補償があります。ただし、その補償内容は必ずしも十分とは言えないのが実情です。

11. この研究の資金源は何ですか？

この研究は厚生労働省の助成金で行われ、一部に先端医療振興財団の支援を受けて行われます。研究の結果に関わらず、それが厚生労働省や先端医療振興財団に何ら利益や損害を与えることはありません。

12. この研究で特許等が生み出されることはありますか？

この研究は薬剤の適応拡大を目的とするものではなく、従って、研究成果によって特許等が生み出されることはありません。

13. 質問や問題が生じた場合にはどこに連絡すればいいですか？

下記の担当医または主任研究者までご連絡下さい。

病院名：＿＿＿＿＿＿＿＿＿＿　診療科：＿＿＿＿＿＿＿＿＿＿

担当医：＿＿＿＿＿＿＿＿＿＿　電話番号（内線）：＿＿＿＿＿＿＿＿＿＿

主任研究者：広島大学大学院脳神経内科教授　松本昌泰

〒734-8551　広島市南区霞 1-2-3　電話番号：082-257-5201

同意書（担当医用）

病院　病院長殿

平成　　年　　月　　日

（説明者）
所属
氏名 _____

□ 1）脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA 還元酵素阻害薬の予防効果に関する研究

□ 2）高脂血症治療薬 HMG-CoA 還元酵素阻害薬の総頸動脈内中膜複合体厚へ及ぼす効果に関する研究

□ 3）高脂血症治療薬 HMG-CoA 還元酵素阻害薬の高感度 CRP 濃度へ及ぼす効果に関する研究

同意される研究のチェックボックスすべてにチェックをつけてください。

私は上記の研究において下記の項目について担当医より説明を受け、理解いたしました。
そこで、今回、これらの研究に参加することに同意します。

記

1. 研究の目的と方法
2. 研究に参加することの恩恵と危険性
3. 私が同意しない場合であっても、不利益は受けないこと
4. 私が同意した場合でも、不利益なくそれを撤回できること
5. その他、人権の保護に関する事項
6. 医療費等について

同意年月日　平成　　年　　月　　日
本人：住所

_____

氏名 _____ 印（又は自署名）

生年月日　　年　　月　　日

同意書（患者さま用）

病院　病院長殿

平成　　年　　月　　日

（説明者）
所属
氏名 _____

□ 1）脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA 還元酵素阻害薬の予防効果に関する研究

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同意される研究のチェックボックスすべてにチェックをつけてください。

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同意年月日　平成　　年　　月　　日
本人：住所

_____

氏名 _____ 印（又は自署名）

生年月日　　年　　月　　日

同意撤回書

病院　病院長殿

□ 1）脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA 還元酵素阻害薬の予防効果に関する研究

□ 2）高脂血症治療薬 HMG-CoA 還元酵素阻害薬の総頸動脈内中膜複合体厚へ及ぼす効果に関する研究

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該当する研究のチェックボックスすべてにチェックをしてください。

私は上記の研究への参加に同意しましたが、同意を撤回します。

同意撤回年月日　平成　　年　　月　　日

本人：　住所

氏名　　印（又は自署名）

生年月日　　年　　月　　日生

（資料.３）文献

Primary Cardiovascular Events and Serum Lipid Levels in Elderly Japanese with Hypercholesterolemia Undergoing 6-Year Simvastatin Treatment: A Subanalysis of the Japan Lipid Intervention Trial

Hisanori Horiuchi, MD, Toru Kita, MD,* Hiroshi Mabuchi, MD,† Masunori Matsuzaki, MD,‡ Yuji Matsuzawa, MD,§ Noriaki Nakaya, MD,‖ Shinichi Oikawa, MD,¶ Yasushi Saito, MD,# Jun Sasaki, MD,** Kazuaki Shimamoto, MD,†† Hiroshige Itakura, MD,‡‡ and the J-LIT Study Group*

OBJECTIVES: To determine the relationship between serum lipid levels and the incidence of coronary events in older Japanese hypercholesterolemic patients without prior coronary heart disease (CHD).

DESIGN: Post hoc subanalysis of the results in the Japan Lipid Intervention Trial.

SETTING: A large-scale cohort observational study conducted throughout Japan.

PARTICIPANTS: Men aged 35 to 70 and postmenopausal women younger than 70 with serum total cholesterol (TC) level of 220 mg/dL or greater treated for 6 years with low-dose simvastatin (52,421 total patients). After exclusion of 5,127 patients because of prior CHD and 4,934 patients because of incomplete data, 42,360 patients were divided into an older (9,860 patients, aged 65–70, mean age 67.1) and younger (32,500 patients, younger than 65, mean age 54.9) group and analyzed.

MEASUREMENTS: Fasting serum lipid levels were measured every 6 months. Major coronary events, including fatal or nonfatal myocardial infarction, and sudden cardiac death as the primary endpoint and other cardiovascular diseases, including onset of angina pectoris, cerebrovascular events, and any causes of death, as the secondary endpoints were monitored.

RESULTS: Simvastatin treatment in older patients was as safe and effective as in younger patients. Incident rates of major coronary events were 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group. The incidence of a major coronary event was correlated to serum TC and low-density lipoprotein cholesterol (LDL-C) levels in both groups. The absolute risk of major coronary events in the older group was higher than in the younger group at any level of LDL-C, whereas the relative risk increased by 1.7% with an elevation of each 1 mg/dL LDL-C level in both groups. In the older group, the risk of major coronary events also increased as triglyceride level increased, whereas the risk decreased as high-density lipoprotein cholesterol level increased above 60 md/dL.

CONCLUSION: The LDL-C level-dependent increase of relative risk of CHD was similar in elderly and younger patients, whereas the absolute risk at any LDL-C level in elderly patients was higher than in younger patients. J Am Geriatr Soc 52:1981–1987, 2004.

Key words: serum cholesterol; coronary event; J-LIT study; elderly Japanese; simvastatin

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Controlling serum cholesterol levels is a rational strategy for prevention of coronary heart disease (CHD), as epidemiological and lipid intervention studies conducted in the United States and Europe have shown.[1–3] In those countries, CHD has been the main cause of death, and 21% to 24% of people have died of CHD,[4,5] whereas CHD accounts for merely 7% to 8% of deaths in Japanese living in Japan.[6] Despite this striking difference in CHD mortality between these populations, serum lipid levels have recently

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been similar in both populations.[7] The difference in mortality may be due to genetic backgrounds or environmental conditions, which are yet to be clarified.

The American guidelines for CHD prevention, Adult Treatment Panel III,[8] recommend that cholesterol levels should be controlled according to the individual absolute risk of CHD, estimated by the results of the Framingham study.[1] Nonetheless, the estimate of absolute risk of CHD in Japanese individuals is difficult, because no large-scale cohort studies have not been performed so far, only some small studies.[9–11] Recently, the dietary preferences of Japanese people have become progressively westernized, and their serum lipid profiles have been deteriorating rapidly.[12] It has currently become urgent in Japan to evaluate the relationship between lipid levels and the incidence of coronary events based on large-scale cohort studies, which provide fundamental data for preventive medicine. In addition, the elderly population in Japan has been rapidly increasing. In 2020, more than 30 million of 127 million people will be aged 65 and older.[6] Because cardiovascular events more frequently occur in the aged,[1,4,8] the incidence of CHD is likely to increase remarkably in Japan. Under these circumstances, the Japan Lipid Intervention Trial (J-LIT),[13–16] a large-scale observational cohort study in which many physicians throughout Japan participated, was conducted.

Subanalyses of lipid intervention studies with statins (3-hydroxy-3 methyl glutaryl coenzyme A reductase inhibitors) conducted in Western countries revealed that the treatment in older patients was as effective as that in younger patients for the prevention of CHD.[17–21] Recently, the Prospective Study of Pravastatin in the Elderly at Risk[22] conducted in Europe indicated that lipid-lowering therapy reduced CHD risk 21% in high-risk elderly subjects aged 75 to 82, but it was reported that increased serum cholesterol levels correlated with decreased mortality in patients aged 85 and older.[23] Furthermore, the Honolulu study[24] demonstrated that mortality was highest in the lowest quartile of total cholesterol (TC) level in Japanese Americans aged 72 to 92. Thus, lipid-lowering therapy, especially for elderly patients without prior CHD, should be well tuned to accomplish the goal.

To provide fundamental data about the relationship between serum cholesterol levels and CHD risk in elderly Japanese, the results of the J-LIT study were analyzed, focusing on patients aged 65 to 70 without a history of CHD.

METHODS

Study Design

The design of the J-LIT was described previously.[13] Briefly, men aged 35 to 70 and postmenopausal women younger than 70 with serum TC levels of 220 mg/dL or greater were enrolled. The exclusion criteria included recent myocardial infarction (MI) or stroke occurrence within a month, uncontrolled diabetes mellitus, serious complications of hepatic or renal disease, secondary hypercholesterolemia, malignant tumors, and illness with poor prognosis. More than 6,500 general practitioners throughout Japan treated patients with open-label simvastatin (5–10 mg/d) for 6 years during 1993–99. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.

Serum lipid levels, drug-related adverse events, and clinical status were monitored every 6 months. The primary endpoint was a major coronary event, defined as fatal and nonfatal MI, and sudden cardiac death. The secondary endpoints were other cardiovascular diseases, including onset of angina pectoris; cerebrovascular accidents; and any other causes of death. The Endpoint Classification Committee of the study verified all coronary events and death. The Adverse Event Evaluation Committee evaluated the adverse drug events. Each patient was informed of the study purpose, drug efficacy, and need for long-term treatment. Of the 52,421 enrolled patients, 5,127 were excluded because of prior CHD (*International Classification of Disease* code I20 to I25 and prior coronary intervention), and 4,934 patients were excluded for the following reasons: violation of the protocol (n = 995), unwillingness to participate (n = 6), and incomplete data for covariates (n = 3,933). The remaining 42,360 patients were divided into two groups (aged 65–70: 9,860 patients, mean age 67.1; aged <65: 32,500 patients, mean age 54.9) and analyzed.

Statistical Analysis

All data were analyzed using the survival analysis method. The baseline lipid profiles and continuous variables were assessed using the paired or unpaired *t* test or chi-square test. For analysis of baseline characteristics determined using categorical outcomes and adverse drug events, the differences between groups were compared using the chi-square test. The incidence of the events was analyzed in relation to average lipid levels during the follow-up period, and the differences between groups were compared using log-rank test. The relative risk and its 95% confidence interval and incidence of the primary endpoint was calculated using the Cox proportional hazards model with adjustment for baseline characteristics such as sex, hypertension, diabetes mellitus, and smoking. For all statistical analysis, $P < .05$ was considered significant. All statistical calculations were performed using SAS software (version 6.12, SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics

The baseline characteristics of the older and younger groups are shown in Table 1. Fewer men than women were enrolled in both groups. In addition, there was a smaller percentage of male patients in the older group than in the younger group (24.1% vs 35.1%). There were fewer smokers and alcohol consumers in the older group. Other baseline characteristics between the two groups were largely similar (Table 1). Most patients (97%) in both groups took simvastatin 5 mg/d. Other medications were nearly similar in both groups. The most frequently used drugs in both groups were calcium-channel blockers (31.4% in the older group and 21.4% in the younger group), angiotensin-converting enzyme inhibitors (13.0% and 12.4%, respectively), and beta-blockers (7.6% and 9.0%, respectively).

Of enrolled patients without prior CHD, 42,360 (91.5%) were followed, and 4,934 were excluded. No differences were observed in baseline characteristics, including mean age, sex ratio and serum TC level, between the

Table 1. Relative Risk (RR) of Major Coronary Events at Baseline

Risk Factor	Age <65* (n = 32,500) %	Age <65* (n = 32,500) RR (95% CI)	Age 65–70† (n = 9,860) %	Age 65–70† (n = 9,860) RR (95% CI)
Male	35.1	2.25 (1.51–3.34)	21.2	2.03 (1.17–3.52)
Obesity (body mass index >25 kg/m^2)	24.4	0.93 (0.66–1.33)	21.1	1.05 (0.62–1.75)
Hypertension	44.1	2.24 (1.58–3.17)	51.9	2.13 (1.27–3.55)
Diabetes mellitus	15.2	2.11 (1.46–3.06)	15.3	2.36 (1.41–3.95)
Electrocardiogram abnormality	12.0	1.87 (1.25–2.81)	16.4	1.70 (1.00–2.90)
Family history of coronary heart disease	5.1	2.67 (1.63–4.39)	3.5	2.57 (1.11–5.94)
Smoker	18.7	1.64 (1.10–2.45)	9.2	1.46 (0.73–2.89)
Alcohol drinker	32.4	0.63 (0.41–0.98)	17.7	0.63 (0.31–1.29)

Mean ± standard deviation = *54.9 ± 6.7; †67.1 ± 1.6 years old.
CI = confidence interval.

followed and excluded patients in the older group. In the younger group, slight differences between the followed and excluded patients were observed in proportion of men (39.2% vs 35.1%) and mean age (53.9 vs 54.9 years), whereas no difference was observed in TC level. It is unlikely that these differences in the younger group affect the results of this subanalysis.

Lipid Profiles

The baseline levels of TC, LDL-C, and high-density lipoprotein cholesterol (HDL-C) were similar between the two age groups, whereas triglyceride (TG) level was lower in the older group (Table 2). The mean baseline TC levels were 267 mg/dL in the older group and 271 mg/dL in the younger group. The mean reduction rates during the follow-up period under low-dose simvastatin treatment in the older and younger groups were 19.5% and 18.1% for TC, 28.2% and 26.2% for LDL-C, and 14.9% and 16.3% for TG, respectively. HDL-C level was 4.9% and 4.4% elevated, respectively (Table 2). The reduction in LDL-C level in both groups was similar at 6 months of treatment and continued throughout the follow-up period (data not shown). Thus, the lipid profiles of the two groups were similar at baseline and during treatment, indicating that simvastatin is as effective in older patients as in younger patients.

Drug-Related Adverse Events

Overall drug-related adverse events were observed in 3.18% of the older and 3.19% of the younger group ($P = .99$). The most frequently observed adverse events in both groups were hepatic dysfunction (0.99% in the older and 1.02% in the younger group, $P = .79$) and musculoskeletal disorders (0.81% and 0.90%, respectively, $P = .40$). No rhabdomyolysis occurred in either group,

Table 2. Patients' Lipid Profiles at Baseline and During Treatment

Lipid Profile (mg/dL)	Age <65 (n = 32,500) Mean ± Standard Deviation (% Change)	Age 65–70 (n = 9,860) Mean ± Standard Deviation (% Change)
Baseline		
TC	271 ± 36	267 ± 29
LDL-C	183 ± 34	181 ± 31
Triglyceride	202 ± 184	175 ± 110
HDL-C	52.8 ± 15.1	53.4 ± 15.1
During treatment		
TC	222 ± 30 (−18.1)*	215 ± 27 (−19.5)*
LDL-C	135 ± 30 (−26.2)*	130 ± 27 (−28.2)*
Triglyceride	169 ± 110 (−16.3)*	149 ± 68 (−14.9)*
HDL-C	55.1 ± 13.7 (+4.4)*	56.0 ± 13.7 (+4.9)*

*$P < .001$ baseline vs during treatment.
TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

although myopathy was reported in one patient in the older group and three patients in the younger group. The incidence of renal dysfunction was slightly higher in the older group (0.32%) than in the younger group (0.14%) ($P<.01$). None of differences in these adverse events were clinically significant. The incidence of other adverse events was not statistically significantly different between the two groups. It was concluded that simvastatin treatment in older patients aged 65 to 70 was as safe as in younger patients.

Coronary and Cerebrovascular Events and Death

Incidence rates during treatment of major coronary events, including fatal or nonfatal MI and sudden cardiac death, were 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group ($P<.001$) (Table 3). Incidence rates of major coronary events in male patients were 2.45 per 1,000 patient-years in the older group and 1.41 per 1,000 patient-years in the younger group ($P=.003$). In female patients those rates were 1.00 and 0.47 per 1,000 patient-years, respectively ($P<.001$). Incidence rates of total coronary events, including major coronary events and newly developed angina pectoris, were 2.24 per 1,000 patient-years in the older group and 1.35 per 1,000 patient-years in the younger group ($P<.001$) (Table 3).

Incidence rates of ischemic cerebrovascular events, including cerebral thrombosis, cerebral infarction, transient ischemic attack, and reversible ischemic neurological deficit, were 2.61 per 1,000 patient-years in the older group and 1.29 per 1,000 patient-years in the younger group ($P<.001$) (Table 3). Thus, the incidence of major coronary events and ischemic cerebral accidents was higher in the older group.

Overall mortality was 2.4 times higher in the older group than in the younger group (Table 3). The proportions of cardiac deaths, death from malignancy, and death from other causes were similar in both age groups (Table 3).

Effects of Conventional CHD Risk Factors on the Development of Major Coronary Events

The contribution of the conventional risk factors for CHD to the development of major coronary events was analyzed (Table 1). Male sex, hypertension, diabetes mellitus, and family history of CHD were found to be significant risk factors of CHD in both age groups. Electrocardiogram abnormalities and smoking were statistically significant only for the younger group, possibly because of fewer patients enrolled in the older group. Body mass index of 25 kg/m^2 or greater did not increase the risk of CHD in either group in this study. Moderate alcohol consumption seemed to be a negative risk factor for CHD in both groups to a similar extent, although it was statistically significant only for the younger group. These conventional risk factors appear to contribute similarly in both age groups.

Incidence of Major Coronary Events and Lipid Profiles During the Follow-Up Period

The incidence rate of the major coronary events was analyzed in relation to serum lipid levels stratified by the average values during the follow-up period. As shown in Figures 1A and 1B, the incidence rate of major coronary events was higher in the older group than in the younger group at any level of serum TC and LDL-C. In both groups, major

Table 3. Death and Coronary and Cerebrovascular Events During Treatment

Adverse Event	<65 (n = 32,500)		65–70 (n = 9,860)		
	n	Incidence Rate†	n	Incidence Rate†	*P*-value*
Death, total	489	2.79	355	6.70	<.001
Cardiac	45	0.26	38	0.72	<.001
Noncardiac	444	2.53	317	5.98	<.001
Malignancy	185	1.06	132	2.49	<.001
Other	259	1.48	185	3.49	<.001
Coronary endpoint	236	1.35	119	2.24	<.001
Major coronary event	140	0.80	69	1.30	<.001
Myocardial infarction (fatal)	31	0.18	20	0.38	.007
Myocardial infarction (nonfatal)	105	0.60	42	0.79	.12
Sudden cardiac death	4	0.02	7	0.13	.001
Angina pectoris	96	0.55	50	0.94	.002
Cerebrovascular event	397	2.26	211	3.99	<.001
Ischemic cerebrovascular event	226	1.29	138	2.61	<.001
Cerebral thrombosis	120	0.68	66	1.25	<.001
Cerebral infarction	56	0.32	44	0.83	<.001
Transient ischemic attack, reversible ischemic neurological deficit	50	0.29	28	0.53	.008
Cerebral hemorrhage	83	0.47	31	0.59	.30
Subarachnoid hemorrhage	44	0.25	14	0.26	.86
Unclassified stroke	44	0.25	28	0.53	.002

* For log-rank test.
† Per 1,000 patient-years.

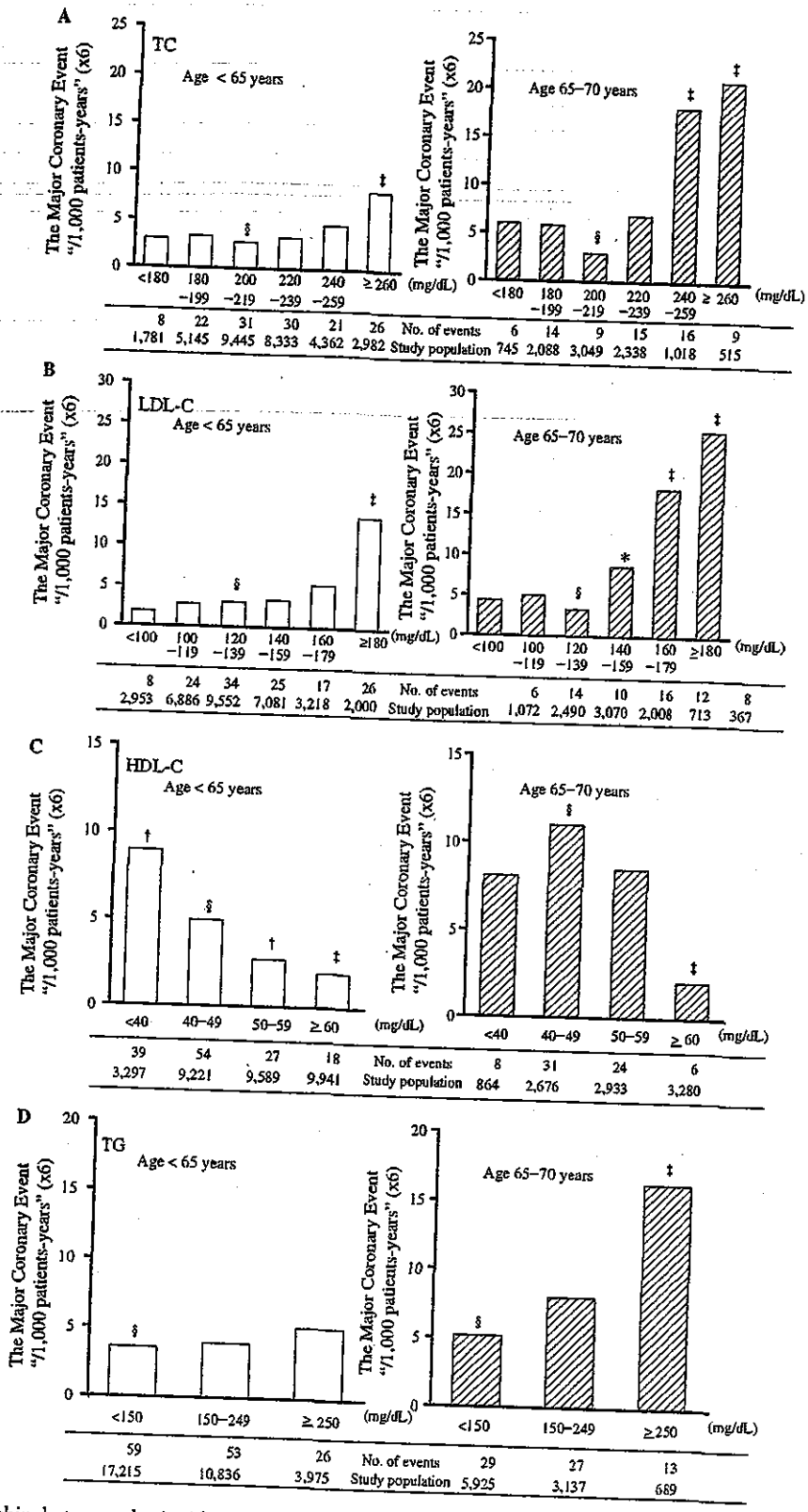

Figure 1. The relationship between the incidence of major coronary events and (A) serum total cholesterol TC, (B) low density lipoprotein-cholesterol LDL-C, (C) high density lipoprotein-cholesterol (HDL-C), and (D) triglyceride (TG) levels in the older and younger groups. The incidence rate of major coronary events was assessed using a Cox proportional hazards model according to stratified mean lipid levels during the follow-up period as indicated in the figures. These data were adjusted for sex, hypertension, diabetes mellitus, and smoking. $^{*}P<.05$; $^{\dagger}P<.01$; $^{\ddagger}P<.001$ versus reference category. Reference categories: TC = 200–219 mg/dL, LDL-C = 120–139 mg/dL, HDL-C = 40–49 mg/dL, and TG = <150 mg/dL.

coronary events increased as serum TC level elevated, and the increase was accentuated in patients with levels of 240 mg/dL or greater in the older group and 260 mg/dL or greater in the younger group (Figure 1A). Similarly, major coronary events increased in an LDL-C level–dependent manner in both groups, and the increase was accentuated in patients with levels of 140 mg/dL or greater in the older group and 180 mg/dL or greater in the younger group (Figure 1B). In a linear regression model, the incidence rate of major coronary events increased by 1.7% with an elevation of each 1 mg/dL LDL-C level in both age groups, although the absolute risk was higher in the older group (data not shown).

Major coronary events decreased as HDL-C level increased in the younger group, whereas in the older group major coronary events were higher in patients with levels lower than 60 mg/dL and declined abruptly in patients with levels of 60 mg/dL or greater (Figure 1C). Major coronary events in the younger group were not correlated with TG level. In the older group, major coronary events increased as TG level increased (Figure 1D).

DISCUSSION

The J-LIT study was the first successful large-scale prospective observational study in Japan. The overall results of the study clearly showed that the risk of CHD was positively correlated with LDL-C level and inversely correlated with HDL-C level in Japanese patients with hypercholesterolemia.[14,15] In this report, the J-LIT data of patients aged 65 to 70 without prior CHD were compared with those of patients aged 35 to 64. It was demonstrated that cholesterol-lowering treatment with simvastatin for older Japanese patients was as safe and effective as for the younger patients and that the absolute risk of CHD in older patients was approximately twice that of younger patients at any LDL-C level. Nonetheless, the LDL-dependent increase of the relative risk of CHD was similar.

Mean baseline TC (267 mg/dL) and LDL-C (181 mg/dL) levels in the older group decreased to 215 mg/dL (−19.5%) and 130 mg/dL (−28.2%), respectively, during the treatment. These values were similar to those in the younger group. In the J-LIT study, most patients (97%) took 5 mg/d of simvastatin. Why such a low dose of simvastatin reduced LDL-C levels by 28% in Japanese patients is not clearly understood.

The incidence of major coronary events, including fatal and nonfatal MI, and sudden cardiac death was 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group. There were fewer men in both groups, possibly because more women than men are treated for hypercholesterolemia in Japan.[25] Additionally, there was a lower percentage of men in the older group than in the younger group (21.2 vs 35.1%). In male patients, the incidence rate of major coronary events was 2.45 per 1,000 patient-years in the older group and 1.41 per 1,000 patient-years in the younger group. In female patients, the incidence rate was 1.00 per 1,000 patient-years and 0.47 per 1,000 patient-years, respectively. The incidence rate of major coronary events in the older group was approximately twice as high in both sex subgroups.

The incidence rate of coronary events was potentially underestimated in the J-LIT study compared with that in the general Japanese population because all subjects were taking simvastatin, which might have direct antiatherosclerotic effects on coronary vessels[26,27] in addition to reducing lipids. In Western countries, statin treatment has been shown to reduce coronary events by 30% to 40% in primary[3,19] and secondary prevention studies.[2,17,20] If this reduction rate could be applied to the J-LIT results, the incidence of coronary events would be predicted to be approximately 1.4 to 1.6 times higher in the general Japanese population. Nevertheless, the incidence rate of coronary events in this study is much lower than in Western populations.[1,3,19] In the West of Scotland Coronary Prevention Study (WOSCOPS),[3] Scottish male hypercholesterolemic patients aged 45 to 64 (mean age 55) were followed with or without pravastatin treatment. In the pravastatin group, baseline TC level was 272 mg/dL and decreased by 20% during the follow-up period.[3] Mean age, baseline TC level, and reduction rate of TC of the pravastatin group were similar to those of the younger male group (mean age 54.9) in the J-LIT study. The incidence rate of coronary events was 11/1,000 patient-years for the pravastatin group in the WOSCOPS whereas the rate was 1.41/1,000 patient-years for the younger male group in the J-LIT study. Although there were differences in study conditions, the incidence of coronary events in Japanese male patients under statin treatment was one-eighth that of Scottish male patients.

The relative risk of major coronary events increased by 1.7% with an elevation of each 1 mg/dL in LDL-C level in both age groups, whereas the absolute risk at any level of TC and LDL-C was higher in the older group. The incidence rate of major coronary events markedly increased with TC level above 240 mg/dL and LDL-C level above 140 mg/dL in the older group. These TC and LDL-C levels were 20 and 40 mg/dL lower than those in the younger group, respectively. Generally, high-risk patients are good candidates for preventive medicines. In this viewpoint, elderly patients might receive more benefit from lipid-lowering therapy, but lipid intervention trials are required to establish the therapeutic benefits and strategies in elderly Japanese.

The preventive effect of HDL-C was also observed in the Japanese population. In the older group, the incidence of major coronary events decreased with HDL-C level above 60 mg/dL, whereas the incidence was HDL-C level–dependent in its wide range in the younger group. The role of TG level for the development of coronary events is controversial,[28] although the evidence is accumulating.[29] In the J-LIT study, TG level above 250 mg/dL was associated with a greater risk of major coronary events in the older patients, whereas no such relationship was observed in the younger group.

The incidence rate of ischemic cerebrovascular events, including cerebral thrombosis and infarction, transient ischemic attack, and reversible ischemic neurological deficit, was 2.61 per 1,000 patient-years in the older group and 1.29 per 1,000 patient-years in the younger group. The ratio of the incidence rate of ischemic cerebrovascular events (the older group/the younger group, 2.02) was larger than that of major coronary events (1.63), suggesting that aging may affect the occurrence of ischemic cerebrovascular events more strongly than of coronary events in the Japanese population.

In summary, the LDL-C level–dependent increase of the relative risk of CHD was similar in elderly and younger patients, whereas the absolute risk at any TC and LDL-C level in elderly patients was twice as high as in younger patients. Further lipid intervention trials would be required to establish the therapeutic benefits and strategies in elderly Japanese.

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Feasibility of the Inoue single-branched stent-graft implantation for thoracic aortic aneurysm or dissection involving the left subclavian artery: Short- to medium-term results in 17 patients

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Objective: This study assessed the short- to medium-term clinical results of the Inoue single-branched stent graft for repair of thoracic aortic aneurysms or dissections involving the left subclavian artery.
Methods: A retrospective review of experiences at two institutions was performed. We analyzed the data of consecutive 17 patients with thoracic aortic aneurysms or dissections who underwent endovascular repairs with the Inoue single-branched stent graft between July 1999 and April 2004. Complete baseline and follow-up data were available on all patients. The mean age was 71 ± 9 years, and 13 of the patients (76%) were men. Eight patients (47%) were considered unfit for open surgery because of advanced age or the presence of comorbid diseases.
Results: The stent grafts were successfully delivered and deployed in all 17 patients. Periprocedural major complications, defined as those that caused any persistent disorder, occurred in one patient who developed spinal ischemia. A postoperative computed tomographic scan revealed three attachment site endoleaks; two endoleaks were from the proximal attachment sites and one endoleak was from the distal attachment site. The mean follow-up period was 26 months (range, 7 to 65 months). Two deaths occurred in the follow-up period from cerebral bleeding and pneumonia, both considered unrelated to the stent grafting. Two patients with attachment site endoleaks needed secondary stent-grafting; one patient required the implantation of a straight stent-graft in the distal attachment site and the other, the implantation of a double-branched stent-graft. Another patient with attachment site endoleak was considered very high-risk for open surgery or secondary stent grafting and did not undergo secondary intervention. The aneurysmal sac size of the patient has been stable for 28 months. The branched section of the stent graft was patent in all patients in the follow-up period.
Conclusion: The results demonstrate the feasibility of the Inoue single-branched stent graft for thoracic aortic aneurysms or dissections involving the left subclavian artery. (J Vasc Surg 2005;41:206-12.)

Open surgical repair is considered the traditional treatment for patients with thoracic aortic aneurysms. Despite recent advances in surgical techniques and anesthetic management, the surgical repair of thoracic aortic aneurysms is still associated with significant mortality and morbidity.[1] Endovascular stent grafting of thoracic aortic aneurysms is emerging as an alternative method for repair in selected patients.[2,3] Although endovascular stent grafting is less invasive than open surgical procedures, involvement of branch vessels in the aortic arch limits the application of stent grafting.

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Competition of interest: Dr Kanji Inoue holds all patents of the Inoue stent graft, which was developed and made by Dr Inoue. Dr Kanji Inoue is the only author who holds patents of the stent graft.
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Thoracic aortic aneurysms that involve the left subclavian artery are not rare. In the combined results of the EUROSTAR and the United Kingdom Thoracic Endograft registries, it was necessary to place a stent graft over the left subclavian artery in 17% of the patients.[4] Thurnher et al[5] reported that they required subclavian artery transposition in 24% of their cases.

Our method of managing the left subclavian artery is to provide a stent graft with a side branch. This method does not require the surgical revascularization of the left subclavian artery. This study assessed the short- to medium-term clinical results of Inoue single-branched stent-graft implantations for thoracic aortic aneurysms involving the left subclavian artery.

METHODS

Patients. Between July 1999 and April 2004, endovascular grafting with the Inoue single-branched stent graft was undertaken in 17 patients with thoracic aortic aneurysms or dissections at Kokura Memorial Hospital, Kokura and Kyoto University Hospital, Kyoto, Japan. All patients gave their informed consent in conformance with the protocols approved by the institutional review board of each

Table I. Demographics and comorbidities of the patients

Patients	*Sex*	*Age*	*Etiology*	*Maximum diameter of aneurysm (mm)*	*Unfit for open surgery*	*Risk of open surgery*
No. 1	M	77	degenerative	50	No	
No. 2	F	66	aneurysmal degeneration of a long standing aortic dissection	64	No	
No. 3	M	60	chronic aortic dissection	60	No	
No. 4	M	48	chronic aortic dissection	47	No	
No. 5	M	81	aneurysmal degeneration of a long standing aortic dissection	62	Yes	Advanced age*
No. 6	M	69	acute aortic dissection	46	No	
No. 7	M	80	degenerative	61	Yes	Advanced age
No. 8	M	79	degenerative	75	No	
No. 9	M	75	chronic aortic dissection	70	No	
No. 10	M	67	degenerative	68	Yes	Cerebrovascular disease Prior thoracotomy
No. 11	M	73	degenerative	43	No	
No. 12	M	66	acute aortic dissection	39	Yes	Traumatic injury (rib fracture)
No. 13	—	74	degenerative	50	Yes	Lung disease
No. 14	F	71	degenerative	56	No	
No. 15	M	81	degenerative	70	Yes	Advanced age
No. 16	M	70	degenerative	60	Yes	Lung disease
No. 17	F	78	Ductus diverticulum	68	Yes	Lung disease

F = female; *M* = male.
*Advanced age was defined as over 79 years.

hospital. The mean age was 71 ± 9 years, and 13 patients (76%) were men. Eight patients (47%) were considered unfit for conventional surgical repair because of advanced age or the presence of comorbid diseases. The remaining nine patients rejected open surgery and strongly preferred endovascular repair.

The etiologies of the aneurysms were atherosclerotic aneurysms in nine patients, chronic dissecting aneurysms with patent false lumens in four patients, aneurysmal degeneration of long-standing aortic dissections with thrombosed false lumens in two patients, one traumatic acute aortic dissection, and one aneurysm of the ductus diverticulum.

The Inoue single-branched stent graft was placed into the distal aortic arch, including the origin of the left subclavian artery and the descending aorta. The proximal and distal landing zones required at least 10 mm in length. The front part of the proximal landing zone was at least 5 mm distal to the left common carotid artery. The mean diameter of the aneurysms was 58 ± 11 mm. The demographics and comorbidities of the patients are presented in Table I. Complete baseline and follow-up data are available on all patients.

Device. The Inoue endovascular grafting system consists of a stent graft, a detachable carrying wire, two detachable traction wires, a balloon catheter, and an introducer sheath (Fig 1). The size of the introducer sheath was determined individually, but was usually 20F to 24F.

The Inoue stent graft is constructed from a woven Dacron polyester fabric cylinder. The outside surface of the stent graft is supported with multiple rings of extra-flexible nickel titanium wire covered by Dacron filaments. Small Dacron cuffs are attached to the first and second rings from each end to improve the sealing function. The Inoue single-branched stent graft consists of an aortic section and a branched section. The aortic section and the branched section are sewn together.

The Inoue stent grafts were custom made. We used a specialized computer system for designing the Inoue stent graft.[6] A three-dimensional model was constructed from helical computed tomography (CT) images for the aneurysm. The stent graft was designed and positioned endoluminally on the computer (Fig 2). The diameter and length of each section of the stent graft was determined for each patient. The diameter of the aortic section of the graft was usually oversized by 2 mm and the branched section by 1 mm to achieve effective sealing. The ring of nickel titanium wire attached to the graft was oversized by more than 2 mm.

Each section of the stent graft was individually folded using loops of thread and nickel titanium wire. By removing the nickel titanium wire, each section of the stent graft was unfolded. Three detachable wires were also attached to the stent graft. A carrying wire was attached to the proximal end of the aortic section, and a traction wire was attached to the distal end of the aortic section. Another traction wire was attached to the branched section. The Inoue stent graft was delivered through the introducer sheath with the aid of the carrying and traction wires. A large compliant balloon was used in the dilatation of the aortic graft section. The balloon was custom made and inserted via the introducer sheath (Fig 1).

Implantation technique. All 17 procedures were performed in the cardiac catheterization laboratory under local anesthesia. The patient's femoral artery was surgically iso-

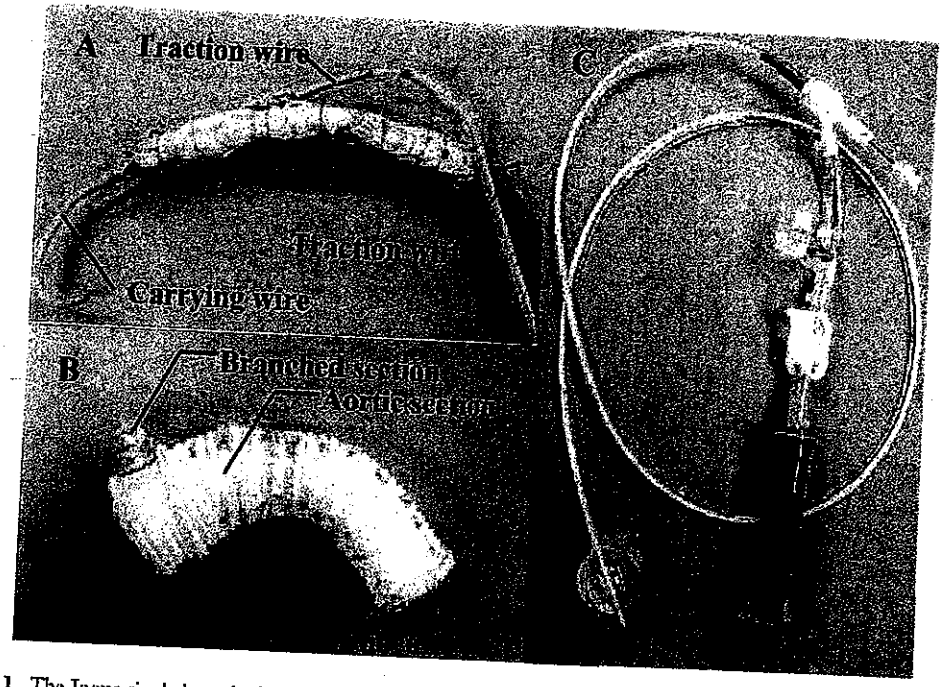

Fig 1. The Inoue single branched stent-graft (*A* and *B*) and the balloon (*C*). A. The folded state. The carrying wire is attached to the proximal end of the aneurysm. Each traction wire is attached to the branched section and the aortic section. B. The unfolded state. The stent-graft consists of the aortic section and the branched section.

lated and a transverse arteriotomy performed. A 7F sheath was inserted percutaneously in the left brachial artery. The introducer sheath was inserted through the femoral artery and advanced to the descending thoracic aorta under fluoroscopic guidance. After administration of 10000 U of heparin, the folded stent graft was introduced into the sheath, advanced to the descending thoracic aorta, and released from the sheath. The folded graft was then pushed to the distal aortic arch.

A 7F catheter with a gooseneck wire was inserted through the 7F sheath in the left brachial artery. The free end of the traction wire attached to the tip of the branched graft section was caught by the gooseneck wire and then pulled back into the left subclavian artery. The carrying wire and the traction wire were manipulated to properly position the aortic and branched graft sections.

After unfolding the graft, the aortic section and the branched section of the graft were dilated by a compliant balloon. The balloon was custom made and inserted via the introducer sheath. We did not use hypotension to place the graft or for balloon inflation. The carrying wire and the traction wires prevented migration of the stent graft during balloon inflation.

The sheath was removed, and the incision was closed. Fig 3 shows a successful implantation. Detailed information concerning the implantation techniques is available in previous reports.[7,8]

Follow-up protocol. All patients were examined with contrast enhanced helical CT scans before hospital discharge. The scans were repeated every 6 months. The mean follow-up period was 26 months (range, 7 to 65 months).

RESULTS

The stent grafts were successfully delivered and deployed in all patients. The mean procedure time, measured from the incision of the skin to surgical closure of the femoral access site, was 219 ± 68 minutes. The mean contrast media used in the procedures was 249 ± 99 mL.

All patients were transferred immediately to the ward without staying in the intensive care unit. Four patients required a blood transfusion. Major complications, defined as that caused any persistent disorders, occurred in one patient. The patient developed paraparesis that was probably caused by the accidental embolization of the Adamkiewicz artery. The graft of the patient was too short to cover the location of the Adamkiewicz artery, and the preprocedural images showed irregular, shaggy mural thrombus in the thoracic aorta.

Three access site complications occurred: a lymphorrhea, a pseudoaneurysm, and an intimal injury of the iliac artery. The lymphorrhea was resolved without aspiration. The pseudoaneurysm was successfully repaired by surgery. The intimal injury required a metallic stent implantation in the iliac artery. The three patients with minor complications were discharged without any disorders.

Complete exclusion of the inlet of the aneurysm or the primary entry tear of the aortic dissection at the time of the first postoperative CT scan was achieved in 14 patients

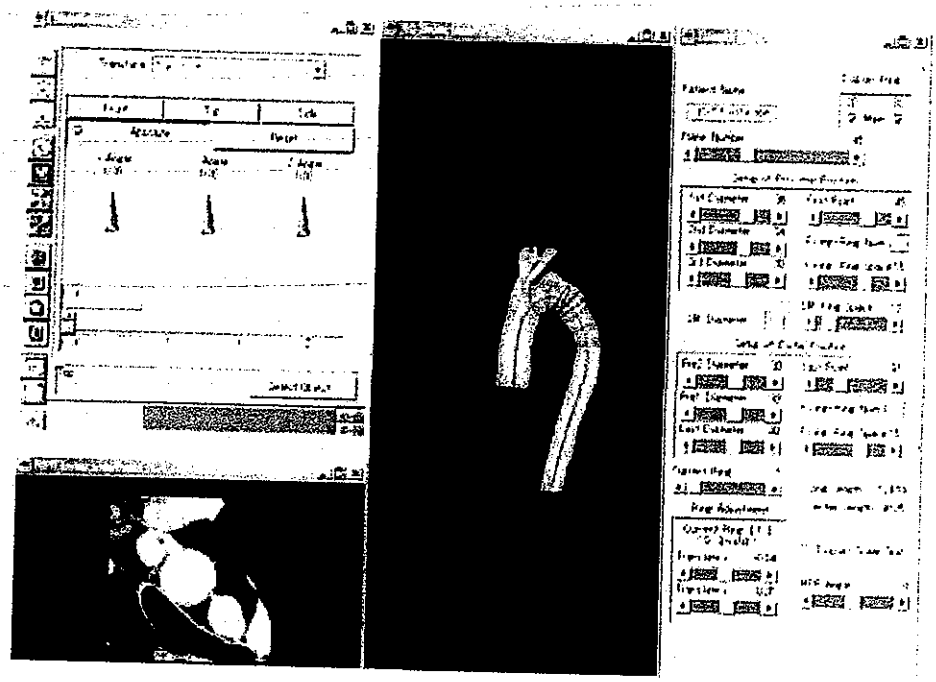

Fig 2. Monitor display of the computer program used to design the Inoue stent graft.

(82%). Attachment site endoleaks were revealed in three patients; two leaks were from the proximal attachment sites, and one leak was from the distal attachment site. The cause of the two endoleaks in the proximal attachment sites was considered unrelated to the branched section; they were instead considered caused by difficulties in implanting the stent graft in a curved position. The primary endoleak rate was 18%.

The average hospital stay after the procedure was 19 ± 27 days (range, 2 to 120). The patient who developed paraparesis required a distinctly prolonged hospital stay of 120 days for rehabilitation. All patients were discharged alive, and the 30-day mortality was 0%.

The mean follow-up period was 26 months (range, 7 to 65 months). More than a 3-mm sac size change was defined significant. Significant sac size shrinkage was achieved in 8 patients (47%). Sac size change was measured at the most recently obtained CT scan. Two of the three patients with attachment site endoleaks at the first postoperative CT scan required secondary stent grafting; one patient required implantation of a straight stent graft at the distal attachment site; the other patient required implantation of a double-branched stent graft.

Another patient with attachment site endoleak had a history of cerebral infarction, which occurred during previous open surgical replacement of a thoracoabdominal aortic aneurysm. We estimated that the risk of a repeat open surgery or secondary stent grafting procedure outweighed the risk of rupture. The aneurysmal sac size of the patient has not changed for 28 months.

Enlargement of the aneurysmal sac or secondary endoleak requiring secondary intervention has not been revealed in any of the other patients. CT scan confirmed that the branched section of the stent graft was patent in all cases. No stent graft migration occurred in any patient.

Two deaths occurred in the follow-up period. The cause of death was cerebral bleeding and pneumonia, both considered unrelated to the stent grafting. The initial and follow-up results are summarized in Table II.

DISCUSSION

Endovascular repair of thoracic aortic aneurysms may reduce morbidity and mortality.[2,3] The procedure is considered most suitable when the proximal end of the aneurysm is 1 to 2 cm from the left subclavian artery. Implantation can be difficult when the landing zone distal to the left subclavian artery is not sufficient.

Several options have been proposed to overcome this problem. The most traditional is prophylactic transposition or bypass graft placement to provide flow to the arm.[9-11] Some recent reports have described the safety of the intentional occlusion of the left subclavian artery by the stent graft without prophylactic surgical transposition. If arm, hand, or cerebral symptoms develop after coverage of the left subclavian artery, surgical revascularization of the subclavian artery is performed.[12-14] Although the early results of this option suggest that it is safe in most patients, some patients require transposition of the left subclavian artery in the follow-up.

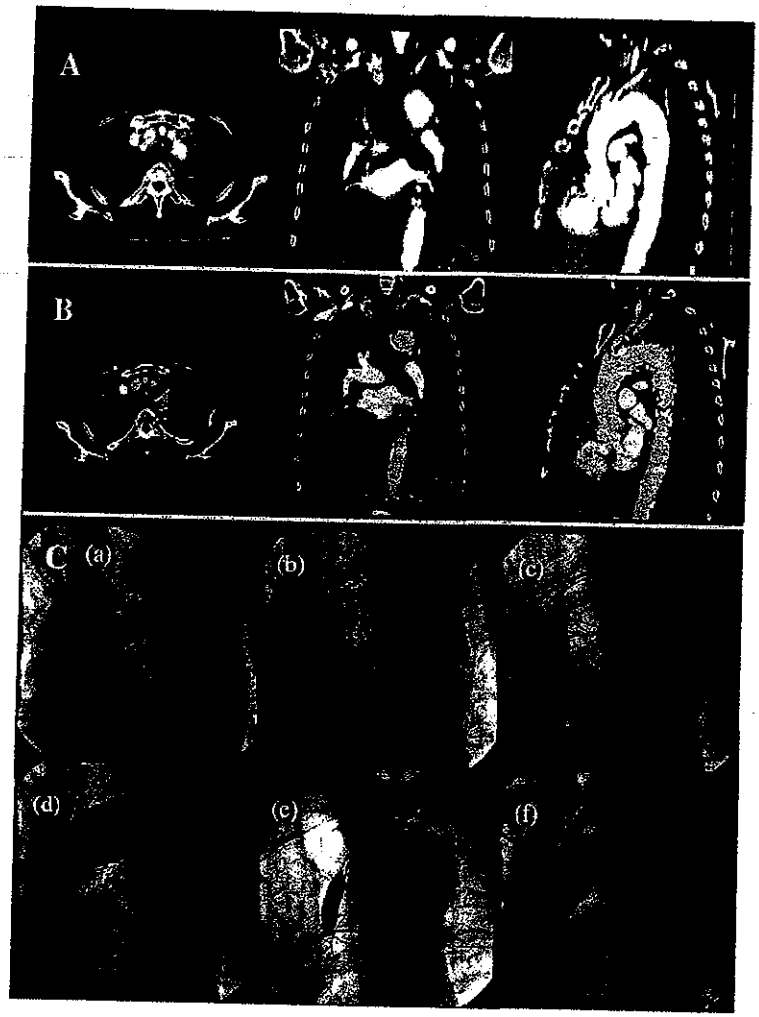

Fig 3. The successful implantation of the Inoue single-branched stent graft is shown for patient 16 in Table 1. **A**, Enhanced computed tomography (CT) scan before treatment. **B**, Enhanced CT after treatment. **C**, Angiogram during the procedure. *a*, The folded Inoue stent-graft was delivered and positioned. *b*, The distal part of the aortic section of the graft was unfolded. *c*, After unfolding the proximal part of the aortic section of the graft, the distal neck was dilated. *d*, The proximal part of the aortic section was dilated. *e*, The branched section was dilated. *f*, The final angiogram revealed complete exclusion of the aneurysm.

Tiesenhausen et al[14] reported on eight patients who underwent thoracic aortic stent grafting without revascularizations of the left subclavian arteries. No immediate neurologic deficit or left arm ischemia occurred, but three patients required surgical revascularization of the left subclavian artery during follow-up. Furthermore, the occluded subclavian artery poses another problem: it may be a potential source of retrograde inflow into the excluded aneurysms or the false lumen.

Another option is to cross the origin of the left subclavian artery with the uncovered lesion of the stent graft.[15] The Talent LPS stent graft (Medtronic AVE, Santa Rosa, Calif) is usually used in this option. This option has limitations, however. The uncovered proximal stent aids in anchoring—not sealing—and leaks may occur. The uncovered stent may erode through the aorta.

Our option is to provide a stent graft with a side branch to the left subclavian artery.[7,8] This method does not require surgical transposition of the left subclavian artery and is widely applicable. However, except for the Inoue stent grafts, reports of endovascular techniques of complex aneurysm repair with branched stent grafts have been limited to animal studies and incidental case reports.[16,17]

In their initial experience with the branched stent-graft implantations, Inoue and colleagues[8] reported embolic cerebrovascular accident as the major complication. We consider that the risk of cerebral infarction is very low in the placement of a stent graft with a side branch to the left subclavian artery.

Table II. Initial and follow-up results of the patients. Corresponding patients' numbers are shown in Table I.

Patients	*Etiology*	*Hospital stay (day)*	*Complication*	*Endoleak at the first postoperative CT scan*	*Follow-up period (month)*	*Event in the follow-up period*
No. 1	Degenerative	19	No	No	65	Sac size stable
No. 2	Aneurysmal degeneration of a long standing aortic dissection	7	No	Yes (from the distal attachment site)	9	Sac size increased Secondary stent-grafting
No. 3	Chronic aortic dissection	4	No	No	54	Sac size reduced
No. 4	Chronic aortic dissection	3	No	No	53	Sac size reduced
No. 5	Aneurysmal degeneration of a long standing aortic dissection	3	No	No	50	Sac size stable
No. 6	Chronic aortic dissection	2	No	Yes (from the proximal attachment site)	35	Sac size increased Secondary stent-grafting
No. 7	Degenerative	26	Pseudoaneurysm	No	14	Sac size stable
No. 8	Degenerative	120	Paraparesis	No	9	Death (cerebral bleeding) Sac size stable
No. 9	Chronic aortic dissection	8	No	No	35	Death (pneumonia) Sac size reduced
No. 10	Degenerative	21	No	Yes (from the proximal attachment site)	28	Sac size stable
No. 11	Degenerative	29	Lymphorrhea	No	21	Sac size stable
No. 12	Acute aortic dissection	19	No	No	17	Sac size reduced
No. 13	Degenerative	13	No	No	17	Sac size reduced
No. 14	Degenerative	17	No	No	14	Sac size reduced
No. 15	Degenerative	14	No	No	13	Sac size stable
No. 16	Degenerative	10	No	No	9	Sac size reduced
No. 17	Ductus diverticulum	16	Intimal injury of the iliac artery	No	7	Sac size reduced

CT, computed tomography.

In normal human anatomy, the right common carotid artery and the right subclavian artery branch from the brachiocephalic artery, whereas the left common carotid artery and the left subclavian artery branch from the aorta directly. The right subclavian artery involves the common carotid artery, but the left subclavian artery does not. Thus, the single-branched stent-graft implantation is much safer than the double- or triple-branched stent-graft implantation in terms of the risk of cerebral infarction.

No cerebrovascular embolic events occurred in this study. Branched stent-graft implantation does not require surgical transposition of the left subclavian artery. Furthermore, this method offers another advantage: it may prevent the migration of the graft. Concerns about stent-graft migration in the long term have been reported.[18] Migration is associated with late aneurysm rupture, proximal endoleak, and graft kinking. The Inoue stent graft has no barbs to hold it in place. The branched section secures the proximal fixation and prevents later migration of the graft.

Our data suggest the feasibility of the single-branched stent-graft implantation for thoracic aorta. The Inoue single-branched stent graft offers an alternative mode of management for thoracic aortic aneurysms that involve the left subclavian artery and may expand the indication of thoracic stent grafting.

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INVITED COMMENTARY

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In the accompanying paper, Saito et al describe their use of the Inoue system, a novel prosthesis with a side branch to the left subclavian artery, to achieve promising results in 17 cases of distal aortic arch repair. The Inoue system has several unusual features that lend themselves to this particular application:

- A supporting framework of nickel titanium rings confers great flexibility and is capable of sealing within a very short attachment site between the left subclavian and left carotid arteries.
- A corset of diameter-restricting ties allows final adjustments in the orientation and position of the unsheathed, but still constrained, prosthesis, as the subclavian side-branch is retrieved using a transbrachial snare and drawn all the way into the subclavian artery.
- Once deployed, the fully embedded unibody side branch has less effect on proximal aortic implantation than a conventional (external) modular attachment cuff that would have to remain within the aorta.

Their results show that the technique appears to be both safe and effective in the short-to-medium term: serious complications were rare, aneurysm dilatation was rare, and most type I endoleaks were treatable by endovascular means. Yet, it is too early to say that this approach is clearly better than the endovascular alternatives.

The attachment means is one cause for concern. Unbarbed nickel titanium rings have not generally been effective in preventing late-occurring migration and type I endoleak. An oversized ring buckles, distorts the profile of the attached graft orifice, and induces dilatation of the surrounding aorta, whereas an undersized ring exerts no outward force and produces neither seal nor resistance to migration. The stated 2% oversizing used by Inoue et al contains no margin for error. Perhaps the side branch of the Inoue device helps secure stent-graft position, but it would help more if it had the stiffness of a stent rather than the flexibility of a series of rings.

Stroke is notably absent from the current report. In previous reports, endovascular repair of the distal arch has often been complicated by embolic stroke, and multibranched versions of the current system are no exception. The current single-branched version requires less manipulation but does not altogether avoid instrumentation of the ascending aorta and arch. I suspect this system could still produce a high stroke rate in less experienced hands, which together with the high cost of customized device manufacture, would impede widespread application.

The most widely practiced alternative involves stent-graft coverage of the subclavian artery origin. Some provision for subclavian flow must be made in any patient with an internal mammary coronary graft, a dominant left vertebral artery, a high risk of paraplegia (distal thoracic aortic aneurysm or dissection), subclavian steal, or left arm claudication. I remain to be convinced that the single side-branch is superior to carotid-subclavian bypass or transposition.