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# Sex-Based Differences in Clinical Practice and Outcomes for Japanese Patients With Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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***Background:*** Limited data are available for sex-based differences in Japanese patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI).

***Methods and Results:*** The study patients comprised 1,197 women and 3,182 men who underwent primary PCI for AMI in 2005–2007. Compared with the men, the women were significantly older, and had significantly longer onset-to-balloon time and lower rate of follow-up coronary angiography. In-hospital mortality was higher among women than men (8.7% vs. 4.9%, P<0.001). Although the cumulative incidence of all-cause death at 3 years was also higher for women (17.7% vs. 10.7%, P<0.001), the adjusted risk for all-cause death was comparable [hazard ratio (HR, women vs. men)=0.94, 95% confidence interval (CI): 0.71–1.24, P=0.66]. The incidence (12.1% vs. 12.4%, P=0.77) and the adjusted risk (HR=0.99, 95% CI 0.78–1.24, P=0.92) for any clinically-driven coronary revascularization were both comparable. However, regarding any non-clinically-driven coronary revascularization, the incidence (19.6% vs. 27.8%, P<0.001) and the adjusted risk (HR=0.79, 95% CI 0.65–0.95, P=0.012) were both lower in women relative to men.

***Conclusions:*** In current Japanese clinical practice for AMI, onset-to-balloon time was significantly longer in women than in men. Female sex was associated with lower follow-up coronary angiography rate and lower incidence of any non-clinically-driven coronary revascularization, whereas the incidence of any clinically-driven coronary revascularization was comparable between the sexes. (*Circ J* 2013; **77:** 1508–1517)

**Key Words:** Acute myocardial infarction; Outcomes; Percutaneous coronary intervention; Women

Higher unadjusted risks for mortality and major complications have been demonstrated in female relative to male patients with acute myocardial infarction (AMI). However, there remains controversy with respect to sex differences in adjusted clinical outcomes.[1–4] The inconsistency in unadjusted and adjusted results of comparisons of clinical outcome between women and men has been often ascribed to women's older age, accumulated comorbidities, and less frequent application of evidence-based treatments. However, there are a few studies suggesting that female sex is an independent predictor of better long-term survival after coronary revascularization.[5–7] In addition, because the low rate of

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restenosis achieved with drug-eluting stents (DES) has enabled percutaneous coronary intervention (PCI) for lesions with smaller reference diameters, female patients benefit more from DES implantation, partly because of their smaller coronary artery diameters than in male patients.[8,9] Other factors that could cause sex-based differences in outcome include differences in prehospital case fatality,[10] access to emergency care and unawareness among women of the importance of secondary prevention for coronary artery diseases (CADs).[11,12]

The purpose of this study was to clarify sex-based differences in risk factor profiles, treatments and outcomes among Japanese patients with AMI undergoing primary PCI in the DES era.

## Methods

### Study Subjects

The Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) registry cohort-2 is a physician-initiated, non-company sponsored multicenter registry that enrolled patients from 26 centers in Japan during January 2005 to December 2007 after the approval of sirolimus-eluting stents.[13] The relevant review boards or ethics committees in all 26 participating centers (**Appendix S1**) approved the research protocol. Because of the retrospective enrollment, written informed consent from the patients was waived, although we excluded those patients who refused participation in the study when contacted for follow-up. This strategy is in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

During the 3 years of the enrollment, 5,486 patients with AMI were enrolled. After excluding 57 patients who refused study participation, and patients with malignant disease or prior PCI/CABG, and those treated with CABG, 4,379 patients were analyzed in the current study. Baseline characteristics, comorbidity, treatments, and in-hospital as well as long-term outcome measures including death, cardiovascular death, MI, stroke and any coronary revascularization procedures were compared between women and men.

### Data Collection, Definitions and Follow-up

Clinical and analytical data for the study subjects were collected from hospital charts or databases in each center by independent clinical research coordinators (**Appendix S2**). The baseline data for the patients included: age, sex, smoking habit, body mass index, systolic blood pressure on admission, heart rate on admission, and comorbidities such as hypertension, diabetes mellitus, dyslipidemia (low-density lipoprotein-cholesterol [LDL-C] ≥140 mg/dl, triglycerides [TGs] ≥150 mg/dl, high-density lipoprotein-cholesterol [HDL-C] <40 mg/dl), chronic kidney disease, high white blood cell (WBC) count ($>11\times10^9$/L),[14] anemia (blood hemoglobin level <11 g/dl), hyperglycemia on admission (blood glucose level >198 mg/dl),[15] peripheral arterial disease (PAD: patient being treated for carotid, aortic and/or other peripheral vascular diseases or scheduled for interventions), atrial fibrillation (AF), history of heart failure (HF), prior MI, prior cerebrovascular accident, Thrombolysis In Myocardial Infarction (TIMI) flow grade at initial coronary angiography (CAG), and whether the index PCI was successful or not. Diabetes was diagnosed by each physician, based on the diagnosis and classification of diabetes mellitus of the expert committee.[16] Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients,[17] and chronic kidney disease was defined as an eGFR $<30\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$. The initial perfusion status of the infarct-related artery was assessed according to the TIMI study classification.[18] Successful PCI was defined as procedural success for the culprit lesion determined by the physician without slow flow/no reflow phenomenon in the infarct-related artery, equivalent to final TIMI flow grade 3. The patients were followed up with respect to mortality for a median of 3.0 years. All deaths were confirmed by medical records or telephone interviews with the patients' families, and death was regarded as being cardiovascular in origin unless obvious non-cardiovascular causes were identified. MI was defined according to the Arterial Revascularization Therapy Study.[19] In the present study, major adverse cardiovascular events (MACE) were defined as a composite of cardiovascular death, MI and stroke. Bleeding events were evaluated with respect to intracranial bleeding, severe bleeding as defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification, and gastrointestinal bleeding.[20] CAG was not performed routinely, but left to the discretion of the attending physician. In the current analysis, follow-up CAG includes both scheduled follow-up CAG and unscheduled clinically-driven CAG. Any coronary revascularization included any PCI or CABG performed during follow-up. In this registry, clinically-driven coronary revascularizations were distinguished from non-clinically-driven revascularizations. Any clinically-driven coronary revascularizations were defined by the existence of at least one of the following: angina symptoms (chest pain at rest, AMI, unstable angina pectoris, and stable effort angina) or objective ischemia shown by a stress test.

### Statistical Analysis

Continuous variables are expressed as the mean±standard deviation, except for the time from symptom onset to admission, onset-to-balloon time, door-to-balloon time, and highest creatinine phosphokinase, expressed as the median (interquartile range). Differences in the baseline clinical characteristics and treatments between women and men were evaluated by Pearson chi-square test for categorical variables and Student's t-test for continuous variables. Cumulative incidences were estimated by the Kaplan-Meier method and differences between women and men were examined by log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HR) of sex, adjusting for baseline differences. We listed the following 46 clinically relevant factors as potential independent risk-adjusting variables for clinical outcomes: age ≥75 years; sex; body mass index $\geq 25\,kg/m^2$; hypertension; diabetes on insulin therapy; LDL-C ≥140 mg/dl; TG ≥150 mg/dl; HDL-C <40 mg/dl; current smoking; prior MI; prior stroke; history of HF; mitral regurgitation ≥grade 3; AF; dialysis; eGFR $<30\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$, not on dialysis; anemia; WBC count $>11\times10^9$/L; platelets $<100\times10^9$/L; blood glucose level >198 mg/dl; chronic obstructive pulmonary disease; liver cirrhosis; PAD; highest creatinine phosphokinase ≥3,000 IU/L; cardiogenic shock at presentation; multivessel CAD; target of left main coronary artery (LMCA); target of proximal left anterior descending artery; target of chronic total occlusion; target of bifurcation; TIMI flow grade 0 at initial CAG; successful PCI; total stent length ≥28 mm; minimal stent diameter <3.0 mm; DES use; aspirin; cilostazol; statins; angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB); $\beta$-adrenergic blockers; calcium-channel blockers; nitrates; nicorandil; warfarin; proton-pump inhibitors; and

**Table 1. Comparisons of the Baseline Characteristics of the AMI Patients by Sex**

| | Women | Men | P value |
|---|---|---|---|
| No. of patients | 1,197 | 3,182 | |
| Age (years±SD) | 74.1±10.9 | 64.5±11.7 | <0.001 |
| Age ≥75 years (%) | 624 (52.1) | 670 (21.1) | <0.001 |
| BMI (mean±SD) | 22.9±3.7 | 23.9±3.4 | <0.001 |
| BMI ≥25 kg/m² (%) | 285 (23.8) | 993 (31.2) | <0.001 |
| SBP on admission (mmHg) | 134.5±31.7 | 135.4±29.6 | 0.38 |
| Heart rate on admission (beats/min) | 77.6±20.4 | 77.7±21.7 | 0.91 |
| Hypertension (%) | 966 (81.0) | 2,442 (76.7) | 0.005 |
| Diabetes (%) | 380 (31.8) | 1,046 (32.9) | 0.48 |
| Oral hypoglycemic medication | 237 (19.8) | 619 (19.5) | 0.80 |
| Insulin use | 56 (4.7) | 129 (4.1) | 0.36 |
| No medical treatment | 104 (8.7) | 341 (10.7) | 0.048 |
| LDL-C ≥140 mg/dl (%) | 272 (27.9) | 643 (24.9) | 0.068 |
| Triglyceride ≥150 mg/dl (%) | 138 (13.1) | 578 (20.7) | <0.001 |
| HDL-C <40 mg/dl (%) | 240 (23.7) | 1,012 (37.1) | <0.001 |
| Current smoking (%) | 175 (14.6) | 1,652 (51.9) | <0.001 |
| LVEF (mean±SD) | 54.6±13.4 | 53.1±12.5 | 0.003 |
| ≤40% (%) | 153 (16.8) | 384 (15.5) | 0.36 |
| Prior MI (%) | 28 (2.3) | 106 (3.3) | 0.089 |
| Prior stroke (%) | 128 (10.7) | 270 (8.5) | 0.024 |
| Heart failure (%) | 44 (3.7) | 36 (1.1) | <0.001 |
| Mitral regurgitation ≥3 (%) | 59 (4.9) | 65 (2.0) | <0.001 |
| Atrial fibrillation (%) | 138 (11.5) | 261 (8.2) | <0.001 |
| Dialysis (%) | 22 (1.8) | 39 (1.2) | 0.12 |
| eGFR <30 ml·min⁻¹·1.73 m⁻², not on dialysis (%) | 84 (7.0) | 98 (3.1) | <0.001 |
| White blood cell count (mean±SD) | 9,493±3,480 | 10,562±3,682 | <0.001 |
| >11×10⁹/L (%) | 288 (24.8) | 1,188 (38.0) | <0.001 |
| Anemia (hemoglobin <11 g/dl) (%) | 232 (19.4) | 166 (5.2) | <0.001 |
| Platelets <100×10⁹/L (%) | 19 (1.6) | 52 (1.6) | 0.91 |
| Blood glucose level (mean±SD) | 182.4±88.4 | 176.7±88.9 | 0.059 |
| >198 mg/dl (%) | 341 (29.1) | 824 (26.4) | 0.077 |
| Chronic obstructive pulmonary disease (%) | 51 (4.3) | 90 (2.8) | 0.017 |
| Liver cirrhosis (%) | 25 (2.1) | 64 (2.0) | 0.87 |
| Peripheral arterial disease (%) | 30 (2.5) | 95 (3.0) | 0.40 |
| Time from symptom onset to admission (h)* | 4.0 (1.8–11.4) | 3.0 (1.4–9.2) | 0.016 |
| Medications before admission (%) | | | |
| Aspirin | 161 (13.5) | 402 (12.6) | 0.47 |
| Thienopyridine | 69 (5.8) | 201 (6.3) | 0.50 |
| Ticlopidine | 60 (87.0) | 187 (93.0) | 0.12 |
| Clopidogrel | 9 (13.0) | 14 (7.0) | 0.12 |
| Cilostazol | 12 (1.0) | 29 (0.9) | 0.78 |
| Statins | 220 (18.4) | 361 (11.4) | <0.001 |
| Antihypertensive drugs | 669 (69.3) | 1,274 (52.2) | <0.001 |

*Data are median (interquartile range).
AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LVEF, Left ventricular ejection fraction; MI, myocardial infarction; SD, standard deviation; SBP, systolic blood pressure.

H2 blockers. We then selected risk-adjusting variables that showed univariate P-values <0.05 as those to include simultaneously in each multivariate model. The continuous variables were dichotomized by clinically meaningful reference values. All analyses were conducted using JMP version 5 (SAS Institute Inc, Cary, NC, USA). All reported P-values are 2-sided and P<0.05 was considered to indicate statistical significance.

## Results

### Baseline Characteristics

The baseline clinical characteristics of the women and men are listed in Table 1. The women were approximately 10 years older than the men, and 52% of the female patients as compared with 21% of the men were ≥75 years of age. Compared with the men, the women more frequently had hypertension, eGFR <30 $ml\cdot min^{-1}\cdot 1.73\,m^{-2}$ and not on dialysis, prior stroke,

**Table 2. Characteristics of the Index AMI**

| | Women | Men | P value |
|---|---|---|---|
| Onset-to-balloon time (h)* | 6.1 (3.5–15.4) | 4.9 (3.1–12.6) | 0.030 |
| >180 min (%) | 860 (81.5) | 2,159 (75.8) | <0.001 |
| Door-to-balloon time (h)* | 1.7 (1.1–2.8) | 1.7 (1.1–2.5) | 0.80 |
| >90 min (%) | 579 (55.9) | 1,503 (53.9) | 0.27 |
| Highest creatinine phosphokinase (IU/L)* | 1,531 (695–3,173) | 2,230 (999–4,212) | <0.001 |
| >3,000 IU/L (%) | 311 (26.3) | 1,196 (38.0) | <0.001 |
| Killip class ≥3 (%) | 230 (19.2) | 464 (14.6) | <0.001 |
| Cardiogenic shock at presentation (%) | 197 (16.5) | 410 (12.9) | 0.002 |
| Cardiopulmonary arrest at presentation (%) | 29 (2.4) | 108 (3.4) | 0.100 |
| Use of intra-aortic balloon counter pulsation (%) | 161 (13.5) | 495 (15.6) | 0.082 |
| Use of percutaneous cardiopulmonary support (%) | 24 (2.0) | 95 (3.0) | 0.075 |
| Infarcted region (%) | | | |
| Anterior wall | 537 (44.9) | 1,503 (47.2) | 0.26 |
| Inferior wall | 453 (37.8) | 1,138 (35.8) | |
| Lateral wall | 57 (4.8) | 123 (3.9) | |
| Posterior wall | 150 (12.5) | 418 (13.1) | |
| TIMI flow grade 0 at initial CAG (%) | 666 (55.6) | 1,790 (56.3) | 0.71 |
| Successful PCI (%) | 1,054 (88.1) | 2,862 (89.9) | 0.070 |
| Major complications (%) | | | |
| Severe arrhythmia | 189 (15.8) | 567 (17.8) | 0.11 |
| Ventricular tachycardia | 93 (7.8) | 317 (10.0) | 0.026 |
| Ventricular fibrillation | 55 (4.6) | 200 (6.3) | 0.033 |
| Complete atrioventricular block | 65 (5.4) | 163 (5.1) | 0.68 |
| Other arrhythmia | 15 (1.3) | 26 (0.8) | 0.18 |
| Right ventricular infarction | 24 (2.0) | 53 (1.7) | 0.45 |
| Cardiac tamponade | 14 (1.2) | 14 (0.44) | 0.007 |
| Cardiac rupture | 20 (1.7) | 7 (0.22) | <0.001 |
| Mitral regurgitation grade ≥3 | 8 (0.67) | 11 (0.35) | 0.15 |
| Ventricular septal perforation | 5 (0.42) | 1 (0.03) | 0.002 |

*Data are median (interquartile range).
AMI, acute myocardial infarction; CAG, coronary angiography; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

history of HF, AF, and anemia, whereas higher prevalences of body mass index ≥25 kg/m$^2$, untreated diabetes, TG ≥150 mg/dl, HDL-C <40 mg/dl, current smoking status and WBC count >11×10$^9$/L were seen in the men. There were no significant differences in the prevalences of diabetes, diabetes on insulin therapy, diabetes on oral hypoglycemic medication, LDL-C ≥140 mg/dl, prior MI, hemodialysis, and PAD between the women and men. The time from symptom onset to admission was significantly longer in the women than in the men.

## Characteristics of Index MI

The characteristics of the index MI are shown in Table 2. The median time from the onset of MI to balloon was significantly longer in the women than in the men (6.1 vs. 4.9 h), but the door-to-balloon time was comparable. Distribution of infarct location was comparable between the sexes, although the men had larger infarcts estimated by highest creatinine phosphokinase level: median highest creatinine phosphokinase was 1,531 IU/L for the women and 2,230 IU/L for the men. The female patients were more likely to be in a higher Killip class at admission, and had a higher prevalence of cardiogenic shock than the male patients. However, frequency of the use of intra-aortic balloon pumping or percutaneous cardiopulmonary support device was not different by sex. The rates of patients with TIMI flow grade 0 at initial CAG and those with successful PCI were comparable between sexes. The severe acute complications of AMI, such as cardiac tamponade, cardiac rupture, and ventricular septal perforation, occurred more frequently in the women than in the men, although the prevalence of ventricular tachycardia and ventricular fibrillation was lower in the women. The prevalences of complete atrioventricular block, right ventricular infarction, and severe mitral regurgitation were comparable.

## Lesion Characteristics and Treatments

Comparisons of the lesion characteristics and of treatments during hospitalization between the women and men are shown in Table 3. There were no significant differences in the rates of multivessel disease, unprotected LMCA, and chronic total occlusion between the women and men. Regarding the diseased vessel, it was less commonly the proximal left anterior descending artery in the women than in the men.

The rate of using a stent was lower in the women than in the men (89.3% vs. 92.3%, P=0.002) and the difference arose from the significantly lower rate of use of bare metal stents (BMS) in the women than in the men (68.4% vs. 73.9%, P<0.001); the rate of DES use was comparable between the women and men. The success rate of stent implantation was very high in both the women and the men, although the BMS implantation success rate was slightly lower in the women than in the men

| Table 3. Lesion Characteristics, Revascularization Procedures, and Medications | Women | Men | P value |
|---|---|---|---|
| **Lesion characteristics (%)** | | | |
| Multivessel disease | 615 (51.4) | 1,609 (50.6) | 0.63 |
| Unprotected left main coronary artery | 48 (4.0) | 143 (4.5) | 0.48 |
| Chronic total occlusion | 113 (9.4) | 347 (10.9) | 0.16 |
| **Revascularization procedures (%)** | | | |
| Target of left anterior descending artery | 669 (55.9) | 1,852 (58.2) | 0.17 |
| Target of left main coronary artery | 32 (2.7) | 122 (3.8) | 0.063 |
| Target of proximal left anterior descending artery | 622 (52.0) | 1,761 (55.3) | 0.045 |
| Target of chronic total occlusion | 28 (2.3) | 128 (4.0) | 0.007 |
| Target of bifurcation | 317 (26.5) | 871 (27.4) | 0.56 |
| Stent use | 1,069 (89.3) | 2,936 (92.3) | 0.002 |
| BMS (%) | 819 (68.4) | 2,350 (73.9) | <0.001 |
| BMS only | 691 (64.9) | 1,980 (67.5) | 0.13 |
| DES | 374 (35.1) | 955 (32.5) | 0.13 |
| SES only | 223 (24.4) | 540 (21.4) | 0.064 |
| Stent deployment success (%) | 1,065 (99.6) | 2,935 (100) | 0.01 |
| BMS | 815 (99.5) | 2,348 (99.9) | 0.022 |
| SES | 339 (99.7) | 887 (99.9) | 0.48 |
| Side-branch stenting (%) | 37 (3.1) | 105 (3.3) | 0.73 |
| No. of implanted stents (mean±SD) | 1.73±0.03 | 1.72±0.02 | 0.81 |
| Total stent length (mm; mean±SD) | 35.4±0.47 | 36.1±0.79 | 0.46 |
| >28 mm (%) | 457 (42.9) | 1,289 (43.9) | 0.57 |
| Minimal stent diameter (mm; mean±SD) | 2.91±0.01 | 3.04±0.008 | <0.001 |
| <3.0 mm (%) | 465 (43.7) | 945 (32.2) | <0.001 |
| **Medications at discharge (%)** | | | |
| Aspirin | 1,175 (98.2) | 3,142 (98.7) | 0.15 |
| Thienopyridine | 1,127 (94.2) | 3,063 (96.3) | 0.002 |
| Ticlopidine | 1,016 (90.2) | 2,798 (91.4) | 0.42 |
| Clopidogrel | 109 (9.7) | 262 (8.6) | 0.42 |
| Other thienopyridine | 2 (0.18) | 3 (0.1) | 0.42 |
| Cilostazol | 383 (32.0) | 1,131 (35.5) | 0.029 |
| Statins | 624 (52.1) | 1,724 (54.2) | 0.23 |
| ACEI/ARB | 830 (69.3) | 2,321 (72.9) | 0.018 |
| $\beta$-adrenergic blocker | 416 (34.8) | 1,334 (41.9) | <0.001 |
| Calcium-channel blocker | 265 (22.1) | 615 (19.3) | 0.039 |
| Nitrates | 376 (31.4) | 909 (28.6) | 0.065 |
| Nicorandil | 294 (24.6) | 915 (28.8) | 0.006 |
| Warfarin | 121 (10.1) | 319 (10.0) | 0.93 |
| Proton-pump inhibitor | 441 (36.8) | 1,058 (33.3) | 0.026 |
| H2 blocker | 373 (31.2) | 1,075 (33.8) | 0.10 |
| **Follow-up CAG (%)** | 689 (64.2) | 2,364 (78.9) | <0.001 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMS, bare metal stent; CAG, coronary angiography; DES, drug-eluting stent; SES, sirolimus-eluting stent; SD, standard deviation.

(99.5% vs. 99.9%, P=0.022).

With respect to the medications at discharge, there were no significant differences between the women and men in the proportions of patients treated with aspirin (98.2% vs. 98.7%), statins (52.1% vs. 54.2%), nitrates (31.4% vs. 28.6%), and H2-blockers (31.2% vs. 33.8%). Cardioprotective drugs such as ACEI/ARB (69.3% vs. 72.9%, P=0.018) and $\beta$-adrenergic blockers (34.8% vs. 41.9%, P=0.001) were less frequently prescribed to women than to men, while calcium-channel blockers (22.1% vs. 19.3%, P=0.039) and proton-pump inhibitors (36.8% vs. 33.3%, P=0.026) were more frequently prescribed to women.

The rate of follow-up CAG was significantly lower in the women than in the men (64.2% vs. 78.9%, P<0.001).

## In-Hospital Mortality and Long-Term Clinical Outcomes

The in-hospital mortality rate was significantly higher in the women than in the men (8.7% vs. 4.9%, P<0.001) (Table 4). At 3 years, female sex was associated with significantly higher unadjusted incidences of all-cause death (17.7% vs. 10.7%, P<0.001), cardiovascular death (14.4% vs. 7.8%, P<0.001), and MACE (21.0% vs. 13.9%, P<0.001) (Figure 1). Detailed analyses of the causes of death revealed that female sex was associated with higher unadjusted incidences of death by acute coronary syndrome (9.7% vs. 5.2%, P<0.001) and non-cardiac death (4.8% vs. 3.3%, P=0.019) relative to male sex. The in-

Table 4. Crude In-Hospital Mortality and Long-Term Outcomes for Women and Men Undergoing PCI for AMI

| | Women | Men | P value |
|---|---|---|---|
| **In-hospital outcome (%)** | | | |
| All-cause death | 104 (8.7) | 155 (4.9) | <0.001 |
| MACE | 135 (11.3) | 220 (6.9) | <0.001 |
| Bleeding (%) | | | |
| Intracranial bleeding | 4 (0.3) | 5 (0.2) | 0.25 |
| GUSTO severe | 34 (2.8) | 59 (1.9) | 0.044 |
| *Gastrointestinal bleeding* | 16 (1.3) | 31 (1.0) | 0.30 |
| **Long-term outcome (%)** | | | |
| All-cause death | 192 (17.7) | 313 (10.7) | <0.001 |
| Cardiovascular death | 159 (14.4) | 238 (7.8) | <0.001 |
| Death by ACS | 113 (9.7) | 163 (5.2) | <0.001 |
| Non-cardiac death | 41 (4.8) | 82 (3.3) | 0.019 |
| Sudden death | 8 (1.0) | 33 (1.2) | 0.22 |
| MACE | 233 (21.0) | 414 (13.9) | <0.001 |
| Bleeding | | | |
| Intracranial bleeding | 18 (1.9) | 26 (1.1) | 0.11 |
| GUSTO severe | 51 (4.7) | 100 (3.6) | 0.11 |
| Gastrointestinal bleeding | 31 (3.1) | 70 (2.5) | 0.32 |
| Coronary revascularization | | | |
| Any | 294 (29.3) | 1,039 (36.7) | <0.001 |
| TLR | 199 (19.7) | 678 (23.6) | 0.033 |
| Non-TLR | 162 (16.8) | 574 (20.9) | 0.012 |
| Clinically-driven revascularization | | | |
| Any | 108 (12.1) | 293 (12.4) | 0.77 |
| TLR | 70 (7.3) | 196 (7.5) | 0.79 |
| Non-TLR | 59 (6.6) | 157 (6.6) | 0.77 |
| Non-clinically-driven revascularization | | | |
| Any | 186 (19.6) | 746 (27.8) | <0.001 |
| TLR | 129 (13.4) | 482 (17.4) | 0.006 |
| Non-TLR | 103 (10.9) | 417 (15.3) | 0.001 |

MACE was defined as a composite of cardiovascular death, MI and stroke.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

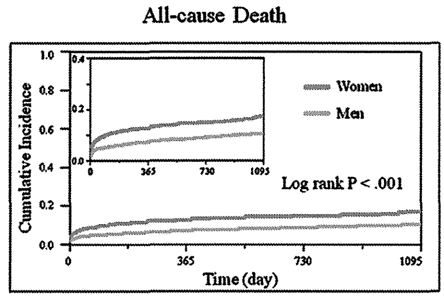
cidence of sudden death was comparable between the women and the men (Table 4). The multivariate Cox proportional hazards models indicated no significant differences between women and men in the long-term adjusted risks of all-cause death [HR 0.94; 95% confidence interval (CI) 0.71–1.24], cardiovascular death (HR 1.06; 95% CI 0.77–1.47), and MACE (HR 1.06; 95% CI 0.83–1.34). The factors that showed a significant effect on long-term all-cause mortality in our analyses included age ≥75 years, LDL-C ≥140 mg/dl, HDL-C <40 mg/dl, AF, dialysis, eGFR <30 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ and not on dialysis, WBC count >$11\times10^9$/L, platelets <$100\times10^9$/L, blood glucose level >198 mg/dl, history of PAD, highest creatinine phosphokinase ≥3,000 IU/L, cardiogenic shock on admission, and multivessel coronary disease (Table S1). The in-hospital incidences of intracranial bleeding and gastrointestinal bleeding were comparable between the women and the men; however, GUSTO severe bleeding occurred more frequently in the women (2.8% vs. 1.8%, P=0.044). The long-term incidences of intracranial, gastrointestinal, and GUSTO severe bleeding at 3 years were all comparable between the sexes (Table 4).

## Coronary Revascularization During Follow-up

The incidence of any coronary revascularization was significantly lower in the women than in the men (at 3 years: 29.3% vs. 36.7%, log-rank P<0.001; Figure 2). There was no significant difference in the incidence of any clinically-driven coronary revascularization, and the difference in the incidence of any coronary revascularization was derived from the difference in the incidence of any non-clinically-driven coronary revascularization (at 3 years: 19.6% in the women vs. 27.8% in the men, P<0.001). The significantly lower incidence of the any non-clinically-driven coronary revascularization in the women was seen both in the setting of target lesion revascularization (TLR) (at 3 years: 13.4% vs. 17.4%, P=0.006) and in non-TLR (at 3 years: 10.9% vs. 15.3%, P=0.001) (Table 4).

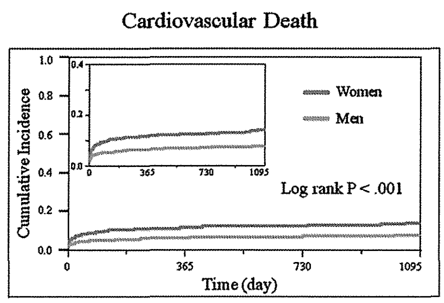
In a multivariate Cox proportional hazards model in all patients, female sex was associated with significantly lower incidence of any coronary revascularization (HR 0.83; 95% CI 0.72–0.96, P=0.010). Other factors that had a significant effect on the incidence of any coronary revascularization were dialysis, multivessel disease, target of unprotected LMCA, total stent length ≥28 mm, and minimal stent diameter <3.0 mm (Table S2). Female sex also had significant effect on the incidence of any non-clinically-driven coronary revascularization (HR 0.79; 95% CI 0.65–0.95, P=0.012), although in the analysis of any clinically-driven coronary revascularization, the

**A**



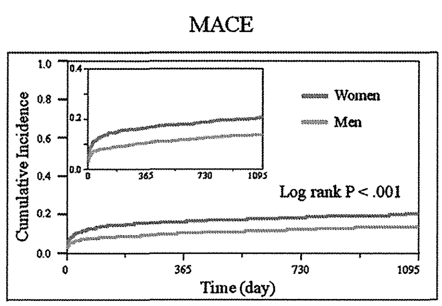

| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 7.6% | 13.0% | 15.0% | 17.7% |
| N of events | | 91 | 153 | 175 | 192 |
| N of patients at risk | 1197 | 1092 | 978 | 765 | 416 |
| **Men** | | | | | |
| Incidence | | 4.3% | 7.6% | 9.3% | 10.7% |
| N of events | | 137 | 238 | 286 | 313 |
| N of patients at risk | 3182 | 3005 | 2817 | 2223 | 1213 |

**B**




| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 7.6% | 11.7% | 12.6% | 14.4% |
| N of events | | 91 | 138 | 148 | 159 |
| N of patients at risk | 1197 | 1092 | 978 | 765 | 416 |
| **Men** | | | | | |
| Incidence | | 4.3% | 6.6% | 7.3% | 7.8% |
| N of events | | 137 | 207 | 227 | 238 |
| N of patients at risk | 3182 | 3005 | 2817 | 2223 | 1213 |

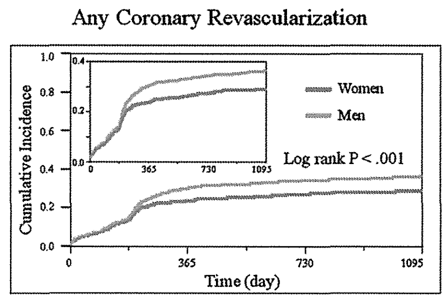
**C**




| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 10.6% | 16.5% | 18.8% | 21.0% |
| N of events | | 126 | 195 | 218 | 233 |
| N of patients at risk | 1197 | 1058 | 930 | 716 | 392 |
| **Men** | | | | | |
| Incidence | | 6.8% | 10.7% | 12.4% | 13.9% |
| N of events | | 215 | 336 | 385 | 414 |
| N of patients at risk | 3182 | 2928 | 2697 | 2100 | 1140 |

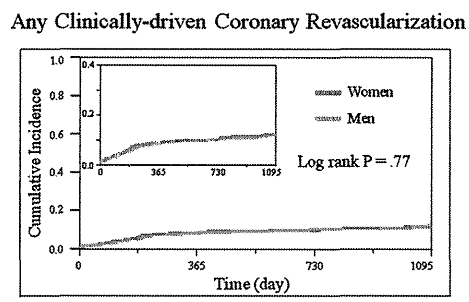
**Figure 1.** Cumulative incidences of (**A**) all-cause death, (**B**) cardiovascular death, and (**C**) major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction and stroke were all significantly higher in the women than in the men who underwent primary percutaneous coronary intervention for acute myocardial infarction.

**A**



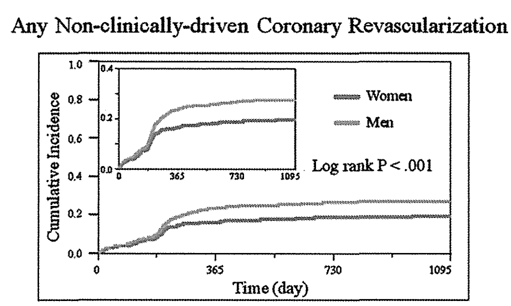

| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 4.7% | 23.9% | 27.4% | 29.3% |
| N of events | | 54 | 250 | 282 | 294 |
| N of patients at risk | 1197 | 1043 | 745 | 547 | 290 |
| **Men** | | | | | |
| Incidence | | 5.1% | 30.5% | 34.6% | 36.7% |
| N of events | | 159 | 895 | 1003 | 1039 |
| N of patients at risk | 3182 | 2856 | 1960 | 1466 | 777 |

**B**




| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 2.0% | 8.9% | 10.3% | 12.1% |
| N of events | | 23 | 88 | 99 | 108 |
| N of patients at risk | 1197 | 1043 | 745 | 547 | 290 |
| **Men** | | | | | |
| Incidence | | 2.2% | 8.8% | 10.6% | 12.4% |
| N of events | | 68 | 238 | 273 | 293 |
| N of patients at risk | 3182 | 2856 | 1960 | 1466 | 777 |

**C**




| Interval | 0 day | 30 days | 1 year | 2 years | 3 years |
|---|---|---|---|---|---|
| **Women** | | | | | |
| Incidence | | 2.8% | 16.5% | 19.0% | 19.6% |
| N of events | | 31 | 162 | 183 | 186 |
| N of patients at risk | 1197 | 1043 | 745 | 547 | 290 |
| **Men** | | | | | |
| Incidence | | 3.0% | 23.8% | 26.8% | 27.8% |
| N of events | | 91 | 657 | 730 | 746 |
| N of patients at risk | 3182 | 2856 | 1960 | 1466 | 777 |

**Figure 2.** Cumulative incidences of (**A**) any coronary revascularization, (**B**) any clinically-driven coronary revascularization and (**C**) any non-clinically-driven coronary revascularization were all significantly lower in the women than in the men who underwent primary percutaneous coronary intervention for acute myocardial infarction.

risks were similar between the women and men (Table S3).

## Discussion

The main findings of the present study are as follows: (1) coronary risk factor profiles differed between female and male Japanese AMI patients undergoing primary PCI in the DES era: the prevalence of older age, hypertension and chronic kidney disease were significantly higher in the women, whereas obesity, high TG and low HDL-C levels, and current smoking were more prevalent in the men; (2) significant differences in patient treatment/management: the onset-to-balloon time was longer and the incidence of non-clinically-driven coronary revascularization was lower in women than in men; (3) unadjusted incidences of all-cause death, cardiovascular death, and MACE were all higher in the women, whereas these outcome measures became comparable between the women and the men after adjustment.

### Differences in Baseline Characteristics Between Female and Male Patients

In our previous study that analyzed the differences in risk factor profiles between female and male Japanese patients with CAD, excluding AMI, the prevalences of diabetes and high LDL-C level were significantly higher in the women than in the men, whereas the prevalence of obesity was comparable.[21] However, in the present study of Japanese AMI patients, the prevalence of obesity was significantly higher in the men than in the women, and the prevalences of diabetes and high LDL-C level were comparable. Because the prevalences of obesity and metabolic syndrome are higher in young AMI patients, particularly young male patients, than in stable CAD patients, our study's distinctive sex-based differences in the risk factor profiles of AMI and stable CAD patients may be concordant with the results of previous studies.[1–4,22–27] Greater difference in age between the two sexes among the AMI patients (approximately 10 years) than in the more stable CAD patients (approximately 5 years) may partly account for this observation.

Despite such differences in the risk factor profiles, no significant differences were found between the two sexes in the severity of CAD assessed as multivessel disease, unprotected LMCA and chronic total occlusion.

### Characteristics Related to MI and Revascularization Procedures, and In-Hospital Mortality

It is still uncertain how sex itself affects the in-hospital outcome of AMI patients. As shown in this study, higher age and higher prevalence of chronic kidney disease were frequently found in the female AMI patients, which could be related to higher in-hospital mortality. In the current study analyzing a recent AMI cohort treated by primary PCI, in-hospital mortality was higher among the women than the men, which is in accordance with a previous study showing higher in-hospital mortality despite lower peak creatinine phosphokinase levels in Japanese female patients with ST-elevation MI (STEMI).[26] Thus, in-hospital mortality was still higher among the women in a more recent cohort with more frequent use of cardioprotective agents and higher success rate of PCI.[26–28] Contrary to this, including the current study, a population-based study of 201,114 people in Scotland showed that the 30-day case fatality rate was lower in women than in men, when deaths from AMI that occur without hospital admission were taken into consideration.[10] Because the current study could not assess prehospital information, our results should be carefully interpreted.

When the timing of revascularization therapy was compared, onset-to-balloon time was significantly longer in the women than in the men, whereas door-to-balloon time was comparable between the sexes. Namely, there was a longer time from onset to presentation at hospital for women. Several previous reports have also demonstrated more frequent time delay to treatment in female AMI patients relative to male. The possible reasons for this sex-related difference include a higher prevalence of atypical symptoms in female AMI patients.[26,29,30] Although the time to primary PCI could be associated with the incidence of in-hospital mortality, the relative importance of onset-to-balloon time and of door-to-balloon time has not been clarified.[31,32]

Previous studies performed outside Japan have suggested that less intensive treatment for women than for men might be a possible explanation for the higher mortality rate among female AMI patients.[25,33] However, in our study there were no significant procedural differences between the women and men in the treatment of AMI, such as in the numbers of stents used. Thus, it is unlikely that procedural differences in the index PCI resulted in the worse in-hospital outcomes in the women.

### Sex-Based Differences in Long-Term Outcomes

Unadjusted survival analyses revealed significantly higher incidences among the female AMI patients with respect to all-cause death, cardiovascular death, and MACE during long-term follow-up, which was in sharp contrast to our previous observation in Japanese stable CAD patients suggesting comparable outcomes for these endpoints.[21] After adjustment for possible confounding factors, risks for mortality and MACE became comparable between the female and male AMI patients after primary PCI. This is also a distinctive finding compared with the result that the adjusted risk for mortality was significantly lower among female than male Japanese patients with stable CAD.[21] The Kaplan-Meier curves indicate sex-based differences in all-cause and cardiovascular deaths, and in MACE, which derives from the higher rate of early mortality among the women. Thus, poorer early outcomes for women after AMI appear to account for the distinctive sex-based differences in long-term outcome. There were also several differences between the women and men that might have also affected the long-term outcomes. Consistent with previous observations, evidence-based medications for patients after MI such as ACEI/ARB and $\beta$-adrenergic blockers were less frequently prescribed for female patients as compared with male patients.[1,11,12] The higher age of the women analyzed in the present study may have affected the prescribing of ACEI/ARB and $\beta$-adrenergic blockers, but better evidence-based medical treatment may be needed to improve the long-term outcome for female AMI patients. The difference in the timing of primary PCI might also affect the long-term outcome according to sex. We have recently shown that shorter onset-to-balloon time was associated with better long-term clinical outcomes in Japanese patients with STEMI.[34] The significantly longer onset-to-balloon time seen in female patients could lead to deterioration in the outcome for female AMI patients.

The risk for any coronary revascularization was lower in the women than in the men, which was a consistent observation with our previous study in stable CAD patients in the BMS era.[21] In the Kaplan-Meier analyses comparing any clinically-driven and any non-clinically-driven coronary revascularization, TLR and non-TLR between the sexes clearly showed that the difference in the risk for any coronary revascularization was caused by the significantly lower incidences of both non-clinically-driven TLR and non-clinically-driven non-TLR in the women. The differences remained significant after adjustment by Cox proportional hazards model. The significantly lower rate of follow-up CAG in the women could account for the lower incidence of non-clinically-driven coronary revascularization based on the angiographic findings at follow-up CAG. Indeed, the divergence in Kaplan-Meier curves for any coronary revascularization and for any non-clinically-driven coronary revascularization appeared at the timing of routine follow-up CAG in this study. It has been previously shown that routine follow-up CAG significantly increases the incidence of any non-clinically-driven coronary revascularization.[35–37] Atypical symptoms, difficulty in identifying myocardial ischemia, less willingness to undergo invasive investigations, and physician-based prejudices about female patients could contribute to the lower rate of follow-up CAG in the women.[38–41] In addition, although the rate of DES use in the current cohort was relatively low, the use of DES might have enhanced the lower risk of any coronary revascularization in the women that was also shown in the cohort in the BMS era.[21] A recent study showed that DES can be used safely and will effectively reduce restenosis and repeat coronary revascularization after PCI.[42] Because women have coronary arteries with smaller diameters and thus a potentially high risk of restenosis, female patients may benefit more than the men from the use of DES.

### Study Limitations

Several limitations must be noted in addition to the limitations that are common to all observational studies caused by differences in the patients' background characteristics. Data for blood tests, smoking habit and medical therapies were only assessed at 1 time point. Therefore, lifestyle modifications after hospitalization and adherence to medical therapies were not considered in the analyses. For instance, the incidence of current smoker was remarkably higher in the men relative to the women, but the rate and effect of discontinuation of smoking were not taken into consideration in the current study. Our database did not include detailed information of patients' clinical histories such as the presence of pre-infarction angina, which might affect patients' in-hospital, as well as long-term, outcomes. In this observational study, indications for revascularization therapies were not defined but depended on the decision of each attending physician. Therefore, a sex-based selection bias might exist in the indication of treatment strategies.

## Conclusions

This observational study revealed sex-related differences in the management of Japanese AMI patients, such as longer onset-to-balloon time and lower follow-up CAG rate among women. Unadjusted long-term clinical outcomes were worse in female than in male patients, but became comparable after adjustment. A lower incidence of non-clinically-driven coronary revascularization might account for the lower risk for any coronary revascularization in the women. The use of cardioprotective drugs, including ACEI/ARB and $\beta$-adrenergic blockers, was less prevalent among the women than the men, and better evidence-based medications may be needed to further improve the outcomes of female AMI patients after primary PCI.

### Acknowledgments

We are grateful for the efforts of the investigators in the 26 participating centers and the clinical research coordinators supporting the study (Appendix S1,S2).

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## References

1. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, et al. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study [Israeli Thrombolytic Survey Group]. *Circulation* 2000; **102:** 2484–2490.
2. Vakili BA, Kaplan RC, Brown DL. Sex-based differences in early mortality of patients undergoing primary angioplasty for first acute myocardial infarction. *Circulation* 2001; **104:** 3034–3038.
3. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, et al. Sex differences in early mortality of patients undergoing primary stenting for acute myocardial infarction. *Circ J* 2006; **70:** 217–221.
4. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: Microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007; **115:** 833–839.
5. Mehilli J, Kastrati A, Bollwein H, Dibra A, Schuhlen H, Dirschinger J, et al. Gender and restenosis after coronary artery stenting. *Eur Heart J* 2003; **24:** 1523–1530.
6. Berger JS, Sanborn TA, Sherman W, Brown DL. Influence of sex on in-hospital outcomes and long-term survival after contemporary percutaneous coronary intervention. *Am Heart J* 2006; **151:** 1026–1031.
7. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, et al. Better outcome for women compared with men undergoing coronary revascularization: A report from the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1998; **98:** 1279–1285.
8. Mehilli J, Ndrepepa G, Kastrati A, Nekolla SG, Markwardt C, Bollwein H, et al. Gender and myocardial salvage after reperfusion treatment in acute myocardial infarction. *J Am Coll Cardiol* 2005; **45:** 828–831.
9. Kornowski R, Vaknin-Assa H, Assali A, Lev EI, Porter A, Battler A, et al. A comparative analysis of major clinical outcomes with drug-eluting stents versus bare metal stents in male versus female patients. *EuroIntervention* 2011; **7:** 1051–1059.
10. MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, et al. Gender and survival: A population-based study of 201,114 men and women following a first acute myocardial infarction. *J Am Coll Cardiol* 2001; **38:** 729–735.
11. Rathore SS, Berger AK, Weinfurt KP, Feinleib M, Oetgen WJ, Gersh BJ, et al. Race, sex, poverty, and the medical treatment of acute myocardial infarction in the elderly. *Circulation* 2000; **102:** 642–648.
12. Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol* 2005; **46:** 1845–1851.
13. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, et al. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther* 2011; **26:** 234–245.
14. Palmerini T, Mehran R, Dangas G, Nikolsky E, Witzenbichler B, Guagliumi G, et al. Impact of leukocyte count on mortality and bleeding in patients with myocardial infarction undergoing primary percutaneous coronary interventions: Analysis from the harmonizing outcome with revascularization and stent in acute myocardial infarction trial. *Circulation* 2011; **123:** 2829–2837, 2827 p following 2837.
15. Ishihara M. Acute hyperglycemia in patients with acute myocardial infarction. *Circ J* 2012; **76:** 563–571.
16. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; **26**(Suppl 1)**:** S5–S20.
17. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, et al. Modification of the modification of diet in renal disease (MDRD) study equation for Japan. *Am J Kidney Dis* 2007; **50:** 927–937.
18. TIMI study group. The Thrombolysis In Myocardial Infarction (TIMI) trial: Phase I findings. *N Engl J Med* 1985; **312:** 932–936.
19. Serruys PW, Ong ATL, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: The final analysis of the Arterial Revascularization Therapies Study (ARTS) Randomized Trial. *J Am Coll Cardiol* 2005; **46:** 575–581.
20. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction.

*N Engl J Med* 1993; **329:** 673–682.
21. Funakoshi S, Furukawa Y, Ehara N, Morimoto T, Kaji S, Yamamuro A, et al. Clinical characteristics and outcomes of Japanese women undergoing coronary revascularization therapy. *Circ J* 2011; **75:** 1358–1367.
22. Furukawa Y, Ehara N, Taniguchi R, Haruna Y, Ozasa N, Saito N, et al. Coronary risk factor profile and prognostic factors for young Japanese patients undergoing coronary revascularization. *Circ J* 2009; **73:** 1459–1465.
23. Marrugat J, Gil M, Masia R, Sala J, Elosua R, Anto JM. Role of age and sex in short-term and long term mortality after a first Q wave myocardial infarction. *J Epidemiol Community Health* 2001; **55:** 487–493.
24. Wong SC, Sleeper LA, Monrad ES, Menegus MA, Palazzo A, Dzavik V, et al. Absence of gender differences in clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction: A report from the SHOCK trial registry. *J Am Coll Cardiol* 2001; **38:** 1395–1401.
25. Kostis JB, Wilson AC, O'Dowd K, Gregory P, Chelton S, Cosgrove NM, et al. Sex differences in the management and long-term outcome of acute myocardial infarction: A statewide study: MIDAS study group: Myocardial Infarction Data Acquisition System. *Circulation* 1994; **90:** 1715–1730.
26. Kosuge M, Kimura K, Ishikawa T, Ebina T, Hibi K, Tsukahara K, et al. Differences between men and women in terms of clinical features of ST-segment elevation acute myocardial infarction. *Circ J* 2006; **70:** 222–226.
27. Park JS, Kim YJ, Shin DG, Jeong MH, Ahn YK, Chung WS, et al. Gender differences in clinical features and in-hospital outcomes in ST-segment elevation acute myocardial infarction: From the Korean Acute Myocardial Infarction Registry (KAMIR) study. *Clin Cardiol* 2010; **33:** E1–E6.
28. Carrabba N, Santoro GM, Balzi D, Barchielli A, Marchionni N, Fabiani P, et al. In-hospital management and outcome in women with acute myocardial infarction (data from the AMI-Florence Registry). *Am J Cardiol* 2004; **94:** 1118–1123.
29. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *Eur Heart J* 2011; **32:** 3107–3114.
30. Kirchberger I, Heier M, Kuch B, Wende R, Meisinger C. Sex differences in patient-reported symptoms associated with myocardial infarction (from the population-based MONICA/KORA Myocardial Infarction Registry). *Am J Cardiol* 2011; **107:** 1585–1589.
31. De Luca G, Suryapranata H, Zijlstra F, van't Hof AW, Hoorntje JC, Gosselink AT, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003; **42:** 991–997.
32. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000; **283:** 2941–2947.
33. Hanratty B, Lawlor DA, Robinson MB, Sapsford RJ, Greenwood D, Hall A. Sex differences in risk factors, treatment and mortality after acute myocardial infarction: An observational study. *J Epidemiol Community Health* 2000; **54:** 912–916.
34. Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, et al. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: Observational study. *BMJ* 2012; **344:** e3257.
35. Ruygrok PN, Melkert R, Morel MA, Ormiston JA, Bar FW, Fernandez-Aviles F, et al. Does angiography six months after coronary intervention influence management and outcome? Benestent II investigators. *J Am Coll Cardiol* 1999; **34:** 1507–1511.
36. Pinto DS, Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, et al. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: Results from the TAXUS-IV trial. *J Am Coll Cardiol* 2006; **48:** 32–36.
37. Uchida T, Popma J, Stone GW, Ellis SG, Turco MA, Ormiston JA, et al. The clinical impact of routine angiographic follow-up in randomized trials of drug-eluting stents: A critical assessment of "oculostenotic" reintervention in patients with intermediate lesions. *JACC Cardiovasc Interv* 2010; **3:** 403–411.
38. Philpott S, Boynton PM, Feder G, Hemingway H. Gender differences in descriptions of angina symptoms and health problems immediately prior to angiography: The ACRE study: Appropriateness of Coronary Revascularisation study. *Soc Sci Med* 2001; **52:** 1565–1575.
39. Hachamovitch R, Berman DS, Kiat H, Bairey-Merz N, Cohen I, Cabico JA, et al. Gender-related differences in clinical management after exercise nuclear testing. *J Am Coll Cardiol* 1995; **26:** 1457–1464.
40. Saha S, Stettin GD, Redberg RF. Gender and willingness to undergo invasive cardiac procedures. *J Gen Intern Med* 1999; **14:** 122–125.
41. Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 1999; **340:** 618–626.
42. Ejiri K, Ishihara M, Dai K, Miki T, Inoue I, Kawagoe T, et al. Three-year follow-up of sirolimus-eluting stents vs. bare metal stents for acute myocardial infarction. *Circ J* 2012; **76:** 65–70.

## Supplementary Files

**Supplementary File 1**

**Appendix S1.** List of Participating Centers and Investigators

**Appendix S2.** List of Clinical Research Coordinators

**Table S1.** Multivariate Analysis for Factors Associated With the Incidence of Long-Term All-Cause Mortality in Women and Men Undergoing PCI for AMI

**Table S2.** Multivariate Analysis for Factors Associated With the Incidence of Any Coronary Revascularization in Women and Men Undergoing PCI for AMI

**Table S3.** Relative Adjusted Risk in the Female AMI Patients for Clinically-Driven or Non-Clinically-Driven Any Coronary Revascularization

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-12-1161

# Asian Cardiovascular and Thoracic Annals

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## Alternative redo sternotomy in a patient with tracheostoma and patent grafts


Kyokun Uehara, Kenji Minakata, Masaki Funamoto, Kazuhiro Yamazaki, Akira Marui and Ryuzo Sakata



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*Case Study*

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# Alternative redo sternotomy in a patient with tracheostoma and patent grafts

**Kyokun Uehara, Kenji Minakata, Masaki Funamoto, Kazuhiro Yamazaki, Akira Marui and Ryuzo Sakata**

**Abstract**

We describe a redo mitral valve replacement operation in a 71-year-old man with a tracheostoma and patent bypass grafts to the coronary arteries. Preoperative investigations revealed that the patent right internal thoracic artery graft ran directly under the sternum just anterior to the ascending aorta, and a saphenous vein graft was adhering to a surgical wire. To prevent injury to the patent grafts and cardiac structures, and to avoid communication with the tracheostoma, the redo procedure was performed via an anterior minithoracotomy combined with a low T-shaped partial sternotomy. The reoperation was successfully completed without any complications.

**Keywords**

Coronary artery bypass, heart valve prosthesis implantation, mitral valve, sternotomy, thoracotomy, Tracheostomy

## Introduction

Occasionally, patients with a permanent tracheostoma require cardiac surgery, but possible communication between the tracheostoma and cardiac structures increases the risk of sternal wound infection and mediastinitis.[1,2] In addition, a complete median sternotomy in reoperative procedures after previous coronary artery bypass grafting increases the risk of hemorrhage because of severe adhesion of the bypass grafts as well as the cardiac chambers and great vessels to the posterior sternal wall.[3–5]

## Case report

A 71-year-old man with a permanent tracheostoma was referred to our institution with worsening of heart failure due to prosthetic valve endocarditis. He had undergone mitral valve replacement and coronary artery bypass grafting using 4 grafts at another institution 13 months earlier. Postoperatively, a permanent tracheostomy was performed following prolonged mechanical ventilation. Echocardiography 10 months after the surgery revealed a mobile mass on the prosthetic mitral valve, caused by methicillin-resistant *Staphylococcus aureus*. The patient's condition deteriorated despite effective medical treatment for methicillin-resistant *Staphylococcus aureus*. Therefore, we planned redo mitral valve replacement. A coronary computed tomography angiogram showed that all bypass grafts were patent (Figure 1). However, it also revealed that the right internal thoracic artery graft ran directly under the sternum just anterior to the ascending aorta, and the proximal part of the saphenous vein graft was adhering to a surgical wire that had been fixed during the previous surgery. To prevent injury to the grafts and the cardiac structures and to avoid communication with the tracheostoma, a redo procedure was planned via an anterior minithoracotomy combined with a low T-shaped partial sternotomy. Upon induction of general anesthesia, the patient was switched from tracheal to oral intubation. A 6-cm right anterior thoracotomy was performed in the third intercostal space. The pleura were opened, a retractor was placed, and the adhesive tissues on the posterior wall of the manubrium and sternum were carefully separated from the right pleural cavity. After visually confirming sufficient space under

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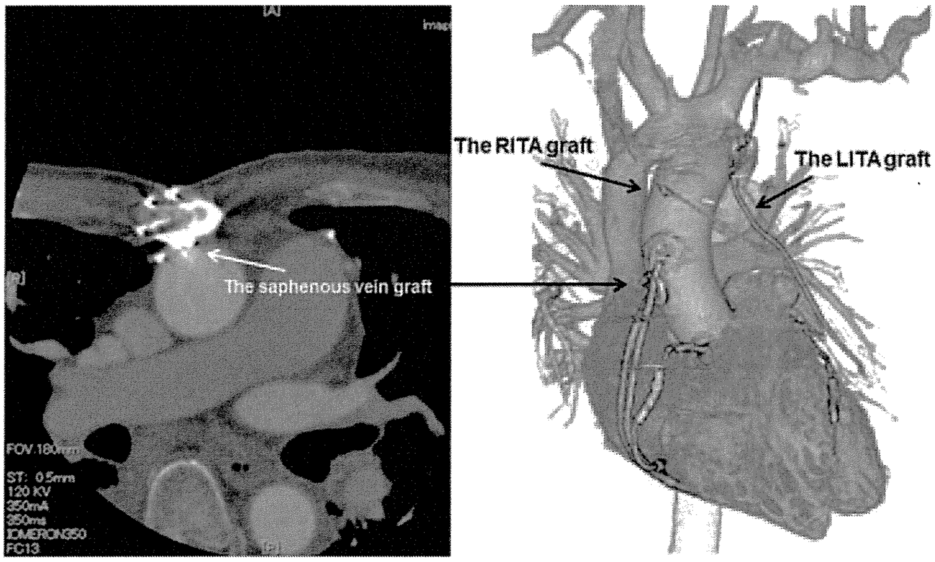


**Figure 1.** Preoperative computed tomographic images demonstrating the patent saphenous vein grafts adhering to the surgical wire, and the right internal thoracic artery (RITA) crossing the sternum at the midline. The left internal thoracic artery (LITA) is also patent.

the posterior wall of the sternum, a lower midline skin incision was made 5 cm caudal to the tracheostomy. A T-shaped lower sternotomy was completed using an oscillating saw (Figure 2). During the sternotomy, peripherally inserted cardiopulmonary bypass (CPB) via the femoral artery and vein was established for a short period, and after completion of the sternotomy, the patient was weaned off CPB. Following dissection of the adhesive tissues surrounding the heart, the superior and inferior venae cavae were taped, and CPB was resumed with additional superior venous cannulation. After aortic crossclamping, via a right-sided left atriotomy, the infected prosthetic mitral valve and mobile vegetation were removed, and a porcine tissue valve was implanted. Although the right internal thoracic artery graft seemed to be patent, several narrow points were observed; therefore, additional coronary artery bypass grafting to the left anterior descending artery was performed using saphenous vein. The operation was completed without any injury to the patent grafts or cardiac structures. The patient was doing well with no surgical site infection or recurrent endocarditis at 6 months postoperatively.

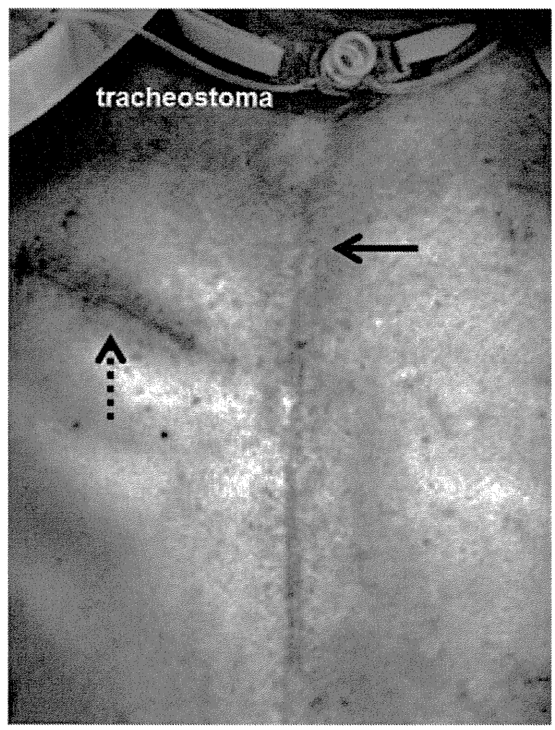


**Figure 2.** Right anterior minithoracotomy (dotted arrow) with a midline skin incision (solid arrow shows the top end of the incision line) at an adequate distance from the tracheostomy.

## Discussion

Several reports have been published on sternotomies in patients with a tracheostoma.[1,2] Mullenix and colleagues[2] reported the usefulness of a full sternotomy with a T-shaped skin incision. Although a full sternotomy may be required for more complicated surgeries such as aortic arch reconstruction, a partial sternotomy is advantageous because the increased distance between the sternotomy and tracheostoma reduces the chance of contamination, and therefore, the risk of wound infection.

In redo cases, various strategies have been advocated to reduce the risk of injury to patent grafts and cardiac structures.[3–5] Recently, Abe and colleagues[4] reported that sternal dissection with mobilization of a patent

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graft under thoracoscopic support can be conducted successfully. However, this approach prolongs the operative time and can be used only in patients with loose adhesions in the thoracic cavity. At our institution, we routinely use peripherally placed CPB to decompress the heart for a short period during a redo median sternotomy. We have found that this technique does not increase the procedure time or the amount of blood transfused, compared to other cases without CPB support. In addition to this strategy, we sometimes use an anterior minithoracotomy to identify patent grafts and dissect them directly, as previously described by Ismail and colleagues.[5] This technique can also be applied to prevent massive bleeding in patients with an ascending aortic aneurysm that adheres to the posterior wall of the sternum. Furthermore, unnecessary adhesiolysis on the posterior wall of the manubrium can be avoided to prevent potentially dangerous communication with the tracheostoma. Another advantage of our procedure is that the manubrium-sparing sternotomy will retain respiratory function in patients with a tracheostoma. A T-shape sternotomy combined with an anterior minithoracotomy is a safe alternative approach for redo surgery in patients with a tracheostoma and patent grafts.

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## Conflicts of interest statement

None declared.

## References

1. Kaneda T, Saga T, Nishino T, Fujii K and Shintaro Y. Usefulness of a partial median sternotomy for acute infectious endocarditis in patients with tracheostoma. *Ann Thorac Cardiovasc Surg* 2011; 17: 528–530.
2. Mullenix PS, McDonald JM, Miller J and Needham CS. Modified sternotomy to minimize infection risk in patients with prior laryngectomy and permanent tracheostomy. *J Card Surg* 2006; 21: 403–405.
3. Inafuku H, Ogino H, Sasaki H, Minatoya K, Yagihara T and Kitamura S. Total arch replacement through re-median sternotomy after coronary surgery. *Gen Thorac Cardiovasc Surg* 2007; 55: 473–475.
4. Abe T, Taniguchi T, Terada T and Sakurai H. Totally endoscopic mobilization of a patent internal thoracic artery graft from the sternum through the left hemithorax in redo coronary artery surgery: a new approach. *J Thorac Cardiovasc Surg* 2011; 142: 946–948.
5. Ismail I, Zhang R, Ringe K, Fischer S and Haverich A. Retrosternal adhesiolysis through an anterior minithoracotomy: a novel approach facilitating complete median redo sternotomy with a patent internal thoracic artery graft. *J Thorac Cardiovasc Surg* 2009; 137: 1034–1035.

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**RESEARCH ARTICLE**

# Protective effect of cardioplegia with poly (ADP-ribose) polymerase-1 inhibitor against myocardial ischemia-reperfusion injury: *in vitro* study of isolated rat heart model

Kazuhiro Yamazaki[1], Seigo Tanaka[2], Ryuzo Sakata[1], Senri Miwa[1], Wnimonk Oriyanhan[1], Kiyoaki Takaba[1] Kenji Minakata[1], Akira Marui[1], Tadashi Ikeda[1], Shinya Toyokuni[3], Masashi Komeda[4], and Kunihiro Ueda[5]

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**Abstract**

Poly(ADP-ribose) polymerase (PARP)-1 inhibitor has been suggested to attenuate the ischemia-reperfusion injury. We investigated the protective effect of the cardioplegia with a PARP-1 inhibitor, 4-hydoxyquinazoline (4-HQ), against myocardial ischemia-reperfusion injury. Isolated rat hearts were perfused on a Langendorff apparatus and cardioplegically arrested for 90 min by perfusion with St. Thomas' Hospital solution (ST-solution). In the Group ST ($n = 8$), the hearts were arrested with the ST-solution alone. The Group HQ ($n = 8$) were treated with the ST-solution containing 4-HQ (10 μM) for cardioplegia. During reperfusion, the Group HQ showed significantly greater functional recovery of $+dp/dt_{max}$ ($p = 0.005$) and lower enzymatic leakage ($p < 0.01$). $NAD^+$ levels were also preserved higher in the Group HQ ($p < 0.01$). Immunohistochemical study revealed lesser extents of oxidative stress and apoptosis, in the Group HQ. Thus, addition of 4-HQ in the cardioplegia may provide a new intervention for myocardial protection against ischemia-reperfusion injury by decreasing $NAD^+$ consumption and suppressing oxidative stress.

**Keywords:** Myocardial protection, cardioplegia, PARP [Poly(ADP-ribose) polymerase] inhibitor, ischemic reperfusion injury, oxidative stress

## Introduction

In cardiac surgery, cardioplegia provides with a bloodless and motionless operating field, but it exposes the cardiomyocytes to the ischemia. Hyperkalemic solutions are conventionally used for rapid electromechanical arrest due to the depolarization of cell membrane, leading to the reduction of cellular energy expenditure during the ischemic period. Despite improvements in cardioplegic techniques, the duration of cardioplegic arrest and reperfusion is known to be positively correlated with the extent of cardiomyocyte damage[1]. This procedure generates reactive oxygen species (ROS), such as hydroxyl radical ($OH^-$), superoxide radical ($O_2^-$), hydrogen peroxide ($H_2O_2$), and peroxynitrite ($ONOO^-$), resulting in the oxidative myocardial injury[2]. ROS can trigger the myocardial apoptosis, that might be involved in the pathogenesis of persistent myocardial dysfunction after cardioplegic arrest. Accordingly, it is important to renovate cardioplegia that can provide greater cardioprotection against ischemia-reperfusion injury.

Ischemia and reperfusion generate ROS, leading to lipid peroxidation, protein oxidation and the formation of DNA single-strand breaks[3]. Poly(ADP-ribose) polymerase (PARP)-1 (EC 2.4.2.30), that is a nuclear enzyme,

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is activated by oxidant-mediated DNA single-strand breaks. Excessive activation of PARP-1 decreases the intracellular level of its substrate, i.e. nicotinamide-adenine dinucleotide ($NAD^+$). As $NAD^+$ is indispensable for mitochondrial respiration, the depletion of $NAD^+$ leads to a deficiency of ATP. Depletion of these critical intracellular energy stores results in cellular dysfunction and, ultimately, cell death. This "energy crisis" hypothesis could explain the molecular mechanism of cell death after oxidative stress[4]. Recent studies have indicated an important role of PARP-1 in both apoptosis and necrosis[5]. Especially, it was clarified that activation of PARP-1 induces apoptosis through mitochondrial injury[6].

A growing number of studies demonstrated the beneficial effects of PARP-1 inhibition in cell cultures, isolated hearts and animal models of ischemia-reperfusion injury and various form of heart failure[7]. Inhibition of PARP-1 has been shown to decrease infarct size and attenuate the myocardial dysfunction[8]. Furthermore, several studies have shown that the administration of PARP inhibitors improved the recovery of myocardial function after cardioplegic arrest[9,10].

In our previous study, we showed that cardioplegia supplemented with 3-aminobenzamide (3-AB), a prototypical PARP inhibitor, provides efficient myocardial protection after cardioplegic arrest[11]. In order to establish the protective effect of PARP inhibitors, on cardiac performance during early reperfusion period, we assessed the ability of another type of inhibitor, 4-hydroxyquinazoline (4-HQ), to attenuate myocardial injury in an isolated rat heart model of cardioplegic ischemia and reperfusion.

## Materials and methods

### Animals

Adult male Sprague-Dawley rats (350–450 g body weight) were used for this study. All animals in this study received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health.

### Heart isolation and perfusion

The animal was anesthetized by inhalation of diethyl ether and intraperitoneal injection of sodium pentobarbital (50 mg/kg), and anticoagulated by intravenous injection of heparin (1,000 IU/kg). Each heart was rapidly excised and positioned on a Langendorff apparatus of non-recirculating circuit. The heart was perfused retrogradely via the aorta at a constant pressure of 75 mmHg by gravity at 37.5°C. Modified Krebs–Henseleit (K–H) solution (NaCl, 118 mM; KCl, 4.7 mM; MgSO4, 1.2 mM; NaHCO3, 25 mM; KH2PO4, 1.2 mM; CaCl2, 2.5 mM; glucose, 11 mM) bubbled with a mixture of 95% oxygen and 5% carbon dioxide was used for perfusion. After a 20 min of perfusion, each isolated heart was arrested with cold St. Thomas' Hospital cardioplegic solution (ST-solution: NaCl, 110 mM; KCl, 16 mM; MgCl, 16 mM; $CaCl_2$, 1.2 mM; $NaHCO_3$, 10 mM) (4°C, 20 mL/kg). The cardioplegia (10 mL/kg) was given three times at 30 min intervals. After a 90 min cardioplegic arrest, warmed K-H buffer (37.5°C, 10 mL/kg) was administered as terminal warm cardioplegia, followed by a 20 min reperfusion with ST-solution. The rats were classified into two groups; Group ST and Group HQ ($n = 8$ each). In the Group ST, the heart was arrested and reperfused without addition of 4-HQ. In the Group HQ, 10 μM of 4-HQ was added to both the ST-solution and the terminal warm cardioplegia.

### Assessment of left ventricular (LV) function

A latex balloon was inserted through the left atrium into the LV cavity and connected to a pressure transducer by using a fluid-filled polyethylene tube. The end-diastolic pressure was maintained at 10 mmHg by inflating the balloon. Heart rate and positive maximum rate of the rise of LV pressure ($+dp/dt_{max}$, mmHg/s) were measured and recorded at the end of the perfusion as baseline measurement, and at 5 and 20 min of reperfusion. The coronary flow was also measured at the same time-intervals by collecting the coronary effluent buffer from the heart.

### Measurement of cardiac enzymes

The released cardiac enzymes were measured in the coronary effluent buffer to assess myocardial damage. The samples were collected at the end of the perfusion as the baseline, and at 5 and 20 min of reperfusion. The concentrations of creatine phosphokinase (CPK), glutamic-oxaloacetic transaminase (GOT) and lactate dehydrogenase (LDH) were measured simultaneously by using an Auto-Analyzer AU550 (Olympus, Tokyo, Japan) and expressed as international units (IU) per min.

### Measurement of $NAD^+$ concentration

After 20 min of reperfusion, the concentration of $NAD^+$ in the perchloric acid extract of the cardiac muscle was measured using an alcohol dehydrogenase reaction[12]. The reaction mixture contained 1000 μL of buffer-substrate [0.1 M Tris-acetate (pH 8.80) and 0.5 M ethanol], 100 μL of the neutralized tissue extract and 20 μl of alcohol dehydrogenase (Wako, Osaka, Japan). The reaction was initiated by the addition of enzyme, and the change in absorbance at 340 nm was recorded by a spectrophotometer.

### Immunohistochemical assay of 8-hydroxy-2′-deoxyguanosine (8-OHdG)

Since 8-hydroxy-2′-deoxyguanosine (8-OHdG) is one of the major products of oxidative DNA modifications, 8-OHdG was measured as a marker of oxidative stress. For immunohistochemical analysis of 8-OHdG using a specific monoclonal antibody (N45.1: Japan Institute for the Control of Aging (JaICA), Shizuoka, Japan), the


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avidin-biotin complex method was used as described previously[13]. After 20 min of reperfusion, we divided each specimen into three areas-anterior, posterior and septal walls-and collected six tissue samples from two specimens (two samples for each area).

The level of 8-OHdG (8-OHdG index) was measured and quantitated as follows[14]:

$$\text{8-OHdG index} = \frac{\sum[(X - \text{threshold}) \times \text{area (pixels)}]}{\text{total cell number}}$$

where X is the staining density indicated in gray scale, using the NIH image 1.61 [Scion Image β 4.02, PC version of NIH Image (Scion Corporation, Frederick, MD) and Photoshop version 6.0 (Adobe Systems Inc, San Jose, CA)].

### Detection of apoptotic cardiomyocytes

A TUNEL assay was performed for detection of apoptotic cells using a commercial kit (apoptosis *in situ* detection kit; Wako, Osaka, Japan) according to the manufacturer's instructions. Digoxigenin-labeled dUTP was catalytically in-corporated into the DNA by terminal deoxynucleotidyl transferase, an enzyme that catalyzes a template-independent addition of nucleotide triphosphate to the 3′-OH ends of double- or single-strand DNA.

### Statistical analysis

Statistical analysis was performed with Statview software (version 5.0. SAS Institute Inc., CA). All data were expressed as the mean ± the standard error of means. Two-way repeated-measures analysis of variance (ANOVA) was used to test the effect of cardioplegia group and time on LV function and cardiac enzymes. When analysis of variance indicated a significant effect of cardioplegia group or time ($p < 0.05$), the differences were specified with the Fisher's test for groups comparison. Differences of the concentration of $NAD^+$ and 8-OHdG index among the groups were analyzed by one-way ANOVA followed by the Fisher's test. Statistical significance was assumed as a probability value lower than 0.05.

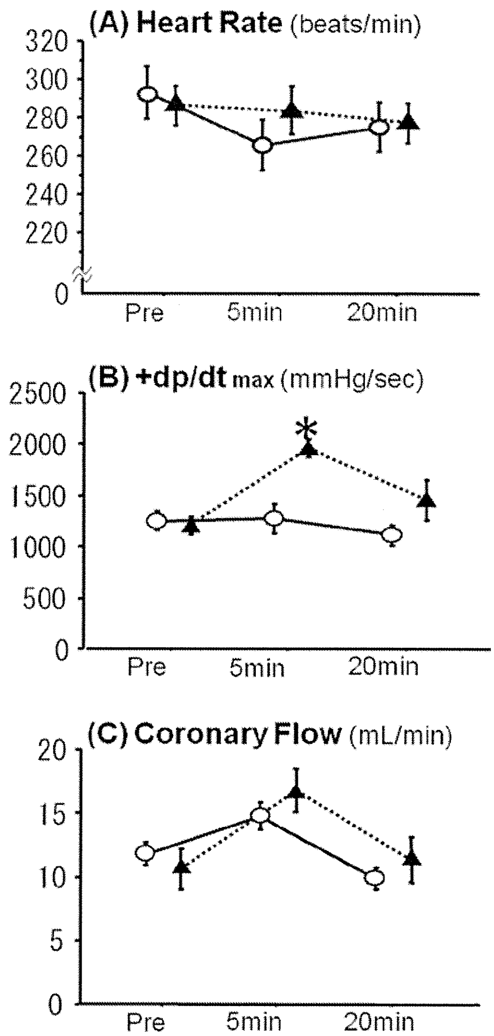


Figure 1. Changes of parameters for cardiac function. The cardiac functions were assessed before cardioplegic ischemia (pre) and at 5 min and 20 min of reperfusion. (A) There were no significant differences in heart rate between the Group ST(○) and Group HQ (▲). (B) The Group HQ showed a significantly greater +dp/dtmax (*$p < 0.01$) than the Group ST at 5 min of reperfusion. However, at 20 min, there was no significant difference between the two groups. (C) No significant differences were found in the volume of coronary flow between the two groups.

## Results and discussion

### Time-dependent changes in LV function

Heart rate did not change significantly both in the Group HQ and Group ST throughout the reperfusion (Figure 1A). The Group HQ showed a significantly higher value of +dp/dtmax than ST group at 5 min of reperfusion ($p = 0.001$). However, at 20 min, there was no significant difference between the two groups (Figure 1B). Coronary flow was increased at 5 min of reperfusion and returned to the baseline value at 20 min in both groups. No significant differences were found in the coronary flow between the two groups (Figure 1C).

### Release of cardiac enzymes

There were no significant differences in the cardiac release of CPK, GOT and LDH between the two groups before cardioplegic ischemia. Although, in both groups, large amounts of these three enzymes were released from the hearts after ischemia, the Group HQ showed a significantly lower level of enzyme release than the Group ST in the early stage of reperfusion (5 min) (Figure 2). The release of enzymes became less abundant in the later stage of reperfusion (20 min), but the releases of enzymes in the Group HQ were still smaller than those in the Group ST.

### Changes of intracellular $NAD^+$ content

The $NAD^+$ content was decreased in the Group ST, while preserved in the Group HQ, after ischemia and reperfusion; the concentration in the the Group ST (0.21 ± 0.02 μmol/g) was almost one-third level of that in the Group HQ

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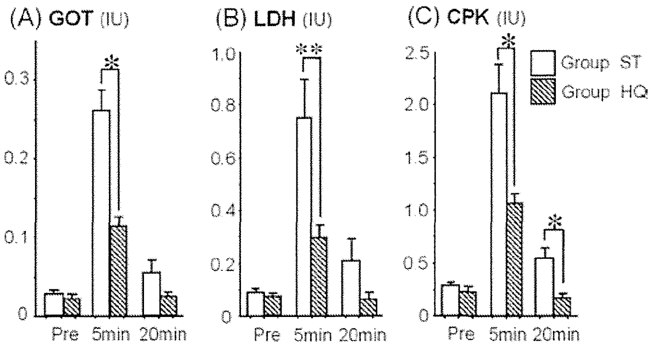


Figure 2. Release of cardiac enzymes. The concentrations of GOT, LDH and CPK in the coronary effluent buffer were measured before cardioplegic ischemia (pre) and at 5 min and 20 min of reperfusion. (A) The Group HQ released a significantly smaller amount of GOT than the Group ST at 5 min of reperfusion (*$p<0.01$). (B) There was a significant decrease in LDH release of the Group HQ at 5 min in comparison with the Group ST (**$P<0.05$). (C) The level of CPK release was significantly lower in the Group HQ at 5 min (*$p<0.01$) and 20 min (*$p<0.01$) than the Group ST.

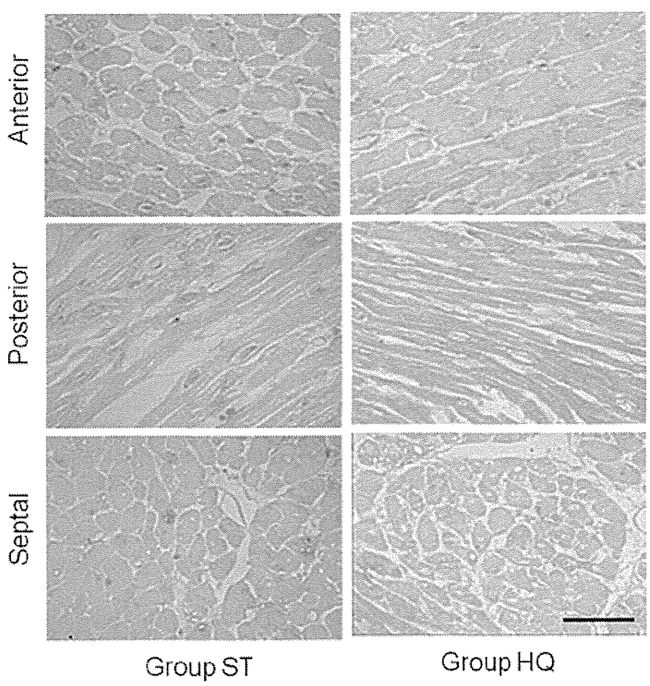


Figure 3. Oxidative stress on DNA after 20 min reperfusion. Immunohistochemical analysis of 8-OHdG was carried out using a specific monoclonal antibody (N45.1). The representative images of anterior, posterior, septal walls in the Group ST and Group HQ are shown here. The cells with dark-stained nuclei suffer from oxidative stress. Addition of 4-HQ in the cardioplegia (Group HQ) resulted in a less amount of nuclear oxidative DNA damage. Scale bar = 50 μm.

(0.63 ± 0.08 μmol/g)($p<0.001$). These results clearly indicate that the addition of 4-HQ in the cardioplegia is effective in suppression of the energy consumption of $NAD^+$.

### Oxidative stress on DNA

Immunohistochemical staining of 8-OHdG was used to evaluate the oxidative stress on DNA in the cardiac tissue. After cardioplegic ischemia and reperfusion, the nuclear staining in the cardiomyocytes became positive both in the Group ST and Group HQ. The staining was apparently more prominent in the Group ST than the Group HQ (Figure 3). In the quantitative analysis, the 8-OHdG index of the Group ST (91.2 ± 30.0) was the higher than that of the Group HQ (22.5 ± 3.4) by more than four times ($p=0.002$).

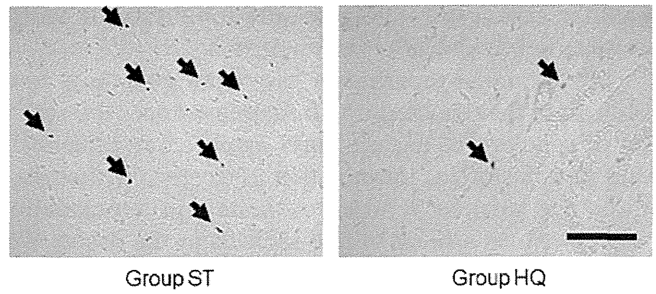


Figure 4. Induction of apoptosis in cardiomyocytes. Immunohistochemical analysis of apoptosis was carried out using the TUNEL method. Representative images of the anterior wall are shown. The positive cells, as indicated by arrows are considered to be apoptotic. Apototic cardiomyocytes were more prominent in the Group ST than in the Group HQ. Scale bar = 50 μm.

### Induction of apoptosis in cardiomyocytes

We then evaluated, by the TUNEL method, the induction of apoptosis in the cardiomyocytes after cardioplegic ischemia and reperfusion. While apoptotic cells were detectable in the whole areas of the heart examined of both groups, the density of positive cells was much higher in the Group ST than Group HQ (Figure 4).

## Discussion

In this study, a PARP inhibitor, 4-HQ, was shown to improve postischemic recovery of LV function during the period of cardioplegic arrest in isolated Langendorff perfusions of the rat. The PARP inhibitor in St.Thomas solution decreased myocardial release of enzymes and inhibited myocardial reduction of $NAD^+$. These findings were associated with a significant decrease in 8-OHdG index and apoptosis, indicating that 4-HQ also has the ability to protect the heart from ischemic-reperfusion injury after cardioplegic arrest.

One of the best characterized mechanisms of tissue injury after PARP activation is related to the disturbance of myocardial energy metabolism. During reperfusion after ischemia, the extensive activation of PARP in response to DNA damage causes a temporary reduction in the cellular $NAD^+$ pool. Therefore, it is considered that preservation of cellular energy is a mechanism by which PARP inhibition contributes to the protection of the heart from reperfusion injury. Under our experimental conditions, it is likely that the 20 min reperfusion was too short for activation of PARP. However, the PARP inhibitors efficiently decreased the $NAD^+$ depletion at the early stage of reperfusion. These results suggest that PARP inhibitors preserve the


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cellular energy through not only inhibition of PARP activation but also other mechanisms.

The ischemia-reperfusion sequence generates free radicals in the myocardium. Ischemia reduces the activity of cellular defense enzymes against free radicals[15], and reperfusion, or introduction of oxygen, further disturbs the balance between oxidants and antioxidants and generates a burst of free radicals in the tissue. We showed by using immunohistochemistry that the level of 8-OHdG, that is a major product of oxidative DNA modifications, increased in cardiomyocytes after myocardial infarction[16]. By calculating the 8-OHdG index, we demonstrated that 3-AB had an ability to protect DNA against oxidative stress in our previous study[11], and also 4-HQ has the same ability of protection in this study. These results suggest that the inhibition of PARP may decrease the DNA damage by suppression of oxidative stress.

The PARP inhibitor suppressed apoptotic DNA fragmentation, as shown in this study. Recently, several studies provided the evidence that the myocardial apoptosis is involved in the pathogenesis of persistent myocardial dysfunction after cardiac surgery[1]. Several mediators of apoptosis, including apoptosis-inducing factor (AIF) and cytochrome c, were activated after 10 to 20 min of cardiopulmonary bypass[17]. It had been proposed that PARP is implicated in various types of cell death by following mechanisms: (a) PARP could deplete $NAD^+$ and ATP of cells, resulting in an energy crisis; (b) PARP serves as a main substrates for caspases; and (c) PARP activation signals AIF release from mitochondria, resulting in a caspase-independent pathway of programmed cell death[6,18]. The addition of PARP inhibitors during cardiopulmonary bypass may contribute to the suppression of cardimyocytic apoptosis and preservation of myocardial function. We conclude that the cardioplegia with PARP inhibitors could be a new intervention for cardiac surgery.

## Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

## References

1. Schmitt JP, Schröder J, Schunkert H, Birnbaum DE, Aebert H. Role of apoptosis in myocardial stunning after open heart surgery. Ann Thorac Surg 2002;73:1229–1235.
2. Hayashi Y, Sawa Y, Ohtake S, Fukuyama N, Nakazawa H, Matsuda H. Peroxynitrite formation from human myocardium after ischemia-reperfusion during open heart operation. Ann Thorac Surg 2001;72:571–576.
3. Le Rhun Y, Kirkland JB, Shah GM. Cellular responses to DNA damage in the absence of Poly(ADP-ribose) polymerase. Biochem Biophys Res Commun 1998;245:1–10.
4. Okamoto H. Regulation of proinsulin synthesis in pancreatic islets and a new aspect to insulin-dependent diabetes. Mol Cell Biochem 1981;37:43–61.
5. Jagtap P, Szabó C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. Nat Rev Drug Discov 2005;4:421–440.
6. Yu SW, Wang H, Poitras MF, Coombs C, Bowers WJ, Federoff HJ et al. Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science 2002;297:259–263.
7. Szabó C. Cardioprotective effects of poly(ADP-ribose) polymerase inhibition. Pharmacol Res 2005;52:34–43.
8. Thiemermann C, Bowes J, Myint FP, Vane JR. Inhibition of the activity of poly(ADP-ribose) synthetase reduces ischemia-reperfusion injury in the heart and skeletal muscle. Proc Natl Acad Sci USA 1997;94:679–683.
9. Khan TA, Ruel M, Bianchi C, Voisine P, Komjáti K, Szabo C et al. Poly(ADP-ribose) polymerase inhibition improves postischemic myocardial function after cardioplegia-cardiopulmonary bypass. J Am Coll Surg 2003;197:270–277.
10. Szabó G, Buhmann V, Andrási T, Stumpf N, Bährle S, Kékesi V et al. Poly-ADP-ribose polymerase inhibition protects against myocardial and endothelial reperfusion injury after hypothermic cardiac arrest. J Thorac Cardiovasc Surg 2003;126:651–658.
11. Yamazaki K, Miwa S, Ueda K, Tanaka S, Toyokuni S, Unimonh O et al. Prevention of myocardial reperfusion injury by poly(ADP-ribose) synthetase inhibitor, 3-aminobenzamide, in cardioplegic solution: *in vitro* study of isolated rat heart model. Eur J Cardiothorac Surg 2004;26:270–275.
12. Bergmeyer.,UH. Nicotinamide-adenine dinucleotides (NAD, NADP, NADH, NADPH). Spectrophotometric and fluorometric methods. Methods Enzymatic Anal 1974;4:2045–2051.
13. Toyokuni S. Reactive oxygen species-induced molecular damage and its application in pathology. Pathol Int 1999;49:91–102.
14. Toyokuni S, Tanaka T, Hattori Y, Nishiyama Y, Yoshida A, Uchida K et al. Quantitative immunohistochemical determination of 8-hydroxy-2′-deoxyguanosine by a monoclonal antibody N45.1: Its application to ferric nitrilotriacetate-induced renal carcinogenesis model. Lab Invest 1997;76:365–374.
15. Ferrari R, Guardigli G, Mele D, Percoco GF, Ceconi C, Curello S. Oxidative stress during myocardial ischaemia and heart failure. Curr Pharm Des 2004;10:1699–1711.
16. Miwa S, Toyokuni S, Nishina T, Nomoto T, Hiroyasu M, Nishimura K et al. Spaciotemporal alteration of 8-hydroxy-2′-deoxyguanosine levels in cardiomyocytes after myocardial infarction in rats. Free Radic Res 2002;36:853–858.
17. Ramlawi B, Feng J, Mieno S, Szabo C, Zsengeller Z, Clements R et al. Indices of apoptosis activation after blood cardioplegia and cardiopulmonary bypass. Circulation 2006;114:I257–I263.
18. Tanaka S, TakehashiM, Iida S, Kitajima T, Kamanaka Y, Stedeford T et al. Mitochondrial impairment induced by poly(ADP-ribose) polymerase-1 activation in cortical neurons after oxygen and glucose deprivation. J Neurochem 2005;95:179–190.

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# エビデンスに基づく至適冠血行再建
## ――CREDO-Kyotoからの検証――

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**The CREDO-Kyoto Investigators**

**冠血行再建治療において本邦からのエビデンスレベルの高い報告は限られており，依然個々の医師・施設の経験に偏りがちな治療選択が行われることも多い．CREDO-Kyotoは本邦初の初回冠血行再建患者の多施設レジストリであり，これから得られるエビデンスが現時点では本邦で最も信頼性が高いと考えられる．2000〜2002年にCREDO-Kyotoに登録された9,877名のうち多枝または左主幹部病変を有する6,327名（PCI/CABG＝3,877/2,450）を対象とした．中央観察期間は3.5年で，PCIのうち85%はベアメタルステントが使用された．プロペンシティスコア解析では，総死亡はPCIで有意に多く（ハザード比および95%信頼区間：1.37［1.15〜1.63］，$p<0.01$），心筋梗塞もPCIで多かった（1.82［1.34〜2.47］，$p<0.01$）．脳卒中はPCIで少なかった（0.75［0.59〜0.96］，$p=0.02$）．さらにEuroSCOREにより患者をリスク層別化しon-pumpとoff-pump CABGの成績を比較したところ，低リスク群（スコア0〜3%），中リスク群（3〜6%）では差を認めなかったが，高リスク群（≧6%）ではon-pumpで脳卒中発症率が高かった（1.80［1.07〜3.02］，$p=0.03$）．しかし死亡に関してはリスクにかかわらず差を認めなかった．多枝または左主幹部病変を有する患者ではCABGはPCIに比して長期予後に優れていることが示された．また特にハイリスク患者の脳梗塞回避においてoff-pump CABGの有用性が示された．日心外会誌42巻1号：16–22（2013）**

キーワード：PCI, CABG, オフポンプ

**Evidence-Based Optimal Myocardial Revascularization : Perspective from the CREDO-Kyoto Registry**

Akira Marui[1,2], Hitoshi Okabayashi[3], Tatsuhiko Komiya[4], Ryuzo Sakata[1] and The CREDO-Kyoto Investigators (Department of Cardiovascular Surgery[1], and Department of Cardiovascular Medicine[2], Kyoto University Graduate School of Medicine, Kyoto, Japan, Department of Cardiovascular Surgery, Iwate Medical University School of Medicine[3], Morioka, Japan, and Department of Cardiovascular Surgery, Kurashiki Central Hospital[4], Kurashiki, Japan)

Although there have been several studies that compared the efficacy of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), the impact of off-pump CABG (OPCAB) has not been well elucidated. Among the 9,877 patients undergoing first myocardial revascularization enrolled in the CREDO-Kyoto Registry (a registry of first-time PCI using bare-metal stents and CABG patients in Japan), 6,327 patients with multivessel and/or left main disease were enrolled in the present study (PCI 3,877/CABG 2,450). Median follow-up was 3.5 years. Propensity-score-adjusted all-cause mortality after PCI was higher than that of CABG (hazard ratio [95% confidence interval] : 1.37 [1.15–1.63], $p<0.01$). The incidence of stroke was lower after PCI than that after CABG (0.75 [0.59–0.96], $p=0.02$). The predicted risk of operative mortality (PROM) of each patient of on-pump/off-pump CABG was calculated by the logistic EuroSCORE. Patients were divided into tertiles based on their PROM. The hazard ratio of the incidence of stroke in on-pump CABG compared with off-pump CABG in the high-risk tertile was 1.80 ([1.07–3.02], $p=0.03$). The adjusted overall mortality was not significantly different between the two procedures even in the high-risk tertile (1.44 [0.98–2.11], $p=0.06$). In patients with multivessel and/or left main disease, CABG was associated with better survival outcomes than PCI using bare-metal stents. Off-pump CABG as opposed to on-pump CABG is associated with short-and long-term benefits in stroke prevention in patients with higher risk as evaluated by the EuroSCORE. No survival benefit of OPCAB was shown, regardless of preoperative risk level. Jpn. J. Cardiovasc. Surg. 42 : 16–22 (2013)

**Keywords** : PCI, CABG, off-pump

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