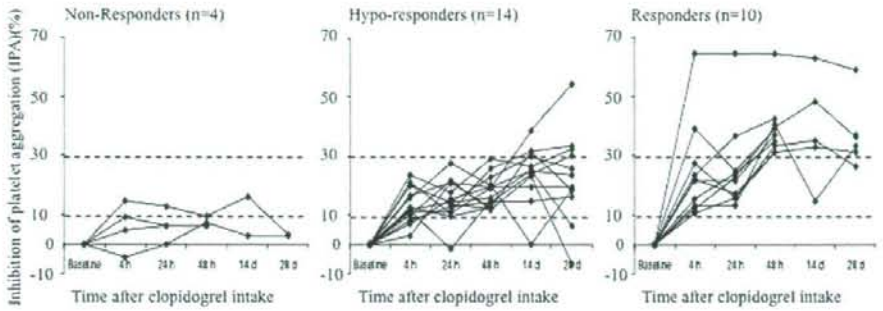


Fig 2. Time-dependent change in the inhibition of platelet aggregation (IPA) after clopidogrel intake for each subject categorized as a responder, hypo-responder or non-responder based on the IPAs with 5 μmol/L ADP stimulation at 48 h after clopidogrel intake, as described in the Methods.

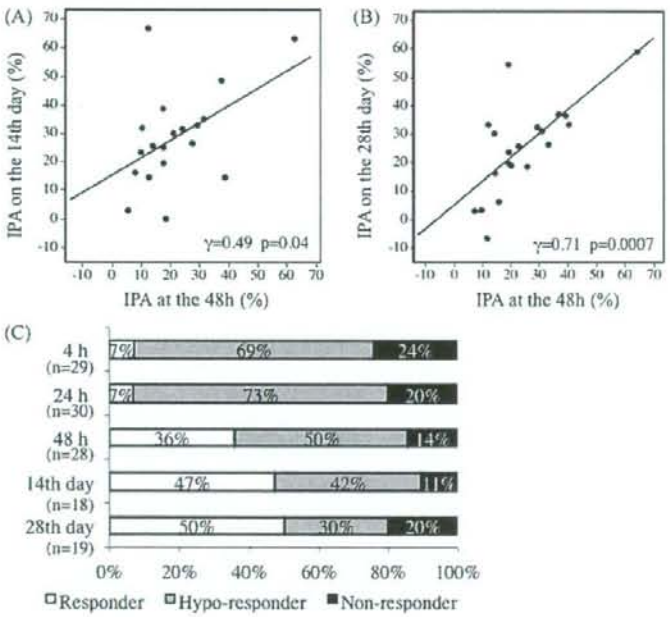


Fig 3. Correlation of the inhibition of platelet aggregation (IPA) with 5 μmol/L ADP at 48 h with values from the 14th day (**A**, n=18) or the 28th day (**B**, n=19) and (**C**) time-dependent change in the ratios of responders, hypo-responders and non-responders at 4 h, 24 h, 48 h, on the 14th day, and on the 28th day after clopidogrel intake using 5 μmol/L ADP as a stimulus are shown according to the definition: IPA<10% as non-responder, 10% ≤IPA<30% as hypo-responder and IPA ≥30%.

ADP-induced MAR at baseline or at 4, 24 or 48 h. Therefore, both groups were analyzed together.

Platelet Aggregation

The MARs induced by 5 μmol/L ADP time-dependently decreased after clopidogrel intake (**Fig 1A**), and the IPA values, which represent the degree of inhibition of platelet aggregability, increased reciprocally (**Fig 1B**). After 300-mg clopidogrel loading, rapid inhibition occurred at 4 h (IPA= 16.4±12.8%, P<0.0001 vs baseline), which continued until 24 h (IPA=17.6±12.1%, P<0.0001 vs baseline). Following 75-mg clopidogrel intake, platelet aggregability was inhibited more intensely after 48 h (IPA=24.0±13.9%, P<0.0001 vs 4 h and P<0.001 vs 24 h). It was noted that IPA did not attain a steady state within 24 h after the initial 300-mg clopidogrel intake. The same trend was observed with 20 μmol/L ADP (**Fig 1C**), for which the IPAs after clopidogrel intake were 11.9±13.6% at 4 h, 12.4±13.9% at 24 h, 16.3±16.3% at 48 h, 22.9±14.5% at 14 days, and 21.3±14.9% at 28 days. These data obtained with 5 or 20 μmol/L ADP stimulation suggest that clopidogrel efficiently exhibited antiplatelet effects and that a 300-mg loading dose might not be immediately sufficient to obtain the maximal antiplatelet effect.

Furthermore, clopidogrel intake also inhibited collagen-stimulated platelet aggregation (**Fig 1D**): IPAs after clopidogrel intake were 26.2±22.4% (4 h), 25.0±19.9% (24 h), 26.8± 22.8% (48 h), 31.7±19.0% (14 days), and 29.5±24.9% (28 days).

Rates of Clopidogrel Responders and Non-Responders

We analyzed the inter-individual variation in 5 μmol/L ADP-induced platelet aggregability. Individual plots of the IPAs are shown in **Fig 2**. The effectiveness of clopidogrel exhibited a wide inter-individual variation and was quite constant in individual patients throughout the study period. The effects of clopidogrel were examined on the 14th and

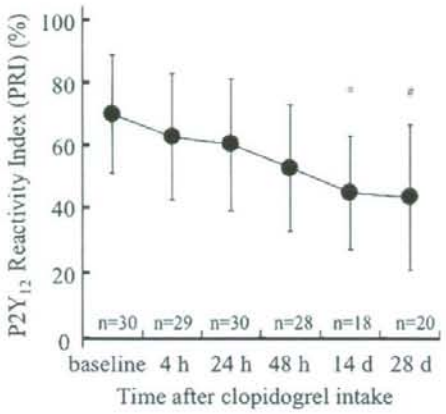


Fig 4. Time-dependent inhibition of P2Y12 reactivity index (PRI), calculated with data based on vasodilator-stimulated phosphoprotein phosphorylation as described in the Methods, at baseline, and at 4 h, 24 h, 48 h, 14th day, and 28th day after clopidogrel intake. By 1-sample t-test compared with data at baseline, *P<0.0001, #P<0.001.

28th days in 21 patients undergoing PCI. Among these patients, the IPAs at 48 h with 5 μmol/L ADP correlated well with those on the 14th day (P=0.04, r=0.49, n=18; **Fig 3A**) and the 28th day (P=0.0007, r=0.71, n=19; **Fig 3B**).

The proportion of responders, hypo-responders, and non-responders at 4 h with 5 μmol/L ADP was 7%, 69%, and 24%, respectively, and 36%, 50%, and 14%, respectively, at 48 h, indicating that the antiplatelet effects of clopidogrel at 48 h were stronger than those at 4 h, although we observed a rapid effect of clopidogrel at 4 h with the 300-mg loading dose. After 48 h, the antiplatelet effects of clopidogrel appeared to reach a plateau (**Figs 1, 2**). The rates of non-responders at 48 h, on the 14th day, and on the 28th day were 14%, 11%, and 20%, respectively, while the rates of responders were 36%, 47%, and 50% (**Fig 3C**).

Clopidogrel Responses Evaluated by VASP Phosphorylation

VASP is an abundant substrate of cAMP-dependent protein kinase in platelets. Binding of ADP to P2Y12 leads to *Gi*-coupled inhibition of adenylate cyclase, causing reduction of cAMP and the VASP-phosphorylation level in platelets. When P2Y12 receptors are successfully blocked by clopidogrel, the addition of ADP will not reduce the PGE_1-indiuced VASP phosphorylation levels. Using these principles, VASP phosphorylation levels were evaluated by flow cytometry in the present study and the PRI was used to evaluate clopidogrel's efficacy: the lower the PRI, the stronger the clopidogrel antiplatelet effect through inhibition of the P2Y12 receptor.

As shown in **Fig 4**, the PRIs gradually decreased after clopidogrel intake in a time-dependent manner: 70.2±19.0% at baseline, 62.9±20.4% at 4 h, 60.4±21.2% at 24 h, 52.9±20.0% at 48 h, 44.9±18.2% on day 14, and 43.8±23.9% on day 28. The PRIs and the IPAs at 48 h after clopidogrel intake were negatively correlated with each other (γ=0.67).

Discussion

In this study, we evaluated the antiplatelet effect of clopidogrel under low-dose ASA therapy in Japanese patients scheduled for PCI, and found that there was a wide inter-individual variation and that the effects in Japanese may not be as strong as for Caucasians at the same dose.

We noted that the effectiveness of clopidogrel was reasonably constant in each patient throughout the study period (**Fig 3**), indicating that responsiveness is individual-specific. In a Western population, the rates of patients with so called 'clopidogrel resistance' ranged between 5% and 44%, although the definitions of clopidogrel resistance varied[9] As shown in **Fig 3**, we also detected 4 (14%) non-responders at 48 h and in 1 patient (3%), clopidogrel suppressed ADP-induced platelet aggregability strongly at 4 h and throughout the study period. These data suggest that there is also a wide variety of responses to clopidogrel in the Japanese.

We used the definition of clopidogrel response proposed by Angiollilo et al because their study design was similar to ours, except that their patients took a higher dose of 250 mg ASA (vs 81–100 mg in our study) and platelet aggregation was evaluated with the optical aggregometer with 6 μmol/L ADP stimulation (vs 5 μmol/L ADP in our study)[14] Therefore, the MAR at baseline in our study (64.5±4.5%) was equivalent to theirs (approximately 60–62%)[14] Importantly, the ratio of responders at 4 h after a 300-mg loading dose was much lower in our study than in their study (7% vs 48%, respectively) and was also the case at 48 h, because the ratios of responders were 36% vs 80%, respectively. Another study conducted in Sweden demonstrated that the mean IPA with 20 μmol/L ADP was approximately 30% at 4 h after a 300-mg loading dose under 325 mg ASA therapy[15] whereas the IPA with 20 μmol/L ADP in our study was 12%. Thus, the degree of platelet inhibition in the Japanese obtained with a similar regimen of clopidogrel, in which a 300-mg loading dose and 75-mg maintenance dose were administered under ASA therapy, might be lower than that in Western populations.

PRI values based on the VASP phosphorylation levels are becoming widely used for the evaluation of the antiplatelet effects of clopidogrel[16,17] We also found them useful because clopidogrel significantly inhibited the PRIs. Using the same loading/maintenance clopidogrel regimen, Grossmann et al report that 10 (17.5%) of 57 patients were inadequate responders (PRI >50%) at 5 days[17] In the present study, the percentages of inadequate responders (RPI >50%) were 16/28 (57%) at 48 h, 10/20 (50%) at 14 days, and 7/21 (33%) at 28 days. Based on these results, we again consider that, at the present dosage, the antiplatelet effect of clopidogrel in the Japanese was not as strong as for Westerners.

Thus, on average, the antiplatelet effects of clopidogrel in Japanese patients are not as strong as those observed in Western people receiving a similar regimen of a 300-mg loading dose followed by a daily 75-mg maintenance dose under ASA therapy. To answer the question whether 75 mg/day clopidogrel is too strong for Japanese, we would answer that, based on the data presented here, it is not the case. Rather, the relatively weaker antiplatelet effect of clopidogrel in Japanese compared with in Western people might cause a higher incidence of stent thrombosis. However, currently we have no data on the degree of antiplatelet effect by clopidogrel that is necessary for the prevention of stent thrombosis in Japanese patients. Furthermore, because little data are available concerning the effect of ticlopidine in Japanese that would be sufficient to prevent stent thrombosis, we cannot conclude that the antiplatelet effect of clopidogrel at the current dosage is insufficient to prevent stent thrombosis. Further study is essential to link the effec-

tiveness of clopidogrel to the clinical outcomes of Japanese patients.

Our study clearly revealed that there are some clopidogrel non-responders among Japanese patients and thus their risk of stent thrombosis would be high. One possible solution could be to add cilostazol to the dual antiplatelet therapy of ASA and clopidogrel, because the functional mechanism of cilostazol, a phosphodiestrase 3 inhibitor, is partly similar to that of clopidogrel toward increasing the cAMP concentration in platelets[5,18] and its addition would enhance the antiplatelet effects of the dual antiplatelet therapy[19,20]

The mechanisms of clopidogrel resistance are considered to involve both acquired and genetic factors[21] Clopidogrel is a pro-drug, which needs to be activated to become the active substance through the action of Cyp3A4 and Cyp2C19. Single nucleotide polymorphisms (SNPs) in Cyp2C19 have been suggested as causes of resistance[22–24] There is an interethnic variability in the rate of the Cyp2C19 SNPs that cause Cyp2C19 to be non-functional and approximately 20% of Japanese people have been reported to possess little Cyp2C19 activity in contrast to only 2.5% of Westerners[25] Therefore, a genetic defect in Cyp2C19 might have a great influence on clopidogrel effectiveness in the Japanese. Further examination is required.

Concomitant treatment with drugs metabolized by Cyp2C19 and Cyp3A4 might reduce the antiplatelet effect of clopidogrel. The proton-pump inhibitor, omeprazole, which is metabolized by Cyp2C19, has been reported to reduce clopidogrel efficacy[26] In our study, only 3 patients were treated with omeprazol and their IPAs at 48 h using 5μmol/L ADP were 6.0%, 14.5%, and 15.9%, respectively. Because the average IPA was 24.0±13.9% among 28 patients, the IPAs in the omeprazol-treated patients tended to be lower (P=0.12, vs IPAs in omeprazol-free patients). A Cyp3A4 metabolizing drug, atorvastatin, has also been reported to affect clopidogrel's efficacy;[27] although other reports showed no effects[28,29] In our study, IPA with 5μmol/L ADP at 48 h was 21.2±10% (P=0.53, vs IPAs in atorvastatin-free patients), suggesting that atorvastatin might not affect the antiplatelet effects of clopidogrel; however, our study was small-scale, so further study with a larger number of patients is essential for drawing conclusions concerning these drug interactions.

We observed a clear reduction of the collagen-induced platelet aggregability by clopidogrel intake under dual antiplatelet therapy with ASA (**Fig 1D**). Collagen may induce aggregation mainly via the ADP pathway under ASA therapy. In other words, the signaling pathway stimulated by collagen might be shifted to the $P2Y_{12}$ ADP-receptor pathway in platelets under ASA therapy, in which platelets cannot adequately generate thomboxane A_2.

Evaluation of the antiplatelet effects of clopidogrel has been performed using several modalities, such as VerifyNow[30] and PFA100;[31] both of which are whole-blood aggregometers, in addition to the optical aggregometer and analysis of VASP phosphorylation used in the present study. Further, the definition of clopidogrel resistance varies in each study. Thus, the method and definition used to evaluate the effect of clopidogrel have not yet been established, which would enable comparison of studies.

In summary, we showed that the antiplatelet effect of clopidogrel varied in Japanese patients, with 14% non-responders, and that, on average, the effect was not as strong as that observed in Western patients with a similar regimen of a 300-mg loading dose followed by a daily 75-mg maintenance dose under ASA therapy.

Acknowledgements

We are grateful to all members in the Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University. This work was supported by Health and Labor Sciences Research Grant for Cardiovascular Research and a Grant from the Japan Cardiovascular Research Foundation.

References

1. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting: Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998; **339:** 1665–1671.
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.
3. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet* 2001; **358:** 527–533.
4. Savi P, Herbert JM. Clopidogrel and ticlopidine: P2Y12 adenosine diphosphate-receptor antagonists for the prevention of atherothrombosis. *Semin Thromb Hemost* 2005; **31:** 174–183.
5. Horiuchi H. Recent advance in antiplatelet therapy: The mechanisms, evidence and approach to the problems. *Ann Med* 2006; **38:** 162–172.
6. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; **107:** 2908–2913.
7. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol* 2005; **45:** 246–251.
8. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, et al. Influence of aspirin resistance on platelet function profiles in patients on long-term aspirin and clopidogrel after percutaneous coronary intervention. *Am J Cardiol* 2006; **97:** 38–43.
9. Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Michelson AD. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 2007; **50:** 1822–1834.
10. Geisler T, Langer H, Wydymus M, Gohring K, Zurn C, Bigalke B, et al. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27:** 2420–2425.
11. Morimoto T, Fukui T, Lee TH, Matsui K. Application of U.S. guidelines in other countries: Aspirin for the primary prevention of cardiovascular events in Japan. *Am J Med* 2004; **117:** 459–468.
12. Born GV, Hume M. Effects of the numbers and sizes of platelet aggregates on the optical density of plasma. *Nature* 1967; **215:** 1027–1029.
13. Tabuchi A, Taniguchi R, Takahashi K, Kondo H, Kawato M, Morimoto T, et al. Action of aspirin on whole blood-aggregation evaluated by the screen filtration pressure method. *Circ J* 2008; **72:** 420–426.
14. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Banuelos C, et al. High clopidogrel loading dose during coronary stenting: Effects on drug response and interindividual variability. *Eur Heart J* 2004; **25:** 1903–1910.
15. Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 2006; **27:** 1166–1173.
16. Aleil B, Ravanat C, Cazenave JP, Rochoux G, Heitz A, Gachet C. Flow cytometric analysis of intraplatelet VASP phosphorylation for the detection of clopidogrel resistance in patients with ischemic cardiovascular diseases. *J Thromb Haemost* 2005; **3:** 85–92.
17. Grossmann R, Sokolova O, Schnurr A, Bonz A, Porsche C, Obergfell A, et al. Variable extent of clopidogrel responsiveness in patients after coronary stenting. *Thromb Haemost* 2004; **92:** 1201–1206.
18. Yamamoto H, Takahashi K, Watanabe H, Yoshikawa Y, Shirakawa R, Higashi T, et al. Evaluation of the antiplatelet effects of cilostazol, a phosphodiesterase 3 inhibitor, by VASP phosphorylation and platelet aggregation. *Circ J* 2008; **72:** 1844–1851.
19. Kim JY, Lee K, Shin M, Ahn M, Choe H, Yoo BS, et al. Cilostazol could ameliorate platelet responsiveness to clopidogrel in patients undergoing primary percutaneous coronary intervention. *Circ J* 2007;

71: 1867–1872.
20. Angiolillo DJ, Capranzano P, Goto S, Aslam M, Desai B, Charlton RK, et al. A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: Results of the OPTIMUS-2 study. *Eur Heart J* 2008; **29:** 2202–2211.
21. Michelson AD. P2Y12 antagonism: Promises and challenges. *Arterioscler Thromb Vasc Biol* 2008; **28:** s33–s38.
22. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood* 2006; **108:** 2244–2247.
23. Fontana P, Hulot JS, De Moerloose P, Gaussem P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J Thromb Haemost* 2007; **5:** 2153–2155.
24. Malek LA, Kisiel B, Spiewak M, Grabowski M, Filipiak KJ, Kostrzewa G, et al. Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. *Circ J* 2008; **72:** 1165–1169.
25. Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005; **20:** 153–167.
26. Gilard M, Arnaud B, Le Gal G, Abgrall JF, Boschat J. Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin. *J Thromb Haemost* 2006; **4:** 2508–2509.
27. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: A new drug-drug interaction. *Circulation* 2003; **107:** 32–37.
28. Wenaweser P, Windecker S, Billinger M, Cook S, Togni M, Meier B, et al. Effect of atorvastatin and pravastatin on platelet inhibition by aspirin and clopidogrel treatment in patients with coronary stent thrombosis. *Am J Cardiol* 2007; **99:** 353–356.
29. Mitsios JV, Papathanasiou AI, Rodis FI, Elisaf M, Goudevenos JA, Tselepis AD. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is administered concomitantly for 5 weeks in patients with acute coronary syndromes. *Circulation* 2004; **109:** 1335–1338.
30. Malinin A, Pokov A, Spergling M, Defranco A, Schwartz K, Schwartz D, et al. Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: The VERIfy Thrombosis risk ASsessment (VERITAS) study. *Thromb Res* 2007; **119:** 277–284.
31. Giusti B, Gori AM, Marcucci R, Sestini I, Saracini C, Paniccia R, et al. Role of glycoprotein Ia gene polymorphisms in determining platelet function in myocardial infarction patients undergoing percutaneous coronary intervention on dual antiplatelet treatment. *Atherosclerosis* 2008; **196:** 341–348.

Resuscitation (2008) 79, 475–481

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/resuscitation

SIMULATION AND EDUCATION PAPER

Public perception of and willingness to perform bystander CPR in Japan☆

Nobuo Kuramoto[a], Takeshi Morimoto[a,*], Yoshie Kubota[b], Yuko Maeda[a], Susumu Seki[a], Kaori Takada[a], Atsushi Hiraide[a]

[a] *Center for Medical Education, Kyoto University Graduate School of Medicine, Konoe-cho, Yoshida, Sakyo-ku, 606-8501 Kyoto, Japan*
[b] *Center for Integrative Education of Pharmacy Frontier, Kyoto University Graduate School of Pharmaceutical Sciences, Kyoto, Japan*

Received 26 March 2008; accepted 9 July 2008

KEYWORDS
Automated external defibrillation (AED);
Cardiac arrest;
Cardiopulmonary resuscitation (CPR);
General public

Summary
Aim: Immediate bystander cardiopulmonary resuscitation (CPR) is the most essential factor for life saving in out-of-hospital cardiac arrest patients. We investigated the characteristics associated with willingness to attempt CPR among the Japanese general population.
Methods: We randomly selected 2400 persons from all over Japan and conducted a questionnaire survey regarding their knowledge, experiences of and attitudes toward CPR. We performed descriptive statistics followed by multivariable logistic regression analyses.
Results: A total of 1132 persons (47%) completed the questionnaire. Only 13% of the subjects were willing to attempt bystander CPR for their families and friends, and 7% were willing to attempt bystander CPR for strangers. Willingness to attempt CPR was independently associated with office workers or skilled workers [odds ratio (OR) 1.8; 95% confidence interval (CI): 1.1–2.7], having trained in CPR [OR: 3.1; 95% CI: 2.1–4.6], actual experience with CPR [OR: 3.8; 95% CI: 1.7–8.3], and having friends with heart diseases [OR: 1.8; 95% CI: 1.05–3.0]. Having trained in CPR was independently associated with younger age [OR: 1.6; 95% CI: 1.2–2.1], office workers or skilled workers [OR: 1.5; 95% CI: 1.1–2.0], having driver's license [OR: 1.7; 95% CI: 1.2–2.4] and awareness of AED placement in a public space [OR: 2.1; 95% CI: 1.4–3.1].
Conclusion: Experience of CPR training closely associated with willingness to attempt CPR, and awareness of AED in a public space are significant factors in CPR training. AED placement might call attention to CPR training and develops willingness to attempt CPR.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2008.07.005.

* Corresponding author. Tel.: +81 75 751 4890; fax: +81 75 751 4250.
E-mail address: morimoto@kuhp.kyoto-u.ac.jp (T. Morimoto).

0300-9572/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2008.07.005

Introduction

Out-of hospital cardiac arrest is a crucially time-dependent event. In order to improve survival and neurological outcome, it is essential to promote bystander cardiopulmonary resuscitation (CPR). Various endeavors have been made to increase the number of people trained in resuscitation and to improve the quality of CPR.[1–3] However, the proportion of CPR-trained persons in the community remains insufficient,[4–6] and the frequencies of immediate bystander CPR remains inadequate, even in recent years in the Western countries.[7,8] Despite marked improvements in the pre-hospital emergency care system and advocacy of upgrade guidelines for resuscitation, only a minority of out-of-hospital cardiac arrest patients survive to hospital discharge.[8,9]

In order to increase the number of persons in the public who have been trained in CPR, it is necessary to assess the perception and attitude of general public toward CPR. Although several studies have reported on the knowledge of CPR and attitudes toward CPR among the general population, nationwide investigations remain sparse.[4,10] This study was designed to assess comprehensive data on knowledge and experience of, and attitudes toward CPR. We investigated the characteristics associated with willingness to attempt CPR among the Japanese general population.

Methods

Participants and setting

This survey was conducted with a representative sample of adults living in Japan, which has 128 million inhabitants (men: 48.8%, mean age: 42.5 years) in August 2006. To be eligible for inclusion, subjects had to be aged 15–79 years and their addresses were registered in the Japanese census. The subjects were selected at random, and were stratified to correlate with the geographic distribution of the population. In August 2006, 200 research assistants visited 2400 subjects. Informed consent was obtained from each subject. This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

Questionnaire

The questionnaire, which is comprised of multiple-choice questions, was designed by the researchers to explore a range of issues including: demographics, medical conditions, knowledge and experience of CPR training, willingness to perform bystander CPR, and to use AED (Appendix A). Eight non-medically trained persons reviewed the questionnaires prior to the survey to improve the clarity and brevity.

Statistical analyses

All questionnaire items were binary or categorical variables other than age. We dichotomized age at 60 years old for univariable and multivariable analyses. Subjects with missing data were eliminated from the analyses, in which the missing data was necessary. We conducted descriptive statistics for the characteristics of the subjects. We determined the willingness to attempt bystander CPR and experience of training of CPR outcomes. We first compared the characteristics of the subjects regarding the willingness to attempt bystander CPR by chi-square tests or Fisher's exact test where appropriate. The characteristics included age, gender, city size, socioeconomic status, existence of heart diseases of their own or friends, experience of emergency situations, awareness of AED placement in a public space, experience of training CPR, and theoretical knowledge of CPR. Variables with p-value less than 0.05 were then included in a logistic regression model to determine the factors associated with willingness to attempt bystander CPR. We used stepwise model selection to eliminate collinear variables, and developed the final model. The results were expressed as odds ratios (OR) and 95% confidence intervals (CI). We conducted the same analyses for experience of training of CPR without the independent variables of experience of training CPR and theoretical knowledge of CPR. The variables with a p-value of 0.05 or less were considered significant. The SAS software, version 9.1 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses.

Results

Demographics

A total of 1132 (47%) subjects completed questionnaires. The age of the subjects ranged from 15 to 79 years and 47% were men. The educational levels of the majority were graduation of high school (Table 1). The majority of annual income ranged from 4 to 8 million. A small number of health care professionals (1 medical doctor, 2 dentists and 13 nurses) were included. Office workers or skill workers, those who worked in office or factory as an employee, represented the largest number in the occupational category, except unemployed. Unemployed persons were largely housewives.

Characteristics of subjects associated with heart disease or CPR

Ninety-five percent of the participants (1077/1132) did not have cardiac disease (myocardial infarction, pectoris angina, or chronic heart failure) and 11% of participants had friends with cardiac diseases (Table 2). We found that 19% of the general public had had an opportunity to witness the collapse of someone. However, no more than 4% of the persons had an experience of actual bystander CPR. In Japan having a driver's license is associated with CPR because CPR training is obligatory prior to obtaining a drivers license. Seventy-six percent of the subjects held a driver's license.

Attitude towards bystander CPR

Only 147 people (13%) responded that they were willing to attempt CPR in the case of collapse of their families and friends. If the collapsed person was stranger this number decreased to 75 (7%). Age, socioeconomic factors, experiences, and knowledge were associated with willingness to attempt bystander CPR by univariate analyses (Table 2).

Table 1 Characteristics of subjects ($n = 1132$)

Characteristics	n	%
Age (years, mean = 49.3)		
15–39	361	32
40–59	410	36
60–79	361	32
Gender		
Men	530	47
Residential area		
Cities of more than 500 thousand population	220	19
Cities with a population of 150–500 thousand	365	33
Cities with a population of 50–150 thousand	271	24
Cites or towns of less than 50 thousand population	276	24
Annual income		
Less than 4 million yen	306	27
Between 4 and 8 million yen	402	36
More than 8 million yen	242	21
Educational level		
Elementary school graduates	18	2
Junior high school graduates	183	16
High school graduates	496	44
Technical school graduates	215	19
University/college graduates, nondegreed	181	16
Beyond bachelor's degree	14	1
Occupation		
Farmers/fishermen	40	4
Self-employed/merchants	112	10
Executives	44	4
Office workers/skill workers	220	20
Labors	113	10
Part time	151	13
Students	63	6
Others	23	2
Unemployed	357	31

In logistic regression model, willingness to attempt bystander CPR for families, friends, or strangers was shown to be associated with higher educational level (OR: 1.9; 95% CI: 1.3–2.8), office worker or skilled worker (OR: 1.8; 95% CI: 1.1–2.7), having friends with heart diseases (OR: 1.8; 95% CI: 1.1–3.0), experience of actual bystander CPR (OR: 3.8; 95% CI: 1.7–8.3), and experience of training in CPR (OR: 3.1; 95% CI: 2.1–4.6). As for knowledge or skills related to CPR, knowing the importance of immediate CPR (OR: 1.9; 95% CI: 1.3–2.8), and those who can use AED without hesitation (OR: 4.0; 95% CI: 2.5–6.6) were independent factors in the willingness (Figure 1).

Experience of training in CPR

Over one-third (393/1132) of the subjects were trained in CPR at least once (Table 2). Among them, 50% (195/393) had been trained only once, 30% (117/393) twice, and 20% (79/393) more than three times.

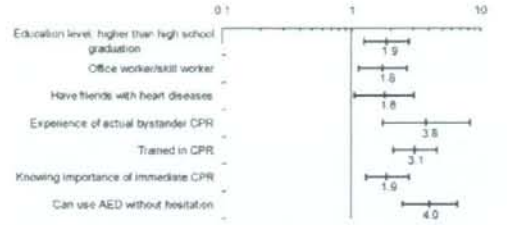


Figure 1 Factors for willingness to attempt bystander cardiopulmonary resuscitation. Vertical bars indicate the odds ratios and horizontal bars indicate the 95% confidence intervals, based on multiple logistic regression models. *X*-axis is an exponential scale.

In logistic regression model, it was shown that younger age (OR: 1.6; 95% CI: 1.2–2.1), office worker or skilled worker (OR: 1.5; 95% CI: 1.1–2.0), having a drivers license (OR: 1.7; 95% CI: 1.2–2.4), having witnessed collapsed persons (OR: 1.5; 95% CI: 1.1–2.0), and awareness of AEDs often in public spaces (OR: 2.1; 95% CI: 1.4–3.1) were independently associated with having trained in CPR (Figure 2).

Discussion

Our nation-wide survey showed that one-fifth of general public had an opportunity to witness the cardiac arrest of someone, but very small number of them attempted CPR, which accounted for less than 5% of entire population. Willingness to attempt CPR was associated with having trained in CPR and experience of actual CPR.

It is essential to collect information both from reports of out-of-hospital cardiac arrests and from persons who have the potential for bystander witness of arrests, in order to make systematic analyses and improvements of care in out-of-hospital cardiac arrests. Features of collapsed patients with cardiac arrest out-of-hospital have been comprehensively described with standardized registration using the Utstein style.[11] Surveys based on large-scale populations

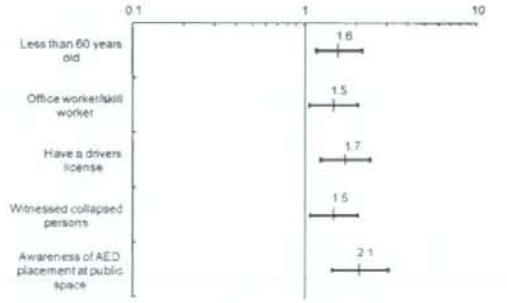


Figure 2 Factors for trained in cardiopulmonary resuscitation. Vertical bars indicate the odds ratios and horizontal bars indicate the 95% confidence intervals, based on multiple logistic regression models. *X*-axis is an exponential scale.

Table 2 Characteristics associated with willingness to attempt bystander cardiopulmonary resuscitation for families, friends, or strangers

Characteristics	Overall ($n=1132$)	Willing ($n=147$)	Relactant ($n=985$)	p-Value
Less than 60 years old, *n* (%)	771 (68)	117 (80)	654 (66)	0.001
Men, *n* (%)	530 (47)	80 (54)	450 (46)	0.05
Resident in the city of less than 150 thousand population, *n* (%)	547 (48)	68 (46)	479 (49)	0.6
Annual income: more than 4 million yen, *n* (%)	826 (73)	117 (80)	709 (72)	0.05
Education level: higher than high school graduation, *n* (%)	479 (42)	91 (62)	388 (39)	<0.0001
Office worker/skill worker, *n* (%)	220 (19)	51 (35)	169 (17)	<0.0001
Employed, *n* (%)	967 (85)	138 (94)	829 (84)	0.002
Have no heart diseases, *n* (%)	1077 (95)	141 (96)	936 (95)	0.6
No periodical visits to hospital, *n* (%)	710 (63)	97 (66)	613 (62)	0.4
Have friends with heart diseases, *n* (%)	129 (11)	24 (16)	105 (11)	0.04
Have a drivers license, *n* (%)	864 (76)	126 (86)	738 (75)	0.004
Witnessed collapsed persons, *n* (%)	219 (19)	32 (22)	187 (19)	0.4
Experience of actual bystander CPR, *n* (%)	40 (4)	14 (10)	26 (3)	<0.0001
Awareness of AED placement at public space, *n* (%)	134 (12)	33 (23)	101 (10)	<0.0001
Trained in CPR, *n* (%)	393 (35)	96 (65)	297 (30)	<0.0001
Know the meaning of 'heart massage', *n* (%)	919 (81)	137 (93)	782 (79)	<0.0001
Know the most critical skills for CPR, *n* (%)	853 (75)	127 (86)	726 (74)	0.0009
Know importance of immediate CPR, *n* (%)	489 (43)	89 (61)	400 (41)	<0.0001
Know how to use AED, *n* (%)	197 (17)	57 (39)	140 (14)	<0.0001
Know administrator's permission of lay person to use AED, *n* (%)	214 (19)	60 (41)	154 (16)	<0.0001
Can use AED without hesitation, *n* (%)	100 (9)	42 (29)	58 (6)	<0.0001

have revealed the descriptive features of out-of-hospital cardiac arrests, such as age and sex,[12] incidence and survival rates[13] and the location of arrest[14] in Osaka prefecture, Japan. The nation-wide Utstein population-based survey system was recently introduced by the Fire and Disaster Management Agency in Japan.[15] It is expected to elucidate more detailed features of out-of-hospital cardiac arrest.

Several studies extended the focus from these people with bystander CPR or CPR training to the broad community. The surveys varied from a large city[5] to suburban and rural places.[16] However, the nationwide survey has been limited. Thus, we extended the area to the whole of Japan.

Although the number of participants of our study was limited to 1132, we believe that we could elucidate the general features of perception and willingness of the Japanese people toward CPR in terms of age, sex, educational level, and occupational states. In the results of our sampling, the age distribution of the samples was 32, 36, and 32% for 15–39, 40–59, and 60–79 years of age, respectively. In the national data of Japanese population, the age distribution was 40,856 (39%), 34,989 (34%), and 27,979 (27%) thousand, respectively, for these ages.[17] The participants of our study had a slightly larger number in the age group of 60–79 years of age compared to the people with 15–39 years of age in he Japanese national data. In our data the proportion of males was 47%, compared with 49% in Japanese national population in corresponding ages. With these comparisons we believe that our sampling would not be biased based on the nation standard.

It is noteworthy that although 20% of the general public had an opportunity to witness someone collapse, only less than 5% of the people had an experience to attempt CPR. Therefore, to evaluate the factors concerned with public willingness to attempt CPR becomes a key factor in improving the current situation of poor outcome in our community. In the logistic regression analysis, knowing importance of immediate CPR and being confident in the use of AED were highlighted as factors associated with willingness to attempt CPR. Similar observations reported elsewhere emphasizing that lacking knowledge of early activation of resuscitation and skills in AED usage are factors related to the public reluctance for CPR.[18] Simplification in teaching CPR[18] and publicizing cardiac arrest survival figures[5] were suggested to promote the public willingness to attempt CPR. These proposals might be worthy to consider in promoting the public willingness to perform CPR.

In our findings it is of interest that the willingness to perform CPR was associated with higher education level and office workers or skill workers. We suspect that these findings are related not only with the reason for their responsible position for other workers but also because of their awareness of CPR. In Japan, the importance of AED and bystander CPR became widely recognized recent years. Their educational levels and positions might be related to their awareness of these newer topics.

While the effectiveness of CPR training on bystanders' attitudes has been reported,[16] our results clearly demonstrated that CPR training is a significant positive factor associated with the willingness of public to perform CPR. Therefore analyses for the factors associated with CPR training would become very important in promoting the public willingness for CPR. In the logistic regression analysis, having

a driver's license was an independent factor associated with the experience of CPR training. In Japan, the obligation to receive CPR training when people get a driver's license was introduced in 1994. This is the reason why having a driver's license is related to experience with CPR training.

Awareness of the presence of AED in public spaces is a striking positive factor in CPR training in the regression model. In recent years the numbers of AED in public spaces increased rapidly in Japan. The report at Chicago airports shows that in the case of survival most of the users of AED had no prior training.[19] However, recent social situations of expanding AED placement might call attention to CPR training via awareness of highly visible public devices, and promote the willingness to attempt CPR.

Several limitations inherent to study design with a questionnaire survey, were inevitable. The response rate was 47%, which must be regarded as relatively good in this kind of survey. However, there still may be a sampling bias present in this survey; people with information and interest in resuscitation would seem more likely to complete a survey involving this topic. Concerning the willingness to attempt CPR and to use AEDs, we evaluated participants' attitudes rather than actual behaviors. There are inherent possibilities that participants might answer dishonestly. As a result, the data may overestimate the knowledge, experience of and willingness to attempt CPR and to use AEDs. With regard to most variables, there were a number of missing data, especially in annual income (182 persons). Since the data is gathered only from the Japanese public, these results might be affected by differences in cultural, ethical aspects and other social circumstances compared with those of other countries.

Conclusions

This study showed the Japanese nation-wide general public knowledge, experience and attitude toward CPR. Experience of CPR training had an impact on the willingness comparable with experience of actual bystander CPR. Awareness of the presence of AEDs in public spaces is a significant factor in CPR training. The prevalence of AEDs might promote interest in CPR training and advance public willingness to attempt CPR.

Conflict of interest

None.

Acknowledgements

This study was supported by Grant-in-aid for instituting the widespread application of new methods on resuscitation training (AH) and grants 19390458 (AH), 17689022 (TM), and 18659147 (TM) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. None of these grants had role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Appendix A. Questionnaire

Age:
Gender:
Home address:
Occupation:
Annual income:
Highest education:
Past medical history:
Periodical visits to hospitals or clinics (yes/no)
Admission to hospitals in these 2 years (yes/no)
Family medical history:
Diseases of you friends or acquaintances:
Driver's license (Yes/no)

1. What do you think "heart massage" means?
   (a) To rub chest.
   (b) To compress chest strongly.
   (c) To open the chest wall and to rub heart directly.
   (d) To open the chest wall and compress heart directly.
   (e) Have no idea.

2. Which of the following do you think is the most important procedure for cardiopulmonary resuscitation (CPR)?
   (a) Heart massage.
   (b) Artificial breathing.
   (c) Both heart massage and artificial breathing.
   (d) Have no idea.

3. Have you witnessed collapses of other persons? If you have, who?
   (a) My family. (Proceed to question 4)
   (b) My friends or acquaintances. (Proceed to question 4)
   (c) Strangers. (Proceed to question 4)
   (d) Have never witnessed. (Proceed to question 5)

For those who have witnessed collapse of other persons:

4. What actions did you take when you witnessed collapse of other persons?
   (a) Attempted CPR.
   (b) Called for ambulance.
   (c) Called for people or telephoned.
   (d) Only watched or left.

For every respondent:

5. If you witness collapses of your families of friends hereafter, what actions will you take?
   (a) Attempt CPR.
   (b) Call for ambulance.
   (c) Call for people or telephone.
   (d) Only watch or leave.

6. If you witness collapses of strangers hereafter, what actions will you take?
   (a) Attempt CPR.
   (b) Call for ambulance.
   (c) Call for people or telephone.
   (d) Only watch or leave.

7. What is the reason for hesitation in resuscitating your families or friends, if any?
   (a) Lacking knowledge or skills for providing CPR.
   (b) Limited knowledge of skills for providing CPR.
   (c) Fear of injuring patients.
   (d) Having no interest in CPR for my family or friends.

Appendix (*Continued*)

(e) Fear of legal liability.
(f) Fear of other liability.
(g) Objection for lay people to attempt CPR.
(h) Reluctance to perform mouth-to-mouth ventilation.
(i) Fear of infections through mouth-to-mouth ventilation.
(j) Lack of courage.
(k) Reluctance to expose their chest in public.

8. What is the reason for hesitation in resuscitating strangers, if any?
(a) Lacking knowledge or skills for providing CPR.
(b) Limited knowledge of skills for providing CPR.
(c) Fear of injuring patients.
(d) Having no interest in CPR for my family or friends.
(e) Fear of legal liability.
(f) Fear of other liability.
(g) Objection for lay people to attempt CPR.
(h) Reluctance to perform mouth-to-mouth ventilation.
(i) Fear of infections through mouth-to-mouth ventilation.
(j) Lack of courage.
(k) Reluctance to expose their chest in public.

9. Have you ever trained in cardiopulmonary resuscitation?
(a) Yes. (Proceed to question 10)
(b) No. (Proceed to question 14)

For those who had trained in CPR:

11. Where have you attended CPR courses?
(a) Fire stations.
(b) Hospitals.
(c) Driver's school.
(d) Workplace.
(e) Others.

12. How often have you trained in CPR?
(a) Once.
(b) Twice.
(c) Three times.
(d) More than four times.

13. Did you use AEDs in the CPR course?
(a) Used more than once.
(b) Not used.
(c) Not remember.

For those who had never trained in CPR:

14. What is the reason for not having attended CPR training courses?
(a) Have no interest in CPR.
(b) Objection for lay people to attempt CPR.
(c) No CPR training in my neighborhood.
(d) Have no time to attend CPR training course.
(e) No information about CPR training course.
(f) Other reasons:

15. How much do you know CPR training course?
(a) Know the content of training course.
(b) Know only the name.
(c) Do not know at all.

For every respondent:

16. How much do you know AEDs?
(a) Know the name and how to use them.
(b) Know only the name but not how to use them.
(c) Know that they give electrical shock, although I do not know the name.
(d) Do not know at all.

17. How often have you been aware of AEDs in public space?
(a) Very often.
(b) Occasionally.
(c) Once or twice.
(d) Noticed only posters.
(e) Never.

18. How much do you know that lay people can use AEDs?
(a) Know well.
(b) Have heard that.
(c) Do not know at all.

19. Can you use AEDs for patients of cardiac arrest without hesitation?
(a) Yes. (Proceed to question 21)
(b) No. (Proceed to question 20)

For those who cannot use AED:

20. What is the reason for hesitation of using AEDs?
(a) Do not know how to use AEDs.
(b) Fear of injuring patients.
(c) Objection for lay people to use AEDs.

For every respondent:

21. How much time do you think the delay of CPR can be permissible for its effectiveness?
(a) 1 min.
(b) 5 min.
(c) 10 min.
(d) 30 min.
(e) Have no idea.

22. How much do you think CPR provided by lay people is effective?
(a) Very effective.
(b) Moderately effective.
(c) Little effective.
(d) Not effective.
(e) Have no idea.

23. How prevalent do you think CPR by lay people is in Japan?
(a) Very prevalent.
(b) Moderately prevalent.
(c) Little prevalent.
(d) Not prevalent.
(e) Have no idea.

24. How much do you think CPR by lay people is necessary to be prevalent?
(a) Very necessary.
(b) Moderately necessary.
(c) Little necessary.
(d) Not necessary.

References

1. Lynch B, Einspruch EL, Nichol G, Becker LB, Aufderheide TP, Idris A. Effectiveness of a 30-min CPR self-instruction program for lay responders: a controlled randomized study. Resuscitation 2005;67:31–43.

2. Marco CA, Larkin GL. Public education regarding resuscitation: effects of a multimedia intervention. Ann Emerg Med 2003;42:256–60.
3. Assar D, Chamberlain D, Colquhoun M, et al. Randomized controlled trials of staged teaching for basic life support. 1. Skill acquisition at bronze stage. Resuscitation 2000;45:7–15.
4. Axelsson AB, Herlitz J, Homberg S, Thoren AB. A nationwide survey of CPR training in Sweden: foreign born and unemployed are not reached by training programmes. Resuscitation 2006;70:90–7.
5. Donohoe RT, Haefeli K, Moore F. Public perceptions and experiences of myocardial infarction, cardiac arrest and CPR in London. Resuscitation 2006;71:70–9.
6. Smith KL, Cameron PA, Meyer AD, McNeil JJ. Is the public equipped to act in out of hospital cardiac emergencies? Emerg Med J 2003;20:85–7.
7. Swor R, Khan I, Domeier R, Honeycutt L, Chu K. Compton CPR training and CPR performance: do CPR-trained bystander perform CPR? Acad Emerg Med 2006;13:596–601.
8. Eckstein M, Stratton SJ, Chan LS. Cardiac arrest resuscitation evaluation in Los Angeles: CARE-LA. Ann Emerg Med 2005;45:504–9.
9. Fairbanks RJ, Shah MN, Lerner EB, Ilangovan K, Pennington EC, Schneider SM. Epidemiology and outcomes of out-of-hospital cardiac arrest in Rochester, New York. Resuscitation 2007;72:415–24.
10. Rasmus A, Czekajlo MS. A national survey of the Polish population's cardiopulmonary resuscitation knowledge. Eur J Emerg Med 2000;7:39–43.
11. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data form out-of-hospital cardiac arrest: the Utstein style. Circulation 1991;84:960–75.
12. Iwami T, Hiraide A, Nakanishi N, et al. Age and sex analyses of out-of-hospital cardiac arrest in Osaka, Japan. Resuscitation 2003;57:145–52.
13. Nishiuchi T, Hiraide A, Hayashi Y, et al. Incidence and survival rate of bystander-witnessed out-of-hospital cardiac arrest with cardiac etiology in Osaka Japan: a population-based study according to the Utstein style. Resuscitation 2003;59: 329–35.
14. Iwami T, Hiraide A, Nakanishi N, et al. Outcome and characteristics of out-of-hospital cardiac arrest according to location of arrest: a report from a large-scale, population-based study in Osaka, Japan. Resuscitation 2006;69:221–8.
15. Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications; 2008. http://www.fdma.go.jp/en/pam09.html.
16. Jelinek GA, Gennat H, Celenza T, O'Brien D, Jacobs I, Lynch D. Community attitudes towards performing cardiopulmonary resuscitation in Western Australia. Resuscitation 2001;51:239–46.
17. Statistics Bureau, director-general for policy planning (statistical standards) and statistical research and training institute; 2008. http://www.stat.go.jp/english/index.htm.
18. Celenza T, Gennat HC, O'brien D, Jacobs IG, Lynch DM, Jelinek GA. Community competence in cardiopulmonary resuscitation. Resuscitation 2002;55:157–65.
19. Caffrey SL, Willoughby PJ, Pepe PE, Becker LB. Public use of automated external defibrillators. N Engl J Med 2002;347:1242–7.

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

Takeshi Kimura, MD; Takeshi Morimoto, MD; Yutaka Furukawa, MD; Yoshihisa Nakagawa, MD; Satoshi Shizuta, MD; Natsuhiko Ehara, MD; Ryoji Taniguchi, MD; Takahiro Doi, MD; Kei Nishiyama, MD; Neiko Ozasa, MD; Naritatsu Saito, MD; Kozo Hoshino, MD; Hirokazu Mitsuoka, MD; Mitsuru Abe, MD; Masanao Toma, MD; Toshihiro Tamura, MD; Yoshisumi Haruna, MD; Yukiko Imai, MpH; Satoshi Teramukai, PhD; Masanori Fukushima, MD; Toru Kita, MD

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

From the Department of Cardiovascular of Medicine (T. Kimura, H.M., T. Kita) and the Center for Medical Education (T.M.), Graduate School of Medicine, Kyoto University; the Division of Cardiology (Y.F., S.S., T.D., N.O., N.S., M.T., T.T.), Kyoto University Hospital; the Division of Cardiology (Y.N.), Tenri Hospital; the Division of Cardiology (N.E.), Kobe City Medical Center General Hospital; the Division of Cardiology (R.T.), Hyogo Prefectural Amagasaki Hospital; Emergency Medicine (K.N.), Kyoto University Hospital the Division of Cardiology (K.H.), Nagai Hospital; the Division of Cardiology (M.A.), National Cardiovascular Center; the Division of Cardiology (Y.H.), Keihanna Hospital; Translational Research Informatics Center (Y.I.), Foundation for Biomedical Research Innovation; and the Translational Research Center (S.T., M.F.), Kyoto University Hospital, Japan.

Correspondence to Takeshi Kimura, Department of Cardiovascular of Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507 Japan. E-mail taketaka@kuhp.kyoto-u.ac.jp

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.735902**

Table 1. List of Participating Centers and Investigators

Centers	Investigators
Fukuroi Municipal Hospital	Katsuo Okazaki
Hamamatsu Rosai Hospital	Masaaki Takahashi
	Teiji Oda
Hikone Municipal Hospital	Shigeo Matsui
	Naohiro Ohashi
Himeji Medical Center	Eiichi Matsuyama
	Makoto Kadoya
Hyogo Prefectural Amagasaki Hospital	Yoshiki Takatsu
	Shinichi Nomoto
	Kazuaki Kataoka
Japanese Red Cross Society Wakayama Medical Center	Hajime Kotoura
	Masaki Aota
	Akira Miura
Juntendo University Shizuoka Hospital	Satoru Suwa
Kagoshima University Medical and Dental Hospital	Chuwa Tei
	Ryuzo Sakata
	Shuichi Hamasaki
	Hiroyuki Yamamoto
Kansai Denryoku Hospital	Takeshi Aoyama
	Takahiro Sakurai
Kishiwada City Hospital	Mitsuo Matsuda
	Masahiko Onoe
	Yuzo Takeuchi
Kitano Hospital	Ryuji Nohara
	Kimisato Nakano
Kobe City Medical Center General Hospital	Shigefumi Morioka
	Yukikatsu Okada
	Kenichi Shiratori
	Nasu Michihiro
Kokura Memorial Hospital	Masakiyo Nobuyoshi
	Hitoshi Okabayashi
	Hitoshi Yasumoto
	Jyota Nakano,
Koto Memorial Hospital	Tomoyuki Murakami
	Katsuya Ishida
Kumamoto University Hospital	Hisao Ogawa
	Michio Kawasuji,
	Seigo Sugiyama
	Shoichiro Hagiwara
Kurashiki Central Hospital	Kazuaki Mitsudo
	Tatsuhiko Komiya
	Kazushige Kadota
Kyoto University Hospital	Takeshi Kimura
	Masashi Komeda
Maizuru Kyosai Hospital	Ryozo Tatami
	Teruaki Ushijima

(Continued)

Table 1. Continued

Centers	Investigators
Mitsubishi Kyoto Hospital	Akira Yoshida
	Hiroyuki Nakajima
	Shinji Miki
Nara Hospital, Kinki University School of Medicine	Ryuichi Hattori
	Noboru Nishiwaki
	Manabu Shirotani
Nishi-Kobe Medical Center	Hiroshi Kato
	Hiroshi Eizawa
Osaka Red Cross Hospital	Masaru Tanaka
	Kazuaki Minami
Shiga University of Medical Science Hospital	Minoru Horie
	Toru Asai
	Hiroyuki Takashima
	Ryuji Higashita
Shimabara Hospital	Mamoru Takahashi
	Takafumi Tahata
	Yoshiki Matoba
Shimada Municipal Hospital	Kiyoshi Doyama
	Makoto Araki
Shizuoka City Shizuoka Hospital	Akinori Takizawa
	Mitsuomi Shimamoto
	Fumio Yamazaki
Shizuoka General Hospital	Osamu Doi
	Hirofumi Kambara
	Katsuhiko Matsuda
	Satoshi Kaburagi
	Masafumi Nara
Takanohara Central Hosipital	Masaki Kawanami
Tenri Hosipital	Takashi Konishi
	Kazunobu Nishimura
	Seiji Ootani
	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.

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

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-

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).

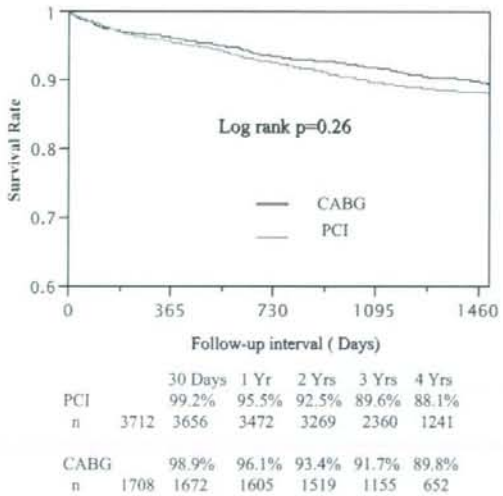


Figure 1. Unadjusted Kaplan-Meier survival curves among all patients.

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).

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).

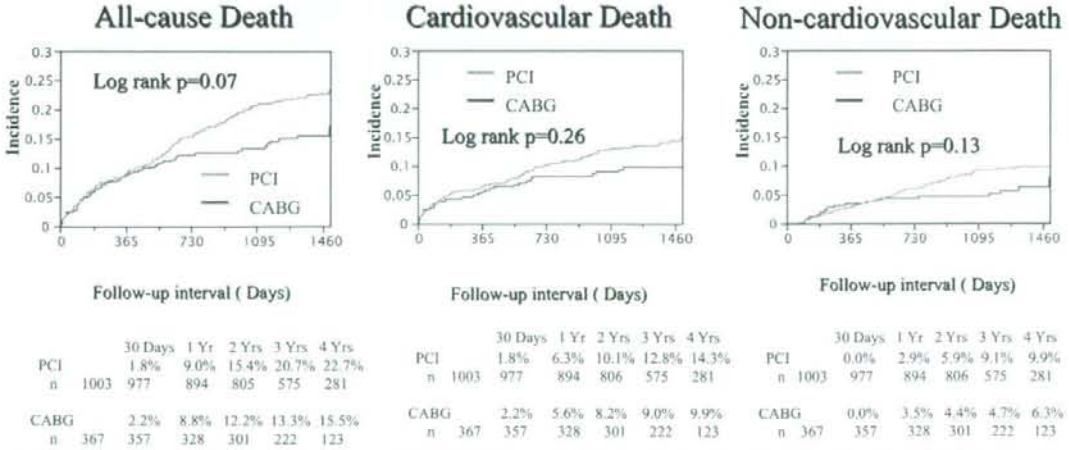
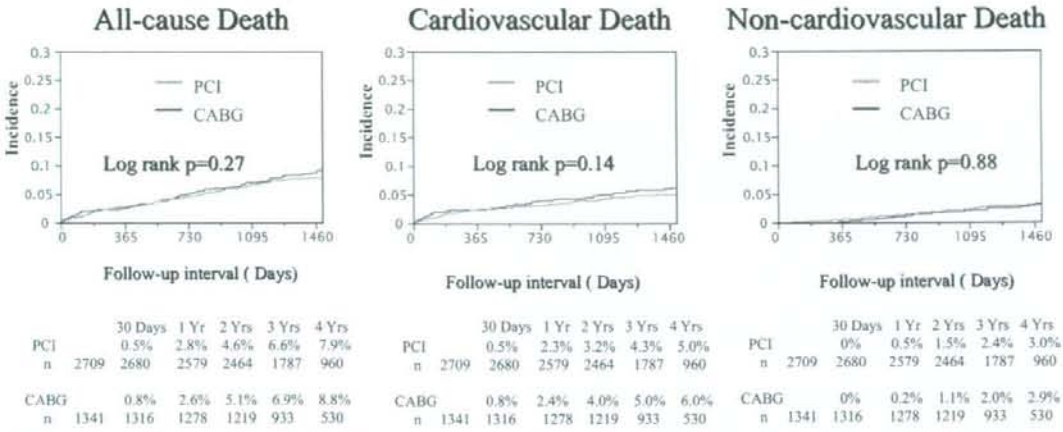


Figure 2. Cumulative incidence of all-cause death, cardiovascular death, and noncardiovascular death among patients with age ≥75.



		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).

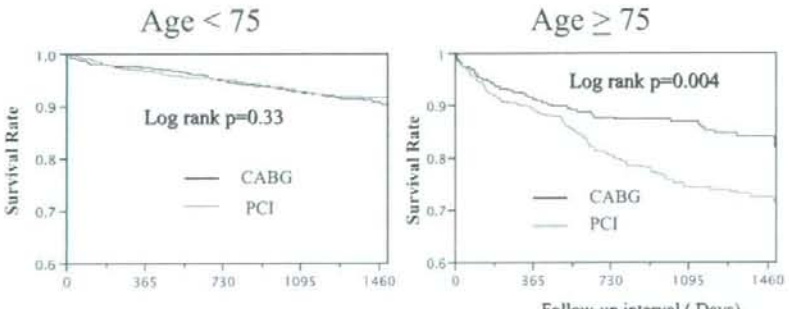
The rates of freedom from death, myocardial infarction, and stroke were similar between the 2 groups (87.8% and 86.8% in the CABG and PCI groups, respectively, at 3 years, log rank $P=0.63$).

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.

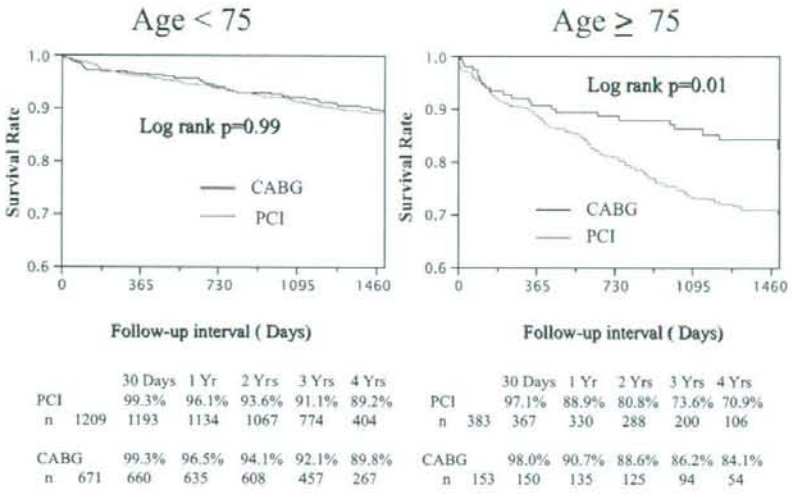
Our current analysis of CREDO-Kyoto registry data demonstrated both similar and discrepant results to those of other large-scale registries.[8,9] Although we also observed trends for better survival outcomes after CABG among overall and diabetic patient populations, in contrast to prior registries, adjusted 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.



		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.

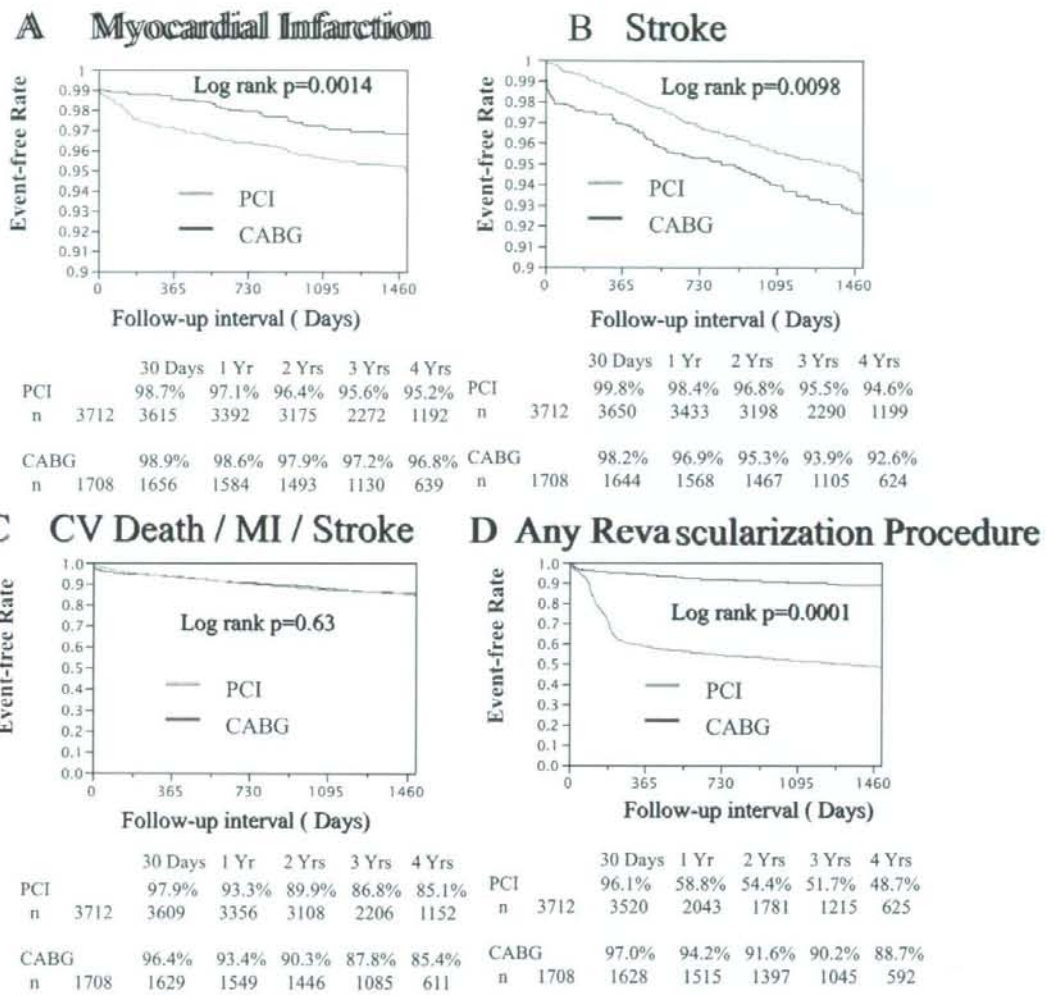
vessel disease were treated by PCI in the New York's cardiac registries and the Northern New England registry, respectively, an observation that is consistent with current guidelines that generally recommend CABG in patients with triple-vessel disease.[11,12] However, when CABG is the preferred treatment 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



		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.