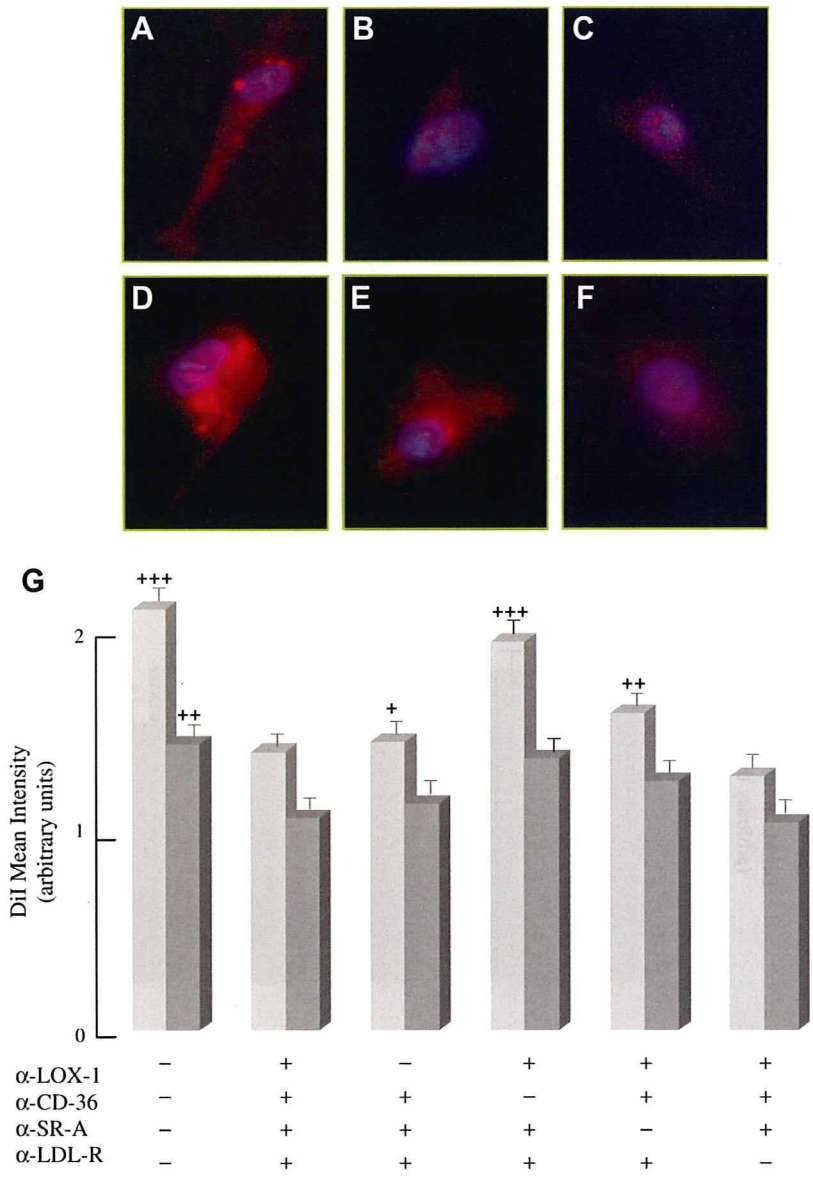


**Fig. 9.** Binding of $ONOO^-$-LDL after receptor blocking. LDL receptor blocking was performed for 1 h at 37 °C and binding was determined at 0 °C with 10 μg/ml DiI-$ONOO^-$-LDL and 10 μg/ml DiI-$ONOO^-$-LDL with 200 μg/ml excess unlabeled LDL for 90 min by the following conditions; (A) no receptor blocking with 10 μg/ml DiI-$ONOO^-$-treated LDL, (B) all four receptor's blocked with 10 μg/ml DiI-$ONOO^-$-treated LDL (C) active LOX-1, (D) active CD36 with 10 μg/ml DiI-$ONOO^-$-treated LDL, (E) active SR-A with 10 μg/ml DiI-$ONOO^-$-treated LDL, and (F) active LDL-R with 10 μg/ml DiI-$ONOO^-$-treated LDL. Binding mean intensity of DiI-$ONOO^-$-treated LDL was quantified using Axiom 200 M Zeiss Fluorescent Microscope (G). Images are not shown for excess unlabeled $ONOO^-$-treated LDL but intensities were quantified. Experiments were performed in triplicate and statistical significance was determined to all receptors blocked to determine receptors significantly involved in the binding of DiI-labeled $ONOO^-$-LDL ($n = 3$, $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). ▒ –10 mg/ml DiI-labeled $ONOO^-$-treated LDL, ■ –10 mg/ml DiI-labeled $ONOO^-$-treated LDL + 200 mg/ml excess unlabeled $ONOO^-$-treated LDL.

ized through an aggregated-LDL uptake mechanism. These findings further support the atherogenic character of $ONOO^-$-treated LDL.

## Discussion

$LDL^-$ may be viewed as a circulating, atherogenic form of LDL *in vivo* and it harbors secondary structural changes in apoB-100 that encompass a significant loss of α-helical structure and increase in β-sheet structure [3]. This study addresses (a) the chemical modifications and structural changes inherent in $LDL^-$ formation, (b) a functional role for $ONOO^-$ in $LDL^-$ formation, and (c) the occurrence of specific cellular receptors for $LDL^-$.

### *Chemical modifications and structural changes in $LDL^-$*

LC/MS/MS (Table 1) and circular dichroism (Fig. 2) analyses indicated apoB-100 protein modifications and conformational changes inherent in $LDL^-$. Although there were no observed nitrated peptides by LC/MS/MS in native- and total-LDL fractions *in vivo*, there was nitration that was quantified by LC/EIS/MS analysis. The amount of nitration observed for native LDL was 100-fold lower than $LDL^-$ and tLDL was approximately 10- to 12-fold lower. These findings further support the notion that the LDL-particle is the modified LDL subfraction *in vivo* as well as may support the $LDL^-$ hypothesis. Tyrosine nitration in $LDL^-$ (Table 1) in $\alpha_1$, $\alpha_2$, and $\alpha_3$ helices as well as $\beta_2$ sheets as well as cysteine oxidation in $\beta_1$ to cysteic acid (Fig. 12) seem to assist the loss of α-helical structure in

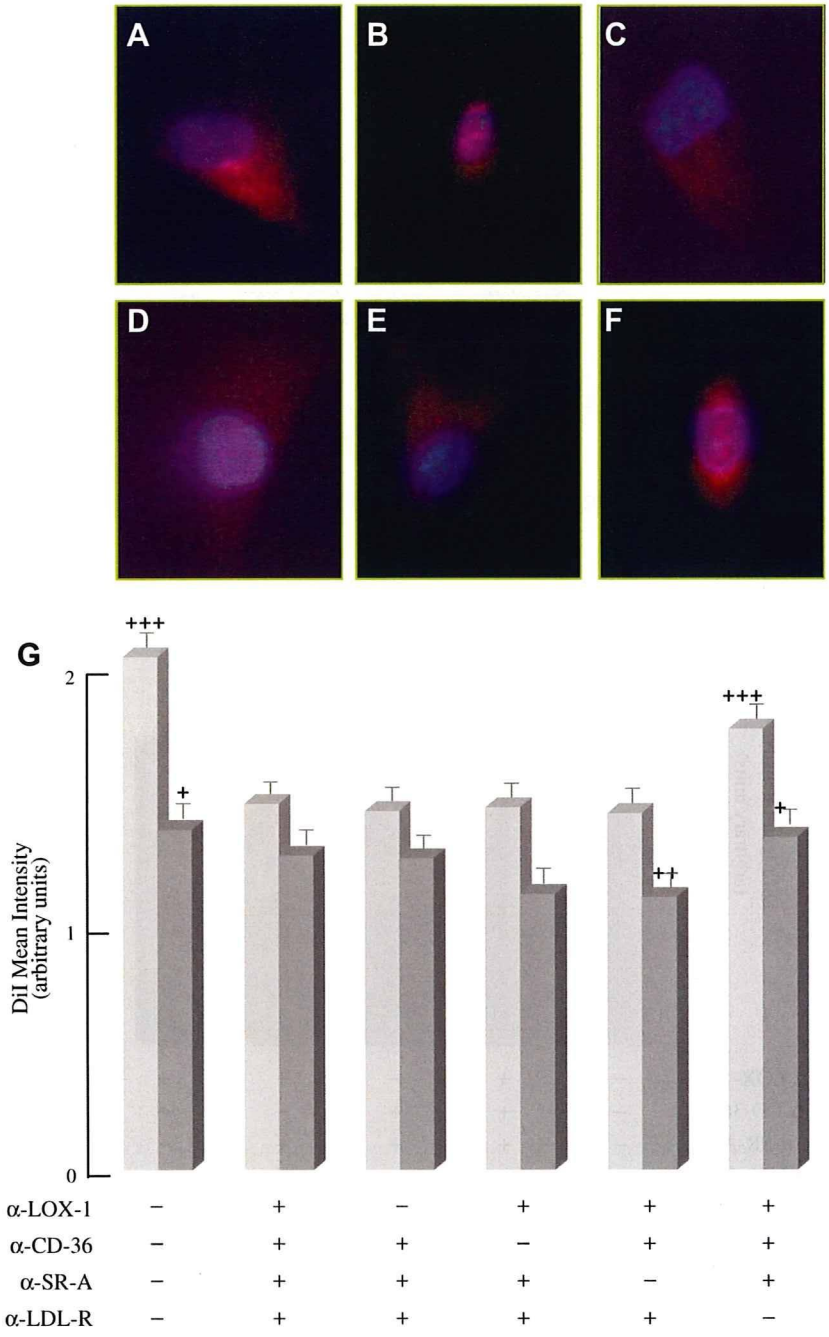


**Fig. 10.** Uptake of control-LDL after receptor blocking. LDL receptor blocking was performed for 1 h at 37 °C and uptake was determined at 37 °C with 10 μg/ml DiI-control-LDL and 10 μg/ml DiI-control-LDL with 200 μg/ml excess unlabeled LDL for 4 h by the following conditions; (A) no receptor blocking with 10 μg/ml DiI-control-LDL, (B) all four receptor's blocked with 10 μg/ml DiI-control-LDL (C) active LOX-1, (D) active CD36 with 10 μg/ml DiI-control-LDL, (E) active SR-A with 10 μg/ml DiI-control-LDL, and (F) active LDL-R with 10 μg/ml DiI-control-LDL. Uptake mean intensity of DiI-control-LDL was quantified using Axiom 200 M Zeiss Fluorescent Microscope (G). Images are not shown for excess unlabeled control-LDL but intensities were quantified. Experiments were performed in triplicate and statistical significance was determined to all receptors blocked to determine receptors significantly involved in the uptake of DiI-labeled control-LDL ($n = 3$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). – 10 mg/ml DiI-labeled control-LDL, – 10 mg/ml DiI-labeled control-LDL + 200 mg/ml excess unlabeled control-LDL.

LDL$^{-}$ and increase β-turn, parallel- and anti-parallel sheets, and random coil structures (Fig. 2). Of note, nitration of apoB-100 occurs in the α-helical structures containing the highest percentage of tyrosine per total amino acid residues: $\alpha_1$ appears to be more susceptible to nitrotyrosine formation, whereas $\beta_1$ seemed resistant to nitration and susceptible to cysteine oxidation. Nitration of α-helices appears to contribute to protein unfolding, whereas the oxidation of one of the nine free cysteines (in $\beta_1$ sheets) may be involved in the increased electronegativity of the particle.

*A functional role for ONOO$^{-}$ in LDL$^{-}$ formation*

Treatment of native LDL with either ONOO$^{-}$ (Fig. 3) or SIN-1 (Fig. 5) resulted in extensive tyrosine nitration (Table 2; Fig. 12), accumulation of lipid peroxides, and loss of α-helical structure (Fig. 4) and, as a corollary, formation of LDL$^{-}$ Figs. 3D, 5D). It may be surmised, hence, that nitrotyrosine- and lipid peroxide accumulation are synergistically responsible for unfolding of α-helices inherent in LDL$^{-}$ formation.

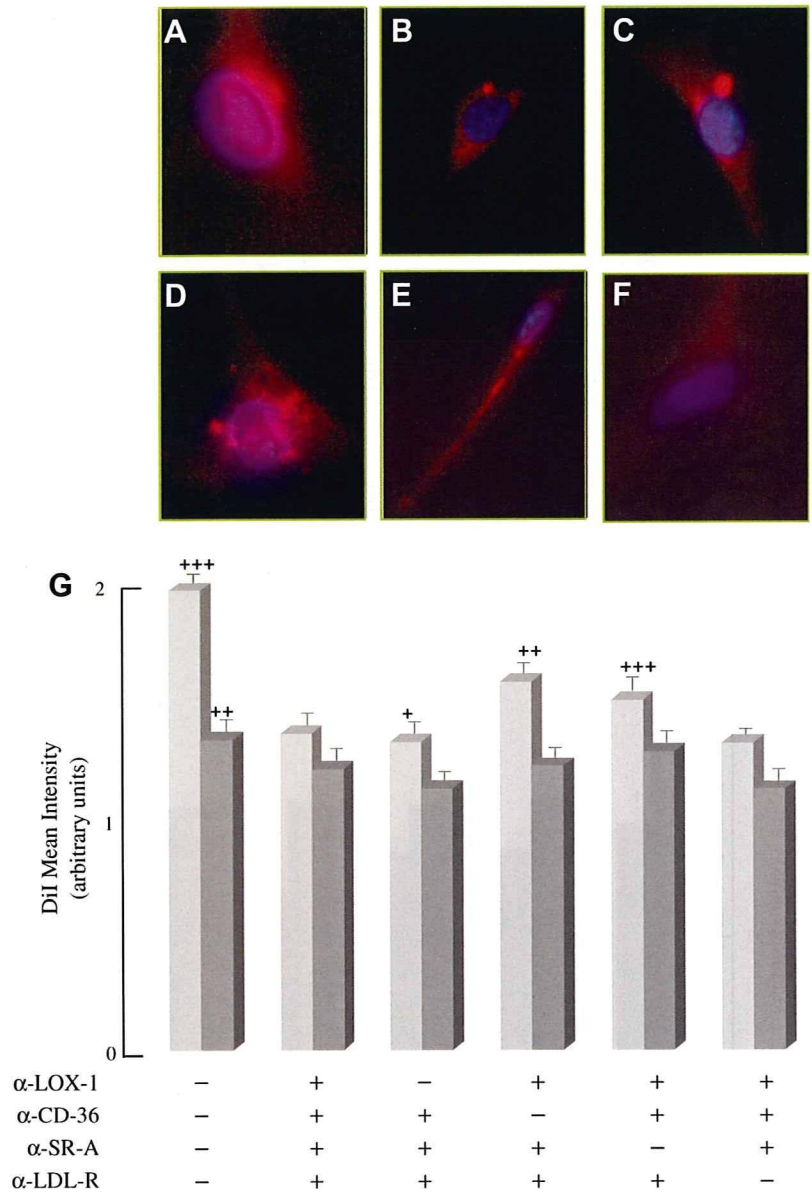


**Fig. 11.** Uptake of $ONOO^-$-LDL after receptor blocking. LDL receptor blocking was performed for 1 h at 37 °C and uptake was determined at 0 °C with 10 μg/ml DiI-$ONOO^-$-LDL and 10 μg/ml DiI-$ONOO^-$-treated LDL with 200 μg/ml excess unlabeled $ONOO^-$-treated LDL for 4 h by the following conditions; (A) no receptor blocking with 10 μg/ml DiI-$ONOO^-$-treated LDL, (B) all four receptor's blocked with 10 μg/ml DiI-$ONOO^-$-treated LDL (C) active LOX-1, (D) active CD36 with 10 μg/ml DiI-$ONOO^-$-treated LDL, (E) active SR-A with 10 μg/ml DiI-$ONOO^-$-treated LDL, and (F) active LDL-R with 10 μg/ml DiI- $ONOO^-$-treated LDL. Binding mean intensity of DiI-$ONOO^-$-treated LDL was quantified using Axiom 200 M Zeiss Fluorescent Microscope (G). Images are not shown for excess unlabeled $ONOO^-$-treated LDL but intensities were quantified. Experiments were performed in triplicate and statistical significance was determined to all receptors blocked to determine receptors significantly involved in the binding of DiI-labeled $ONOO^-$-treated LDL. Experiments were performed in triplicate and statistical significance was determined to all receptors blocked ($n = 3$, $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). –10 mg/ml DiI-labeled $ONOO^-$-treated LDL, ■ –10 mg/ml DiI-labeled $ONOO^-$-treated LDL + 200 mg/ml excess unlabeled $ONOO^-$-treated LDL.

*Specific cellular receptors for LDL⁻*

The aforementioned protein modifications and structural changes in $LDL^-$ may suggest an LDL receptor (LDL-R)-independent mechanism for binding and uptake of $LDL^-$ to and into BAEC cells; this notion is supported by the following (a) LDL nitration coincides with the binding sites to LDL-R (encompassing amino acid residues 3359 and 3369 in $\beta_2$) and (b) there is evidence that $ONOO^-$-treated LDL binds to CD36 [35]. These findings are further confirmed by the binding and uptake of $ONOO^-$-treated LDL to LOX-1, CD36, and SR-A receptors in BAEC with minimal involvement of the non-atherogenic LDL-R. It is worth noting that most uptake and binding in control-LDL was dependent on LDL-R and independent of oxLDL-R suggesting the non-atherogenic properties of control-LDL. However, there was still a minimal binding and uptake to LOX-1, CD36, and SR-A in control-LDL suggesting the importance of *in vivo* modified $LDL^-$. It was also evident that $ONOO^-$-treated LDL did not induce LDL-R mediated uptake suggesting that it is not being endocytosed through an aggregated-LDL uptake mechanism. The *in vivo* $LDL^-$ nitration pattern and structure as well as $ONOO^-$-modified LDL demonstrate that $ONOO^-$ is the most likely mechanism of protein nitration *in vivo* and suggests that protein unfolded LDL induces scavenger receptor dependent binding and uptake and is further supported by enzymatic modifications that induce protein unfolding [3,17]. Nitrated LDL is also involved in an LDL-R independent binding and uptake med-

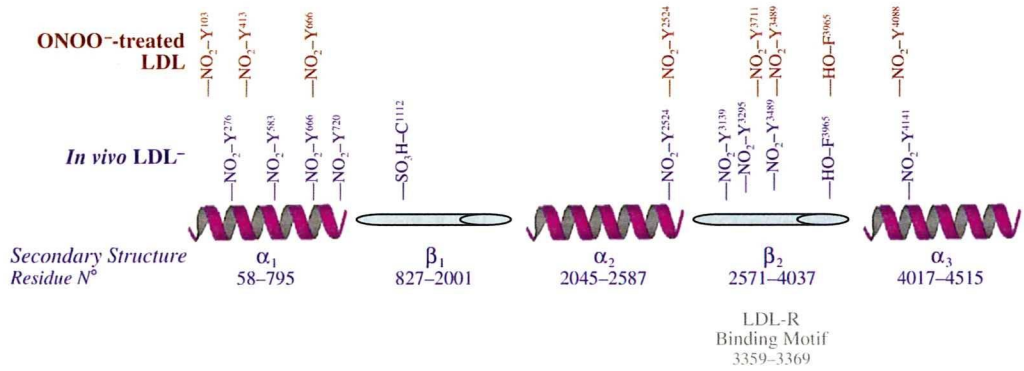


**Fig. 12.** Site of chemical modifications in *in vivo* LDL⁻ and ONOO⁻-treated LDL. The secondary structure of the apoB-100 is shown. The pentapartite structure however is not drawn to scale. Data from Tables 1 and 2 were used to assign the chemical modifications in LDL⁻ and ONOO⁻-treated LDL.

iated by SR-A, LOX-1, and CD36, thus strengthening the pathophysiological significance of ONOO⁻-driven LDL modifications, its unfolding, and the pathogenesis of atherosclerosis.

Tyrosine nitration and lipid peroxidation appear to disturb the phospholipid belt of LDL and hydrophobic stacking of aromatic amino acids in the lipid core. The three α-helices have the highest percentage of tyrosine residues; it may be hypothesized that nitration of these tyrosine residues would have a synergistic affect upon protein unfolding along with lipid peroxide formation. Addition of a nitro group to tyrosine involves the addition of a hydrophilic moiety with a net electrostatic charge (Zwitterion); aromatic groups are involved in hydrophobic stacking interactions in proteins as well as in protein-lipid bilayer interface. Therefore, nitration in α-helices is expected to interfere with hydrophobic stacking in the lipid core of the LDL particle and possibly with the phospholipid belts of $\alpha_2$ and $\alpha_3$ helices, leading to protein unfolding. Furthermore, peroxidation of lipids in LDL seem to cause unfolding of the apoB-100 protein [11]. The phospholipid belt in $\alpha_2$ and $\alpha_3$ is stabilized by electrostatic bonds between negatively charged phospho head groups and positively charged lysine/arginine residues. Peroxidation of long chain poly unsaturated fatty acyl chains of the phospholipid belts and the addition of molecular oxygen will increase the hydrophilicity of the fatty acyl chains of phospholipids, thus resulting in both the migration out of the lipid phase and an increasing surface area to volume ratio of the lipid core (increased hydrophilic surface). This increased strain would induce $\alpha_2$ and $\alpha_3$ to stretch and adopt a new confirmation. This mechanism strengthens the significance of the phospholipid belts ($\alpha_2$ and $\alpha_3$) in maintaining particle protein/lipid integrity, particle structure, proper electrostatic interactions, and aromatic stacking.

Regardless of its mechanism, these findings suggest that protein unfolding may be the main contributor to LDL⁻-induced atherosclerosis. The extensive nitration of apoB-100 in the α-helices and β-sheets of LDL⁻ and its absence in native LDL suggest that the latter is not or has not been subjected to nitrative stress *in vivo*. In response to phospholipase $A_2$ and oxidation *in vitro*, modifications of LDL render the formation of an electronegative sub-fraction with secondary structural changes similar to those of *in vivo* LDL⁻. As an emergent marker for coronary artery disease, nitrotyrosine is prominent in atherosclerotic lesions as well as LDL isolated from atherosclerotic lesions [5]. In this context, this study established similar apoB-100 protein nitration patterns and secondary protein structural changes in *in vivo* circulating LDL⁻ and ONOO⁻-treated LDL. Moreover, binding and uptake of the protein unfolded fraction (LDL⁻) was higher than that of native LDL and uptake of ONOO⁻-treated LDL is dependent on scavenger receptors LOX-1, CD36, and SR-A and is not on dependent on LDL-R whereas the control-LDL subfraction is dependent on anti-atherogenic LDL-R and not dependent on atherogenic LOX-1, CD36, and SR-A scavenger receptors in BAEC.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.abb.2008.07.026.

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SHORT REPORT

# Inoue Stent-Graft Implantation for Thoracoabdominal Aortic Aneurysm Involving the Visceral Arteries

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***Purpose.*** *To assess the efficacy of the Inoue stent-graft placement for thoracoabdominal aortic aneurysm (TAAA).*
***Methods.*** *Patients with TAAA underwent Inoue stent-graft placement with single branched stent-graft in 4 patients, straight graft in 3 patients and double branched stent-graft in 1 patient. Half the patients required additional open surgical revascularizations of involved visceral arteries (Hybrid procedures).*
***Results.*** *Stent-grafts were deployed successfully in all patients. One patient with Hybrid procedure developed major complications, required haemodialysis and died in hospital. In another patient the post-operative CT scan demonstrated a type I endoleak, but this had resolved by 3 months.*
***Conclusion.*** *Inoue stent-grafting for TAAA with or without adjunctive open surgical revascularization is feasible.*
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*Keywords: Endvascular repair; Thoracoabdominal aneurysm; Inoue stent-graft.*

## Introduction

Several centres have described the feasibility of a hybrid endovascular approach for TAAA, with surgical reconstruction of visceral arteries.[1] Alternatively visceral perfusion can be preserved using either fenestrated or branched stent-grafts.[2] The purpose of this study was to assess the feasibility of Inoue stent-graft placement for TAAA.

## Patients and Methods

Between March 2003 and December 2006, endovascular repair using Inoue stent-grafts, was undertaken in 8 patients with TAAAs at Kyoto University Hospital, Japan. All patients gave their informed consent in conformance with protocols approved by the institutional review board of the hospital.

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Patient characteristics are given in Table 1. Endovascular repair, using Inoue branched stent-grafts, was achieved in 4 patients (Branched group). However, the remaining 4 patients required open surgical revascularization of visceral arteries before stent-graft placement (Hybrid group).

Each Inoue stent-graft was custom made for the individual patient. Three kinds of Inoue stent-grafts were used in this study, straight, single branched and double branched stent-grafts (Fig. 1A). The implantation technique has been described previously[3,4] (Fig. 1B).

The coeliac artery (CA), superior mesenteric artery (SMA), and bilateral renal arteries (RAs) were reconstructed in 3 patients. One further patient underwent a combination of open surgical reconstruction and double branched stent-graft implantation (Case 8). The patient had chronic aortic dissection with a patent false lumen; the CA and SMA originated from a common coeliomesenteric trunk (CMT). The origin of the CMT and left RA was from the true lumen, but the right RA originated from the false lumen. Since the insertion of the branched graft to the right RA was difficult, the right RA was revascularized surgically.

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**Table 1. Patient characteristics**

| Case number | Group | Age, Sex | Risk for open replace-ment | Aneurysm etiology | Crawford type | Aneurysm size | Involved visceral arteries | Adjunctive Procedure, Procedure time (minutes) | Stent-graft type, Procedure time (minutes) | Total Procedure time (minutes) | Complications | Hospital stay (days) | Follow-up period (months) | Events in the follow-up | Sac size change |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Branched | 78, M | None | Degenerative | I | 63 | CA | None | Single branched, 267 | 267 | None | 11 | 3 | None | Stable |
| 2 | Branched | 79, M | COPD | Degenerative | I | 51 | CA, SMA | Coil embolization of the CA, 255 | Single branched, 255 | 350 | None | 19 | 24 | Occlusion of the branched section to the SMA | Stable |
| 3 | Branched | 78, M | IP | Degenerative | I | 64 | CA, SMA | Coil embolization of the CA, 195 | Single branched, 195 | 320 | Lymphorrhea | 39 | 17 | None | Stable |
| 4 | Branched | 38, M | None | Chronic aortic dissection | I | 49 | CA, SMA | Coil embolization of the CA, 180 | Single branched, 180 | 360 | Gastric ulcers | 36 | 15 | None | Reduced |
| 5 | Hybrid | 82, F | High age | Pseudoaneurysm, ruptured | III | 83 | CA, SMA, Lt. RA, Rt. RA | Bypass placement (CA, SMA, Rt. RA, Lt. RA), 130 | Straight, 130 | 582 | None | 72 | 20 | None | Reduced |
| 6 | Hybrid | 77, F | None | Degenerative, ruptured | II | 82 | CA, SMA, Lt. RA, Rt. RA | Bypass placement (CA, SMA, Rt. RA, Lt. RA), 580 | Straight, 580 | 819 | Pneumonia, Renal damage | 313 | 10 | Death*** | Stable |
| 7 | Hybrid | 63, F | None | Chronic aortic dissection | II | 65 | Lt. SCA, CA, SMA, Lt. RA, Rt. RA | Bypass placement (CA, SMA, Rt. RA, Lt. RA), 510 | Straight, 510 | 1093 | Type I endoleak** | 59 | 10 | Disappearance of the initial endoleak | Reduced |
| 8 | Hybrid | 40, M | None | Chronic aortic dissection | II | 45 | Celiomesenteric trunk*, Lt. RA, Rt. RA | Bypass placement (Rt. RA), 395 | Double branched, 395 | 585 | None | 35 | 13 | None | stable |

M, Male; F, Female; Lt., Left; Rt., Right.
High age was defined as over 79 years.
* A common origin of the CA and SMA.
** The endoleak was from the distal attachment site, and dissolved 3 months after the stent-graft placement.
*** The cause of death was unrelated to the stent-grafting.

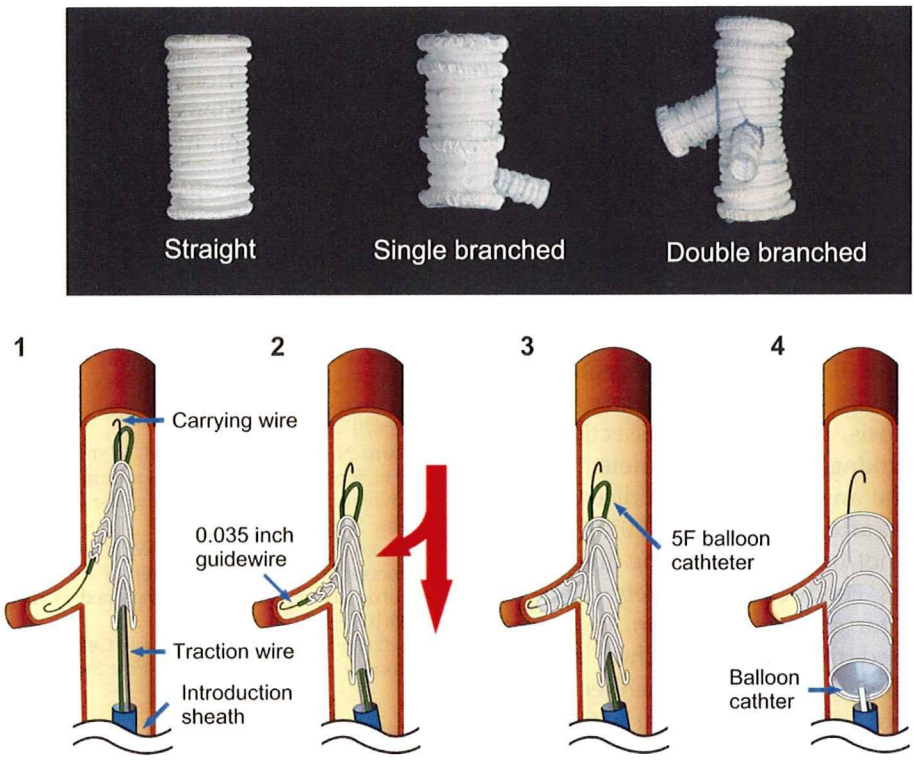


**Fig. 1.** Three kinds of the Inoue stent-graft for TAAA were used in this study. The straight graft was used in 3 patients (Case 5, 6 and 7), the single branched graft in 4 patients (Case 1–4), the double branched graft in 1 patient (Case 8). A. Single branched stent-graft implantation technique. 1. The folded stent-graft is delivered to the thoracoabdominal aorta through the introduction sheath using the carrying wire and traction wire. The 0.035-inch guidewire is selectively advanced to the target visceral artery through the 5F balloon catheters attached to the branched section. 2. The branched section is steered into the target visceral artery by pulling back the traction wire attached to the distal end of the aortic section. 3. The folded aortic section and the branched section are unfolded. The branched section is dilated by the 5F balloon catheter. 4. The aortic section is dilated by the custom made balloon catheter inserted thorough the introduction sheath.

The CMT and left RA were reconstructed using the Inoue double branched stent-graft. Three patients underwent deliberate coverage of the CA by the stent-graft to provide an adequate proximal landing zone and as prophylaxis against type II endoleak, as described previously.[3]

## Results

The initial and follow-up results are summarized in Table 1; average follow-up period was 14 ± 7 months (rang, 3–24 months).

In the 4 patients requiring surgical revascularization of visceral arteries, 13/15 arteries were revascularized using open surgery and 2 arteries were reconstructed by the double branched stent-graft implantation, initial patency rate of 92% (12/13).

Three patients underwent prophylactic coil embolization of the CA.[5] One patient developed multiple gastric ulcers 2days after coil embolization (Case 4), which resolved after treatment with oral proton pump inhibitors. The procedure time for the coil embolization was 133 ± 43 minutes (range 95–180 minutes).

All the stent-grafts were deployed successfully. Average procedure time was 314 ± 164 minutes (range 130–580 minutes). In one patient (Case 6), the bypass graft to the right RA occluded and since the patient developed severe bacterial pneumonia and renal dysfunction, hemodialysis was required resulting in a prolonged hospital stay of 313 days: this patient died in hospital due to gastrointestinal bleeding. Median hospital stay was 40 days (range 11–313 days). Postoperative CT scans demonstrated an endoleak from the distal attachment site in one patient (Case 7), but this appeared to have resolved at 3 month follow up.

Significant sac size shrinkage was achieved in three patients (38%). Sac enlargement and stent-graft

migration were not observed. One branched section to the SMA occluded silently 6 months after the procedure.

## Discussion

Implantation of Inoue branched stent-grafts in the thoracoabdominal aorta requires the following conditions. 1) The thoracoabdominal aorta is not severely tortuous. 2) The visceral artery does not have severe stenosis, calcification, dissection, mural thrombus or kinking, with a diameter of more than 5 mm. 3) The angle between thoracoabdominal aorta and visceral artery is less than 90°. 4) The visceral arteries do not originate from the aneurysm. 5) The procedure is conducted electively, since at 3 days is required for graft construction. In this manner, we have used the Inoue branched stent-graft only to treat successfully TAAA, either with or without adjunctive surgical revascularization of visceral arteries.

*Conflict of interest*

Dr. Kanji Inoue holds all patents of the Inoue stent-graft. The Inouestent-graft have been developed and made by Dr. Kanji Inoue.

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# Long-Term Outcomes of Coronary-Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention for Multivessel Coronary Artery Disease in the Bare-Metal Stent Era

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***Background***—Observational registries comparing coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) have reported long-term survival results that are discordant with those of randomized trials.

***Methods and Results***—We conducted a multicenter study in Japan enrolling consecutive patients undergoing first CABG or PCI between January 2000 and December 2002. Among 9877 patients enrolled, 5420 (PCI: 3712, CABG: 1708) had multivessel disease without left main involvement. Because age is an important determinant when choosing revascularization strategies, survival analysis was stratified by either age ≥75 or <75 years. Analyses were also performed in other relevant subgroups. Median follow-up interval was 1284 days with 95% follow-up rate at 2 years. At 3 years, unadjusted survival rates were 91.7% and 89.6% in the CABG and PCI groups, respectively (log rank $P=0.26$). After adjustment for baseline characteristics, survival outcome tended to be better after CABG (hazard ratio for death after PCI versus CABG [HR], 95% confidence interval [CI]: 1.23 [0.99-1.53], $P=0.06$). Adjusted survival outcomes also tended to be better for CABG among elderly patients (HR [95%CI]: 1.37 [0.98-1.92] $P=0.07$), but not among nonelderly patients (HR [95% CI]: 1.09 [0.82-1.46], $P=0.55$). Unadjusted and adjusted survival outcome for CABG and PCI were not significantly different in any subgroups when elderly patients were excluded from analysis.

***Conclusions***—In the CREDO-Kyoto registry, survival outcomes among patients <75 years of age were similar after PCI and CABG, a result that is consistent with those of randomized trials. (***Circulation*. 2008;118[suppl 1]:S199–S209.)**

**Key Words:** coronary artery disease ■ percutaneous coronary intervention ■ coronary stent ■ coronary artery bypass graft (CABG) surgery ■ long-term outcome

Randomized controlled trials comparing coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) in the bare-metal stent era generally showed similar survival rates up to 5 years.[1-7] However, a recent report from New York's cardiac registries involving 59|314 patients demonstrated higher risk-adjusted survival rates at three years with CABG in all clinical and anatomic subgroups studied.[8] Similarly, an analysis from the Northern New England Registry revealed better survival with CABG among patients with triple-vessel disease.[9]

These conflicting observations between randomized trials and registries have raised much controversy, and the reasons for this discrepancy have not yet been well addressed. To further understand relative survival outcomes of CABG and

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**Table 1. List of Participating Centers and Investigators**

| Centers | Investigators |
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| | Teiji Oda |
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| | Kazunobu Nishimura |
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| | Takaaki Sugita |

PCI, we evaluated long-term outcomes of patients undergoing coronary revascularization in a large-scale multicenter registry in Japan.

## Methods

### Study Population

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) is a multicenter registry in Japan enrolling consecutive patients undergoing first PCI or CABG and excluding those patients with acute myocardial infarction within a week before index procedure. The relevant review boards or ethics committees in all 30 participating centers (Table 1) approved the research protocol. Because of retrospective enrollment, written informed consent was not obtained from the patients; however, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

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Between January 2000 and December 2002, 9877 patients were identified to have undergone either CABG (2999 patients) or PCI (6878 patients) without prior history of coronary revascularization. Patients were enrolled from 21 centers for CABG (median number of patients from each center: 100 [19 to 550, interquartile range 57 to 199]), and from 30 centers for PCI (median number of patients from each center: 129 [16 to 1760, interquartile range 74 to 237]), respectively. Four hundred eighty-four patients undergoing concomitant valvular, left ventricular, or major vascular operation were excluded from the current analysis. Patients with disease of the left main coronary artery (PCI 165 patients, CABG 742 patients) and with single-vessel disease (PCI 3001 patients, CABG 65 patients) were excluded. Therefore, the study group comprised 5420 patients with multivessel coronary artery disease undergoing first coronary revascularization (PCI: 3712 patients, CABG: 1708 patients).

## Data Collection and Definitions

Demographic, angiographic, and procedural data in both groups were collected from hospital charts or databases in each center by independent clinical research coordinators (Appendix) according to prespecified definitions. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians.

Baseline clinical characteristics, such as myocardial infarction, heart failure, diabetes, hypertension, current smoker status, atrial fibrillation, chronic obstructive lung disease, and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Stroke at baseline included asymptomatic stroke detected by noninvasive imaging modalities. Peripheral vascular disease was regarded to be present when carotid, aortic, or other peripheral vascular disease were being treated or scheduled for surgical or endovascular interventions.

Elderly patients were defined as those patients ≥75 years of age. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Patients with LVEF ≤40% were regarded as having left ventricular dysfunction. Chronic kidney disease was regarded as present when creatinine clearance estimated by Cockcloft-Gould formula was less than 60 mL/min. Anemia was defined as blood hemoglobin level less than 12 g/dL.

An independent clinical events committee adjudicated events. Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. Any death during the index hospitalization was regarded as cardiovascular death. Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study.[1] Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke at follow-up was defined as symptomatic stroke.

## Statistical Analyses

After the descriptive statistics, we used Kaplan-Meier estimates to plot the percentage of patients in each group who died for any reason; data on patients who lost follow-up were censored. The log-rank test was used to identify significant differences in unadjusted survival rates. To determine the baseline risk factors for mortality, we conducted Log-rank tests for the following 30 potential variables: age, gender, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes without insulin therapy, diabetes with insulin therapy, hemodialysis, chronic kidney disease, anemia, current smoker status, LVEF, total occlusion, proximal LAD disease, triple vessel disease, and use of medications such as statins, aspirin, thienopyridines, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and nitrates. All continuous variables were dichotomized for fitting proportional assumption according to the predetermined clinical contexts. We plotted log (time) versus log [-log (survival)] stratified by each significant risk factor and evaluated whether the plotted lines were parallel.[10] Those variables for which probability values were less than 0.05 in univariate analyses and proportional assumptions were generally fair were included in the multivariable analysis. We developed multivariable Cox proportional hazard models that controlled for significant risk factors while testing for significant differences in long-term survival between the 2 groups of patients undergoing CABG or PCI.

Analysis of treatment-related differences in long-term survival was stratified whether or not the patients have 5 prespecified risk factors, including triple vessel disease, diabetes, left ventricular dysfunction, proximal LAD disease, and elderly. The same factors used for analysis of the total cohort were incorporated in the multivariable models for subgroup analyses.

All analyses were conducted by the 2 physicians (Takeshi Kimura and Takeshi Morimoto) with the use of SAS software version 9.1 (SAS Institute Inc) and S-Plus version 7.0 (Insightful Corp) and all reported probability values were 2-sided. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

# Results

## Baseline Characteristics

Baseline characteristics of the patients in the 2 groups are shown in Table 2. The PCI group included more elderly patients, particularly those ≥80 years of age. Although malignancy was more often found in the PCI group, the CABG group generally included more high-risk patients, such as those with left ventricular dysfunction, heart failure, prior myocardial infarction, diabetes, stroke, and anemia. However, mean EuroSCORE values were similar between the PCI and the CABG groups.

Regarding the complexity of coronary artery anatomy, the CABG group included more complex patients, such as those with triple-vessel disease, involvement of proximal LAD, and total occlusion. Patients in the CABG group underwent more complete revascularization as indicated by the number of vessels revascularized.

In the PCI group, bare-metal stents were used in 85% of patients. None of the patients received drug-eluting stents. Directional and rotational coronary atherectomy was used in 2% and 7% of patients, respectively. In the CABG group, internal mammary artery graft was used in 95% of patients. Forty-three percent of CABG operations were performed without cardiopulmonary bypass.

Medications such as statins, aspirin, thienopyridines, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and nitrates were more frequently used in the PCI group than in the CABG group. Blood pressure and HbA1c level were significantly higher in the PCI group than in the CABG group.

## Survival Outcome

Clinical follow-up were completed in 98% at 1 year, and 95% at 2 years. The median follow-up interval was 1319 days in the CABG group (interquartile range, 994 to 1642) and 1266 days in the PCI group (interquartile range, 933 to 1567).

In the total patient population, unadjusted survival outcomes were not different between the CABG and PCI groups (hazard ratio for death after PCI versus CABG [HR], 95% confidence interval [CI]: 1.11 [0.93-1.32], $P=0.26$; Table 3). Operative mortality in the CABG group evaluated at 30 days was only 1.1% as compared with 0.8% in the PCI group. At 3 years, unadjusted survival rates were 91.7% and 89.6% in

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**Table 2. Baseline Characteristics**

| | PCI (n=3712) | CABG (n=1708) | *P* Value |
|---|---|---|---|
| Age, y | 68.1±9.9 (11–96) | 66.9±9.4 (11–89) | 0.0001 |
| ≥75 years | 27% | 21% | 0.0001 |
| ≥80 years | 12% | 6% | 0.0001 |
| Female | 30% | 29% | 0.17 |
| Body mass index | 23.8±3.3 | 23.6±3.2 | 0.04 |
| Ejection fraction | 62.1±13.6 | 59.4±14.5 | 0.0001 |
| <40% | 8% | 12% | 0.0001 |
| Heart failure | 15% | 25% | 0.0001 |
| Functional class 3/4 | 5% | 6% | 0.17 |
| Prior myocardial infarction | 26% | 38% | 0.0001 |
| Atrial fibrillation | 6% | 5% | 0.13 |
| Diabetes | 43% | 48% | 0.0002 |
| Insulin treated | 9% | 14% | 0.0001 |
| Oral drug treated | 20% | 21% | 0.24 |
| HbA1c | 7.3±1.5 | 7.0±1.3 | 0.0002 |
| Hypertension | 73% | 71% | 0.1 |
| Blood pressure | | | |
| Systolic | 138.4±22.2 | 131.1±19.9 | 0.0001 |
| Diastolic | 75.6±13.3 | 71.4±11.8 | 0.0001 |
| Current smoker | 28% | 25% | 0.04 |
| Stroke | 17% | 23% | 0.0001 |
| Peripheral vascular disease | 6% | 8% | 0.046 |
| Chronic pulmonary disease | 2% | 2% | 0.86 |
| Malignancy | 8% | 6% | 0.0048 |
| Chronic kidney disease | 42% | 45% | 0.049 |
| Dialysis | 4% | 5% | 0.13 |
| Anemia | 25% | 35% | 0.0001 |
| Emergency procedure | 5% | 4% | 0.1 |
| EuroSCORE | 3.7±2.4 | 3.7±2.5 | 0.74 |
| Triple vessel disease | 38% | 80% | 0.0001 |
| Proximal LAD disease | 74% | 94% | 0.0001 |
| Total occlusion | 34% | 53% | 0.0001 |
| Treatment of ≥2 Vessels | 43% | 95% | 0.0001 |
| No. of target vessels | 1.5±0.6 | 2.6±0.5 | 0.0001 |
| Medication at hospital discharge | | | |
| Statins | 33% | 21% | 0.0001 |
| Aspirin | 89% | 81% | 0.0001 |
| Thienopyridines | 76% | 11% | 0.0001 |
| ACE-I | 27% | 12% | 0.0001 |
| ARB | 16% | 10% | 0.0001 |
| β-blockers | 22% | 10% | 0.0001 |
| Calcium channel blockers | 60% | 61% | 0.56 |
| Nitrates | 72% | 46% | 0.0001 |

ACE-I indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

the CABG and PCI groups, respectively (log rank $P=0.26$) (Figure 1).

Survival rates at 3 years were similar in patients with Euro SCORE below or equal to median (3 points; CABG 96.1% versus PCI 95.6%, log rank $P=0.77$). However, survival rates at 3 years tended to be better for CABG in patients with EuroSCORE above median (CABG 87.5% versus 83.1%, log rank $P=0.06$).

By multivariable analysis, 14 independent predictors of all-cause mortality were identified, including age ≥75 years, chronic kidney disease, hemodialysis, history of heart failure, chronic obstructive lung disease, malignancy, anemia, periph-

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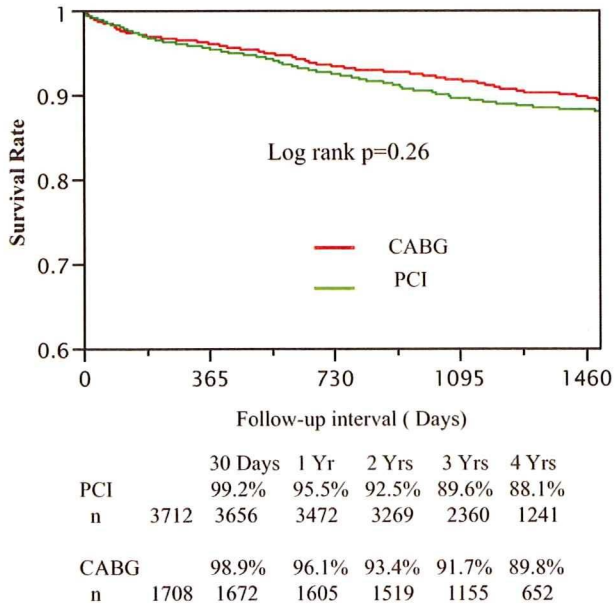
**Table 3. Hazard Ratios for Death After PCI as Compared With That After CABG in Prespecified Subgroups**

| | No. of Patients (Event/Total) | | Hazard Ratio (95% CI) | | Interaction |
|---|---|---|---|---|---|
| | CABG | PCI | Unadjusted *P* | Adjusted *P* | *P* Value |
| All patients | 181/1708 | 423/3712 | 1.11 (0.93–1.32) 0.26 | 1.23 (0.99–1.53) 0.06 | |
| Triple vessel disease | 153/1366 | 195/1412 | 1.29 (1.04–1.59) 0.02 | 1.09 (0.85–1.41) 0.5 | 0.7 |
| Double vessels disease | 28/342 | 228/2300 | 1.23 (0.83–1.83) 0.29 | 1.37 (0.89–2.12) 0.15 | |
| Diabetes | 95/824 | 227/1592 | 1.3 (1.02–1.65) 0.03 | 1.38 (1.02–1.86) 0.04 | 0.003 |
| Nondiabetes | 86/883 | 196/2117 | 0.96 (0.75–1.24) 0.77 | 1.09 (0.8–1.49) 0.6 | |
| Diabetes/Insulin | 36/243 | 61/338 | 1.28 (0.85–1.94) 0.24 | 1.18 (0.7–2.0) 0.53 | 0.57 |
| Diabetes/Noninsulin | 59/581 | 166/1254 | 1.37 (1.01–1.85) 0.04 | 1.46 (1.0–2.14) 0.05 | |
| Diabetes/Triple vessel disease | 83/693 | 108/667 | 1.44 (1.08–1.92) 0.01 | 1.14 (0.8–1.63) 0.46 | 0.41 |
| Diabetes/Double vessel disease | 12/131 | 119/925 | 1.45 (0.8–2.62) 0.22 | 1.88 (0.95–3.74) 0.07 | |
| LVEF ≤40% | 31/195 | 60/273 | 1.56 (1.01–2.41) 0.046 | 1.94 (1.12–3.34) 0.02 | 0.054 |
| LVEF >40% | 140/1430 | 286/3050 | 0.97 (0.8–1.19) 0.8 | 1.16 (0.91–1.47) 0.24 | |
| Proximal LAD | 173/1608 | 324//2729 | 1.14 (0.95–1.37) 0.17 | 1.21 (0.96–1.52) 0.11 | 0.8 |
| No proximal LAD | 8/100 | 99/983 | 1.3 (0.63–2.67) 0.48 | 1.31 (0.58–2.95) 0.51 | |
| Age ≥75 | 65/367 | 222/1003 | 1.29 (0.98–1.7) 0.07 | 1.37 (0.98–1.92) 0.07 | 0.61 |
| Age <75 | 116/1341 | 201/2709 | 0.88 (0.7–1.1) 0.27 | 1.09 (0.82–1.46) 0.55 | |

eral vascular disease, stroke, left ventricular dysfunction, body mass index ≤25.0, diabetes with insulin, absence of statin use, and use of angiotensin converting enzyme inhibitors.

When treatment modalities (CABG/PCI) were incorporated into this multivariable model, survival outcomes tended to be better after CABG (HR [95% CI]: 1.23 [0.99-1.53], $P$=0.06; Table 3).

Survival outcomes were compared in the prespecified high-risk subgroups. Even in high-risk patients, such as those with diabetes or triple-vessel disease, PCI was frequently chosen in this registry (66% and 51% of patients with diabetes and triple-vessel disease, respectively). CABG was associated with significantly better unadjusted-survival outcomes in patients with triple-vessel disease, diabetes, and left ventricular dysfunction (Table 3). After adjustment for baseline characteristics, the CABG group had significantly better survival outcomes in patients with diabetes, but not in patients with triple-vessel disease (Table 3).




| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 99.2% | 95.5% | 92.5% | 89.6% | 88.1% |
| n | 3712 | 3656 | 3472 | 3269 | 2360 | 1241 |
| CABG | | 98.9% | 96.1% | 93.4% | 91.7% | 89.8% |
| n | 1708 | 1672 | 1605 | 1519 | 1155 | 652 |

**Figure 1.** Unadjusted Kaplan-Meier survival curves among all patients.

## Influence of Age on the Survival Outcome After PCI and CABG

Because age is an important determinant in coronary revascularization strategy choice, survival analyses were stratified by age with a prespecified cut-off value of 75 years.

Survival outcomes favored CABG in patients ≥75 years of age (adjusted HR [95% CI]: 1.37 [0.98-1.92], $P$=0.07), but not in patients <75 years of age (adjusted HR [95% CI]: 1.09 [0.82-1.46], $P$=0.55) (Tables 3 and 4 and Figures 2 and 3). The magnitudes of the differences in survival rates between the CABG and PCI groups in patients ≥75 years of age were greater in the high-risk subgroups of triple-vessel disease, diabetes and left ventricular dysfunction (Table 4 and Figures 4 and 5).

In patients ≥75 years of age, unadjusted rates for all-cause mortality at 3 years were 13.3% and 20.7% in the CABG and PCI groups, respectively (log rank $P$=0.07). Rates of noncardiovascular and cardiovascular death tended to be higher in the PCI group. This trend for excessive noncardiovascular death rates in the PCI group was not observed in patients <75 years of age (Figures 2 and 3).

In patients <75 years of age, no differences between the 2 treatment modalities were apparent in either unadjusted or adjusted survival outcomes in any of the high-risk subgroups of triple-vessel disease, diabetes and left ventricular dysfunction (Table 4 and Figures 4 and 5).

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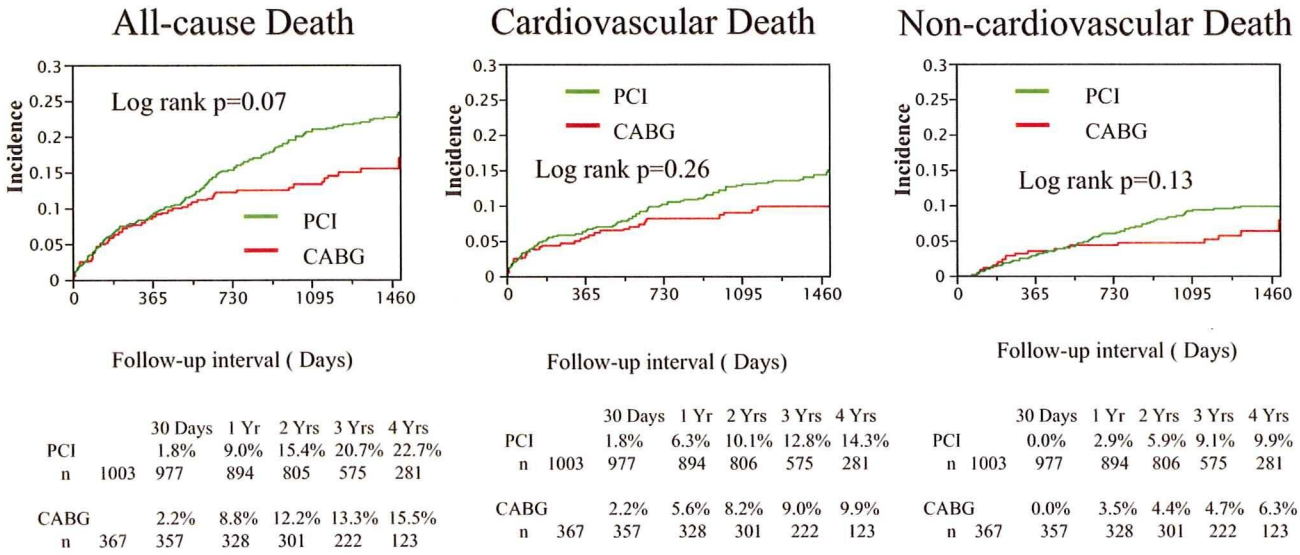
**Table 4. Hazard Ratios for Death After PCI as Compared With That After CABG in Prespecified Subgroups According to Age**

| | No. of Patients (Event/Total) | | Hazard Ratio (95% CI) | | Interaction |
|---|---|---|---|---|---|
| | CABG | PCI | Unadjusted *P* | Adjusted *P* | *P* Value |
| A. Age ≥75 | | | | | |
| Triple vessel disease | 54/297 | 119/429 | 1.6 (1.16–2.21) 0.004 | 1.29 (0.88–1.9) 0.2 | 0.81 |
| Double vessels disease | 11/70 | 103/574 | 1.22 (0.65–2.27) 0.54 | 1.32 (0.64–2.74) 0.46 | |
| Diabetes | 27/153 | 109/383 | 1.73 (1.13–2.63) 0.01 | 1.85 (1.1–3.12) 0.02 | 0.002 |
| Nondiabetes | 38/214 | 113/620 | 1.04 (0.72–1.5) 0.85 | 1.14 (0.72–1.8) 0.59 | |
| Diabetes/insulin | 6/32 | 23/73 | 1.58 (0.64–3.88) 0.32 | 2.16 (0.78–6.01) 0.14 | 0.82 |
| Diabetes/noninsulin | 21/121 | 86/310 | 1.73 (1.07–2.79) 0.03 | 1.75 (0.94–3.24) 0.08 | |
| Diabetes/triple vessel disease | 24/130 | 59/178 | 1.84 (1.15–2.96) 0.01 | 1.36 (0.75–2.46) 0.31 | 0.18 |
| Diabetes/double vessel disease | 3/23 | 50/205 | 2.47 (0.77–7.95) 0.13 | 7.29 (1.45–36.6) 0.02 | |
| LVEF ≤40% | 9/33 | 38/92 | 1.9 (0.92–3.95) 0.08 | 2.94 (1.09–7.95) 0.03 | 0.23 |
| LVEF >40% | 50/309 | 143/785 | 1.14 (0.82–1.57) 0.44 | 1.27 (0.87–1.85) 0.22 | |
| B. Age <75 | | | | | |
| Triple vessel disease | 99/1069 | 76/983 | 0.86 (0.64–1.16) 0.33 | 0.92 (0.64–1.32) 0.65 | 0.27 |
| Double vessels disease | 17/272 | 125/1726 | 1.17 (0.7–1.94) 0.55 | 1.37 (0.79–2.37) 0.26 | |
| Diabetes | 68/671 | 118/1209 | 1.00 (0.74–1.34) 0.99 | 1.21 (0.83–1.78) 0.33 | 0.26 |
| Nondiabetes | 48/669 | 83/1497 | 0.79 (0.55–1.12) 0.18 | 0.99 (0.64–1.54) 0.97 | |
| Diabetes/insulin | 30/211 | 38/265 | 1.06 (0.66–1.72) 0.8 | 0.89 (0.46–1.72) 0.73 | 0.56 |
| Diabetes/noninsulin | 38/460 | 80/944 | 1.07 (0.73–1.59) 0.73 | 1.36 (0.82–2.24) 0.23 | |
| Diabetes/triple vessel disease | 59/563 | 49/489 | 1.02 (0.7–1.48) 0.94 | 0.98 (0.61–1.59) 0.95 | 0.45 |
| Diabetes/double vessel disease | 9/108 | 69/720 | 1.11 (0.55–2.22) 0.78 | 1.44 (0.65–3.2) 0.37 | |
| LVEF ≤40% | 22/162 | 22/181 | 0.95 (0.52–1.71) 0.86 | 1.26 (0.58–2.73) 0.56 | 0.34 |
| LVEF >40% | 90/1121 | 143/2265 | 0.8 (0.62–1.04) 0.1 | 1.08 (0.79–1.48) 0.61 | |

## Other Cardiovascular End Points

Event-free rates from other cardiovascular end points are shown in Figure 6. The rate of freedom from myocardial infarction was significantly higher after CABG as compared with that after PCI. The incidences of myocardial infarction were similar at 30 days in the 2 groups. The 2 event-free curves for myocardial infarction diverged between 30 days and 1 year (incidences of myocardial infarction: 0.3% and 1.6% in the CABG and PCI groups, respectively). On the other hand, the incidences of myocardial infarction between 1 year and 3 years were similar in both groups (1.4% and 1.5% in the CABG and PCI groups, respectively).




| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 1.8% | 9.0% | 15.4% | 20.7% | 22.7% |
| n | 1003 | 977 | 894 | 805 | 575 | 281 |
| CABG | | 2.2% | 8.8% | 12.2% | 13.3% | 15.5% |
| n | 367 | 357 | 328 | 301 | 222 | 123 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 1.8% | 6.3% | 10.1% | 12.8% | 14.3% |
| n | 1003 | 977 | 894 | 806 | 575 | 281 |
| CABG | | 2.2% | 5.6% | 8.2% | 9.0% | 9.9% |
| n | 367 | 357 | 328 | 301 | 222 | 123 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 0.0% | 2.9% | 5.9% | 9.1% | 9.9% |
| n | 1003 | 977 | 894 | 806 | 575 | 281 |
| CABG | | 0.0% | 3.5% | 4.4% | 4.7% | 6.3% |
| n | 367 | 357 | 328 | 301 | 222 | 123 |

**Figure 2.** Cumulative incidence of all-cause death, cardiovascular death, and noncardiovascular death among patients with age ≥75.

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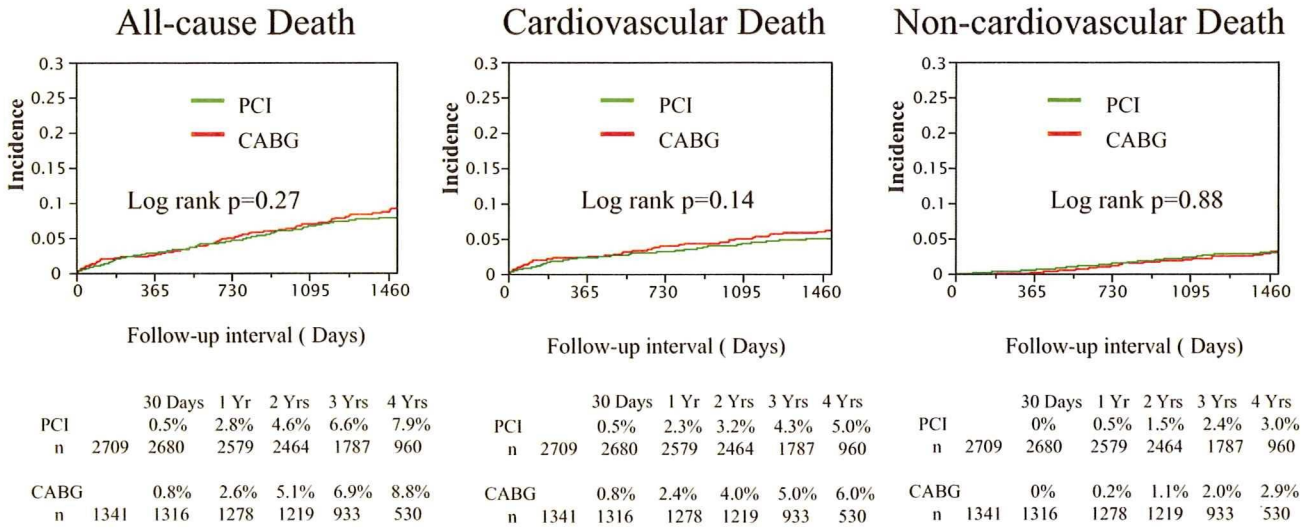



| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 0.5% | 2.8% | 4.6% | 6.6% | 7.9% |
| n | 2709 | 2680 | 2579 | 2464 | 1787 | 960 |
| CABG | | 0.8% | 2.6% | 5.1% | 6.9% | 8.8% |
| n | 1341 | 1316 | 1278 | 1219 | 933 | 530 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 0.5% | 2.3% | 3.2% | 4.3% | 5.0% |
| n | 2709 | 2680 | 2579 | 2464 | 1787 | 960 |
| CABG | | 0.8% | 2.4% | 4.0% | 5.0% | 6.0% |
| n | 1341 | 1316 | 1278 | 1219 | 933 | 530 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 0% | 0.5% | 1.5% | 2.4% | 3.0% |
| n | 2709 | 2680 | 2579 | 2464 | 1787 | 960 |
| CABG | | 0% | 0.2% | 1.1% | 2.0% | 2.9% |
| n | 1341 | 1316 | 1278 | 1219 | 933 | 530 |

**Figure 3.** Cumulative incidence of all-cause death, cardiovascular death, and noncardiovascular death among patients with age <75.

The rates of freedom from stroke were significantly higher after PCI versus CABG, a difference driven by a relatively higher rate of periprocedural stroke in the CABG group (1.8% and 0.2% in the CABG and PCI groups, respectively, at 30 days).

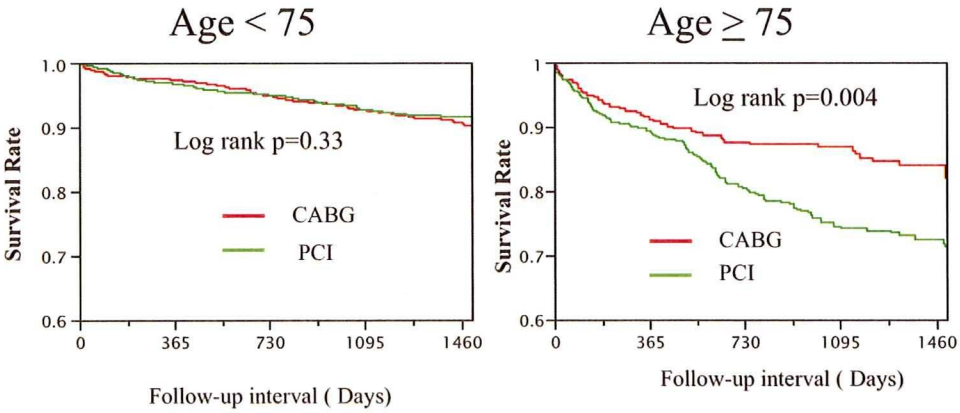
The rates of freedom from death, myocardial infarction, and stroke were similar between the 2 groups (87.8% and 86.8% in the CABG and PCI groups, respectively, at 3 years, log rank $P$=0.63).

The rate of freedom from any revascularization procedures was strikingly lower in the PCI group. At 3 years, only 51.7% of patients in the PCI group were free from any revascularization procedures as compared with 90.2% of patients in the CABG group. The rates of target-lesion revascularization in the PCI group were 33.4%, 35.9% and 37% at 1, 2, and 3 years, respectively. The rate of crossover to CABG in the PCI group was 7.2% at 3 years.

## Discussion

The discrepancy in outcomes between randomized controlled trials and registries comparing PCI with CABG is commonly ascribed to usual enrollment in the former of very selected low-risk patients with multi vessel coronary artery disease who are suitable for PCI, a feature that limits the ability to generalize conclusions to many high-risk patient categories in real-world clinical practice.

Our current analysis of CREDO-Kyoto registry data demonstrated both similar and discrepant results to those of other large-scale registries.[8,9] Although we also observed trends for better survival outcomes after CABG among overall and diabetic patient populations, in contrast to prior registries, adjusted survival outcomes were not significantly different in patients with triple-vessel disease. Differences in the practice pattern might be related to this discrepancy. Only 14% and 10% of patients with triple




| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 99.6% | 96.7% | 95.0% | 92.6% | 91.6% |
| n | 983 | 971 | 927 | 880 | 641 | 337 |
| CABG | | 99.2% | 97.4% | 94.8% | 92.6% | 90.8% |
| n | 1069 | 1050 | 1021 | 975 | 751 | 427 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 97.7% | 89.4% | 80.5% | 74.6% | 72.5% |
| n | 429 | 419 | 379 | 331 | 240 | 120 |
| CABG | | 97.6% | 91.1% | 87.6% | 86.8% | 84.0% |
| n | 297 | 288 | 265 | 242 | 181 | 97 |

**Figure 4.** Unadjusted Kaplan-Meier survival curves according to age in patients with triple vessel disease.

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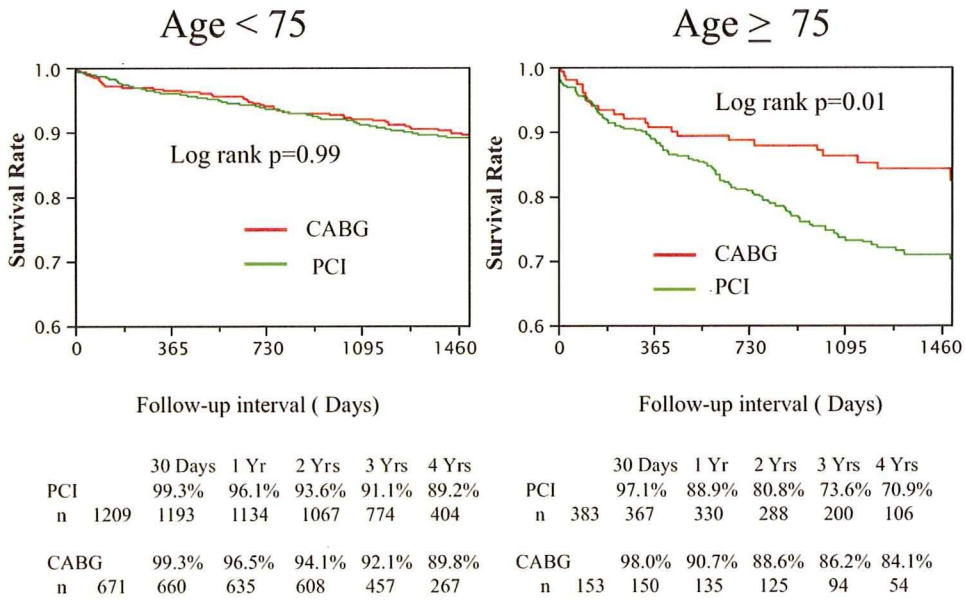


| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 99.3% | 96.1% | 93.6% | 91.1% | 89.2% |
| n | 1209 | 1193 | 1134 | 1067 | 774 | 404 |
| CABG | | 99.3% | 96.5% | 94.1% | 92.1% | 89.8% |
| n | 671 | 660 | 635 | 608 | 457 | 267 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 97.1% | 88.9% | 80.8% | 73.6% | 70.9% |
| n | 383 | 367 | 330 | 288 | 200 | 106 |
| CABG | | 98.0% | 90.7% | 88.6% | 86.2% | 84.1% |
| n | 153 | 150 | 135 | 125 | 94 | 54 |

**Figure 5.** Unadjusted Kaplan-Meier survival curves according to age in patients with diabetes.

vessel disease were treated by PCI in the New York's cardiac registries and the Northern New England registry, respectively, an observation that is consistent with current guidelines that generally recommend CABG in patients with triple-vessel disease.[11,12] However, when CABG is the preferred treatment choice for triple-vessel disease patients, it is possible that the proportion of patients who have comorbidities that preclude choice of CABG would increase in the PCI group. Therefore, the practice pattern in Japan, which is reflected by the choice in the CREDO-Kyoto registry of PCI in 51% of patients with triple-vessel disease, may provide a more appropriate environment to compare PCI with CABG in this subgroup.

Age is an important determinant when considering the choice between CABG and PCI. We observed better survival rate in the CABG group in patients ≥75 years of age, especially in the high risk subgroups such as triple vessel disease and diabetes. Excellent outcome could be achieved by contemporary CABG even in elderly patients. Complex coronary anatomy in elderly patients might be more adequately managed by CABG. However, one could argue this result could be attributable to patient selection bias. Consistent with the latter argument, although better survival after CABG in elderly patients was also reported in the APPROACH registry,[13] the AWESOME randomized trial demonstrated similar survival outcomes in patients ≥70 years of age.[14] In real-world clinical practice, it is likely that elderly patients with significant comorbidities tend to be more often referred for PCI because of its less invasive nature. The trend for excessive noncardiovascular mortality observed among elderly patients who underwent PCI in this study is suggestive of patient selection bias. This trend for excessive noncardiovascular mortality in the PCI group was not seen in patients <75 years of age. Considering the potential presence of profound patient selection bias in the elderly population, it would be appropriate to exclude elderly patients when attempting observational comparisons between CABG and PCI. In the current analyses, unadjusted and adjusted survival rates of CABG and PCI were not different in any of the anatomic and clinical subgroups when elderly patients were excluded from analyses.

In this study, diabetes did not influence survival among nonelderly patients with triple vessel disease, which is an important difference with current guideline and prior studies.[8,9,11,12] This finding might relate to the characteristics of patients with diabetes in our population. Only a quarter of the diabetic patients in this study were insulin-treated diabetes. However, we could not find out any difference in terms of relative survival outcome for CABG as compared with PCI between diabetic patients with or without insulin use.

Another important issue regarding comparisons between CABG and PCI using observational study data are the fact that patients undergoing CABG are more likely to be subjected to extensive scrutiny for comorbidities. Underestimation of comorbidities in the PCI group could lead to results favoring CABG when multivariable analysis is performed to adjust for confounding factors.

Long-term follow-up studies to compare revascularization strategies have the inherent limitation that rapid technical and technological improvements often render the tested strategies obsolete by the time results are available. Although in the current study surgical practices and outcome rates (at least one internal mammary graft in 95% of patients, 43% off-pump procedures, and a 30-day survival rate of 98.8%) were comparable to contemporary ones, contemporary PCI procedures have already shifted from bare-metal to drug-eluting stenting with variable penetration rates. The striking efficacy of drug-eluting stents in preventing both clinical and angiographic restenosis[15,16] has led to a rapid expansion of PCI use particularly for patients with complex multivessel disease; however, improvement of survival has not yet been reported with use of drug-eluting stents.[17] In the ARTS-2 study, survival rates at 3 years were not significantly different

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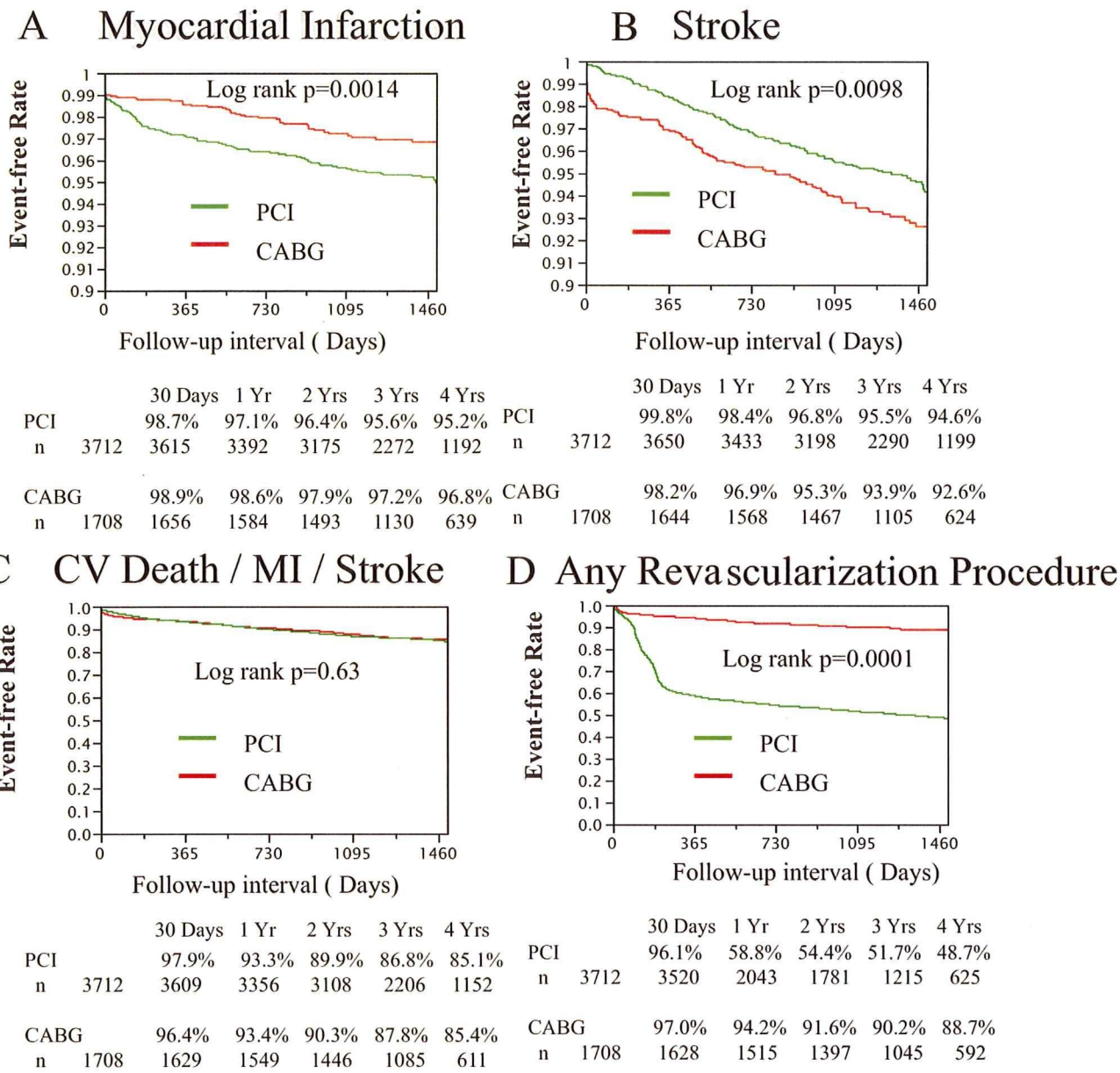


| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 98.7% | 97.1% | 96.4% | 95.6% | 95.2% |
| n | 3712 | 3615 | 3392 | 3175 | 2272 | 1192 |
| CABG | | 98.9% | 98.6% | 97.9% | 97.2% | 96.8% |
| n | 1708 | 1656 | 1584 | 1493 | 1130 | 639 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 99.8% | 98.4% | 96.8% | 95.5% | 94.6% |
| n | 3712 | 3650 | 3433 | 3198 | 2290 | 1199 |
| CABG | | 98.2% | 96.9% | 95.3% | 93.9% | 92.6% |
| n | 1708 | 1644 | 1568 | 1467 | 1105 | 624 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 97.9% | 93.3% | 89.9% | 86.8% | 85.1% |
| n | 3712 | 3609 | 3356 | 3108 | 2206 | 1152 |
| CABG | | 96.4% | 93.4% | 90.3% | 87.8% | 85.4% |
| n | 1708 | 1629 | 1549 | 1446 | 1085 | 611 |

| | | 30 Days | 1 Yr | 2 Yrs | 3 Yrs | 4 Yrs |
|---|---|---|---|---|---|---|
| PCI | | 96.1% | 58.8% | 54.4% | 51.7% | 48.7% |
| n | 3712 | 3520 | 2043 | 1781 | 1215 | 625 |
| CABG | | 97.0% | 94.2% | 91.6% | 90.2% | 88.7% |
| n | 1708 | 1628 | 1515 | 1397 | 1045 | 592 |

**Figure 6.** Unadjusted event-free survival curves for myocardial infarction (panel A), stroke (panel B), cardiovascular death/myocardial infarction/stroke (panel C), and any coronary revascularization procedure (panel D).

among the 3 groups of ARTS-2, ARTS-1 CABG, and ARTS-1 PCI, initial advantage with sirolimus-eluting stent appeared to be diminished at 3 years of follow-up (Serruys PW, MD, unpublished data, 2007). Furthermore, the pooled analysis of the pivotal randomized trials of the sirolimus-eluting stents suggested excessive mortality in diabetic patients treated with the sirolimus-eluting stents as compared with those treated with bare-metal stents.[18] These observations underscore the need for longer-term follow-up of patients with multivessel coronary artery disease treated with drug-eluting stents. When we expand the indications of PCI to more complex subsets of patients by using drug-eluting stents, we should at least confirm that PCI in high risk patients using bare metal stents did not impair the long-term survival as compared with CABG.

Results regarding cardiovascular endpoints other than mortality also deserve some discussion. Although incidences of myocardial infarction were clearly lower after CABG versus PCI, the excess of myocardial infarction in the PCI group was only seen within 1 year after the index procedure. Besides progression of new lesions, abrupt closure, stent thrombosis and restenosis are among the mechanisms of myocardial infarction in this particular time period. Myocardial infarction secondary to these causes might be largely preventable by future development of better drug-eluting stents and improved use and availability of existing and novel adjunctive pharmacology. It is noteworthy that the incidences of myocardial infarction beyond one year were similar in both groups, although this observation needs confirmation with longer-term follow-up.

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Restenosis had been the major drawback of PCI using bare-metal stent. Extremely high rate of repeated revascularization procedures in this study might be largely attributable to expanded use of PCI for more complex subsets of patients and high rate of angiographic follow-up in the Japanese clinical practice. However, the advent of drug-eluting stents have already markedly ameliorated the problems related to restenosis in real world clinical practice.[19]

There are several important limitations of this study. As compared with prior observational studies,[8,9] the sample size was not large enough to detect small differences in survival rates between the CABG and PCI groups. Although the definition of elderly patients was prespecified and seems clinically reasonable, the cut-off value of 75 years of age is arbitrary. Although variations in the frequencies of some anatomic factors such as numbers of diseased vessels, involvement of proximal LAD, and presence of total occlusions were adjusted for comparative analyses, our conclusions might not be applicable to those patients with other anatomic complexities, such as diffuse disease, heavy calcification or bifurcation that were not evaluated in this study. Furthermore, important medications, statins in particular, to prevent cardiovascular events are obviously underused. More optimal use of medications might have changed the long-term outcome of both CABG and PCI. Finally, the baseline characteristics such as age, body mass index, and prevalence of diabetes in the current population were markedly different from prior studies.[8,9] Although it is beyond the scope of the current article to discuss on the contribution of these demographic features to the different outcome in comparison to prior studies, we should admit that differences in racial, cultural, and socioeconomic factors might hinder generalization of the conclusions of this study outside Japan. Relatively low rate of recurrent coronary events in the Japanese population demonstrated in the REACH registry might have favorable influence on survival outcome after PCI.[20]

Despite the abovementioned study limitations, we would conclude that for patients with multivessel coronary artery disease, survival outcomes were similar among those who underwent either CABG or PCI with bare-metal stents in real-world clinical practice in Japan, when elderly patients are excluded from analysis.

## Appendix

### List of Clinical Research Coordinators

Kumiko Kitagawa, Hiromi Yoshida, Misato Yamauchi, Asuka Saeki, Chikako Hibi, Emi Takinami, Izumi Miki, Miya Hanazawa, Naoko Okamoto, Sachiko Maeda, Saeko Minematsu, Saori Tezuka, Yuki Sato, Yumika Fujino, Hitomi Sasae, Rei Fujita, Ayu Motofusa, Takami Hiraoka, Ayumi Yamamoto, Miho Hayashikawa, Yoko Fujiki.

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## Disclosures

None.

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