


# Impact of bleeding on mortality in patients with acute myocardial infarction complicated by cardiogenic shock

Kensaku Nishihira<sup>1</sup>, Satoshi Honda<sup>2</sup>, Misa Takegami<sup>3</sup>, Sunao Kojima <sup>4</sup>, Yasuhide Asami<sup>2</sup>, Makoto Suzuki<sup>5</sup>, Masami Kosuge<sup>6</sup>, Jun Takahashi<sup>7</sup>, Yasuhiko Sakata<sup>7</sup>, Morimasa Takayama<sup>5</sup>, Tetsuya Sumiyoshi<sup>5</sup>, Hisao Ogawa<sup>2</sup>, Kazuo Kimura<sup>6</sup>, and Satoshi Yasuda<sup>2,7\*</sup>; on behalf of the JAMIR investigators

<sup>1</sup>Department of Cardiology, Miyazaki Medical Association Hospital, 1173 Arita, Miyazaki 880-2102, Japan; <sup>2</sup>Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe shin-machi, Suita 564-8565, Japan; <sup>3</sup>Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, 6-1 Kishibe shin-machi, Suita 564-8565, Japan; <sup>4</sup>Department of General Internal Medicine 3, Kawasaki Medical School, 2-6-1 Nakasange, Kita-ku, Okayama 700-8505, Japan; <sup>5</sup>Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu 183-0003, Japan; <sup>6</sup>Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan; and <sup>7</sup>Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

Received 25 October 2020; revised 30 December 2020; editorial decision 2 March 2021; accepted 5 March 2021; online publish-ahead-of-print 3 May 2021

## Aims

Acute myocardial infarction complicated by cardiogenic shock (AMICS) is associated with substantial mortality, although there are limited data available on bleeding in this critical condition. This study sought to investigate the incidence and impact of major in-hospital bleeding on all-cause mortality in patients with AMICS who undergo percutaneous coronary intervention (PCI).

## Methods and results

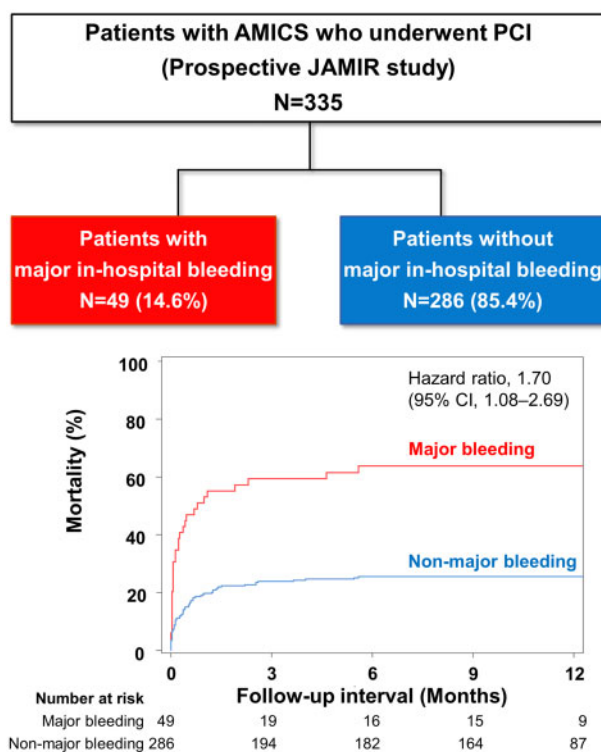
Between 2015 and 2017, a total of 3411 patients hospitalized within 24 h after symptom onset were prospectively enrolled in the Japan Acute Myocardial Infarction Registry (JAMIR) and followed up for a median of 293 (interquartile range, 22–375) days. AMICS developed in 335 (9.8%) patients (mean age, 71.3 ± 13.6 years). Overall, the rate of major in-hospital bleeding (Bleeding Academic Research Consortium types 3 and 5) and in-hospital mortality was 14.6% and 28.7%, respectively. The majority of major in-hospital bleeding (73.5%) occurred within 48 h after PCI. Compared to patients without major in-hospital bleeding, those with it had higher rates of renal failure, left main coronary artery culprit lesion, and intra-aortic balloon pump or extracorporeal membrane oxygenation support, and had longer door-to-device time. The cumulative incidence of 1-year all-cause mortality was significantly higher in the major bleeding group compared to the non-major bleeding group (63.8% vs. 25.5%; log-rank  $P < 0.001$ ). After adjusting for confounders, major in-hospital bleeding was independently associated with increased all-cause mortality (hazard ratio, 1.70; 95% confidence interval, 1.08–2.69).

## Conclusions

These findings of JAMIR indicate that major in-hospital bleeding is associated with all-cause mortality in patients with AMICS who undergo PCI.

\* Corresponding author. Tel: +81 22 717 7151, Fax: +81 22 717 7156, Email: [sysuda@cardio.med.tohoku.ac.jp](mailto:sysuda@cardio.med.tohoku.ac.jp)

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2021. For permissions, please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com).



## Keywords

Acute myocardial infarction • Bleeding • Coronary intervention • Shock

## Introduction

Cardiogenic shock (CS) is the leading cause of death in patients hospitalized due to acute myocardial infarction (AMI). Despite advances in reperfusion therapy and the establishment of cardiac intensive care units, mortality remained high, in the range of 40–50%, during the last two decades.<sup>1,2</sup> Percutaneous coronary intervention (PCI), which is beneficial in achieving rapid reperfusion, is preferred as an effective treatment in this critical condition; the procedure requires dual antiplatelet therapy.<sup>3,4</sup> Additionally, mechanical circulatory support devices to stabilize haemodynamics are widely used for patients with AMI complicated by CS (AMICS); such patients require anticoagulant therapy and insertion of a larger sheath into the femoral artery.<sup>1,5</sup> These invasive and pharmacological therapies and critical end-organ hypoperfusion due to CS, which might subsequently cause disseminated intravascular coagulation, pose increased bleeding risks.<sup>1,2,5–8</sup> However, there have been few reports about the prognostic implication of in-hospital bleeding in patients with AMICS.

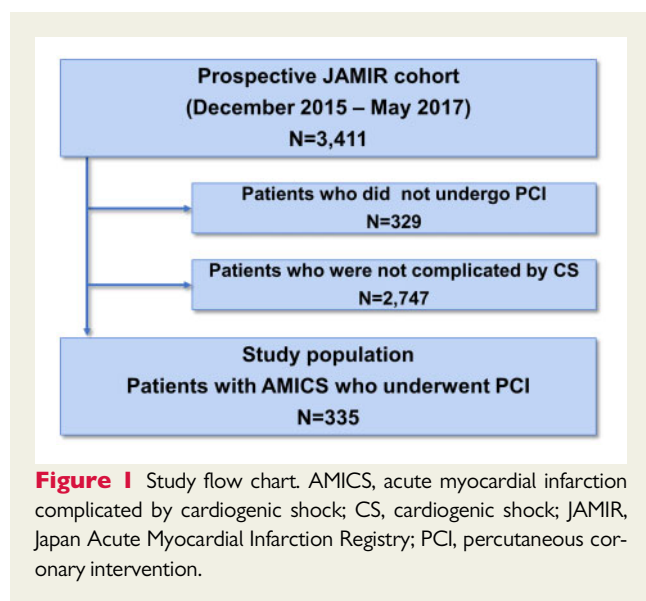
The Japan Acute Myocardial Infarction Registry (JAMIR) study, a multicentre, nationwide, prospective registry, was established to investigate the current antiplatelet therapy with a potent P2Y<sub>12</sub> inhibitor, and the clinical outcomes of patients with AMI in real-world clinical practice.<sup>9,10</sup> The JAMIR dataset included 1-year ischaemic events and bleeding events based on Bleeding Academic Research Consortium (BARC) criteria.<sup>9,10</sup>

The aim of this study was to investigate the incidence and predictors of major in-hospital bleeding, and to evaluate the relationship between this complication and all-cause mortality in patients with AMICS who undergo PCI, using a sub-analysis of the JAMIR study.

## Methods

### Study population

The JAMIR study is a prospective observational multicentre registry. The design and patient enrolment in the JAMIR were described previously.<sup>9,10</sup> Using the database of JAMIR, this study investigated the incidence and clinical characteristics of major in-hospital bleeding, and its impact on all-cause mortality in patients with AMICS who underwent PCI. Briefly, 3411 consecutive patients with type 1 and type 2 myocardial infarction within 24 h after symptom onset were enrolled at 50 Japanese centres between December 2015 and May 2017. AMI was diagnosed by investigators at each study site based on the universal definition, with allowance of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria according to the institutional setting.<sup>11,12</sup> Indeed, 99% of registered patients were diagnosed on the basis of the universal definition.<sup>9</sup> In the present analysis, 329 patients who did not undergo PCI and 2747 patients who were not complicated by CS were excluded. Finally, the study population consisted of 335 patients (Figure 1). Follow-up information was collected by investigators, clinical research coordinators, or local data managers at each study site, 9–15 months after the onset of



AMI. Clinical events were also adjudicated by those at each study site. Quality checks of the database were conducted at an independent data management centre. The median duration of follow-up was 293 (interquartile range, 22–375) days. Complete 1-year follow-up information was available for 91.9% of patients.

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The institutional review boards or ethics committees at all 50 participating centres approved the study protocol. Written informed consent was not obtained from the study subjects because of the observational nature of this registry; however, details about the study were posted on a website and at the study sites to inform the subjects of the content and to ensure that they had the opportunity to refuse inclusion in this registry (opt-out). This study was registered with the Japanese UMIN Clinical Trials Registry (UMIN000019479).

## Definitions and endpoints

CS was defined as systolic blood pressure <90 mmHg or need for supportive measures to maintain systolic blood pressure at ≥90 mmHg with adequate volume, and clinical signs of hypoperfusion, such as cold extremities, oliguria, mental confusion, dizziness, and narrow pulse pressure.<sup>1,13,14</sup>

The primary outcome in this study was all-cause mortality. In-hospital, 1-month, and 1-year all-cause mortality were evaluated. The incidences of major in-hospital bleeding, in-hospital ischaemic event, and cardiac death were also evaluated. Major bleeding during hospitalization was defined as BARC types 3 and 5 bleeding, involving a decrease in haemoglobin of >3 g/dL, need for blood transfusion, cardiac tamponade, surgical intervention, intracranial haemorrhage, or fatal bleeding.<sup>10,15,16</sup> Then, the onset timing of major in-hospital bleeding (within or later than 48 h) was analysed. Ischaemic event included non-fatal myocardial infarction, non-fatal stroke and cardiac death. Investigators, clinical research coordinators, or local data managers at each study site independently evaluated these outcomes and registered the data using the JAMIR registration system.

## Statistical analysis

Categorical variables are presented as numbers and percentages. They were compared using the chi-squared test or Fisher's exact test, as

appropriate. Continuous variables are presented as means and standard deviations or medians and interquartile ranges, according to the distribution of the data. They were analysed using the *t*-test or Mann–Whitney *U* test, as appropriate. We constructed a multivariate logistic regression model to identify predictors of major in-hospital bleeding, with adjustment for variables with a *P*-value <0.1 in univariate analyses. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Then, we used the Kaplan–Meier method to estimate the cumulative incidences of all-cause mortality and assessed the difference using the log-rank test. Additionally, we conducted a landmark analysis at 1-month to evaluate all-cause mortality at different time periods. We also used the following two multivariate Cox proportional hazards models to estimate the hazard ratio (HR) of major in-hospital bleeding for all-cause mortality: Model 1, adjusted for age and sex, and Model 2, adjusted for all variables with a *P*-value <0.1 in univariate analyses. Additionally, we conducted post hoc analyses focusing on cardiac death and onset timing of major bleeding (major bleeding within 48 h vs. major bleeding after 48 h). The results are presented as HRs with 95% CIs. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed, and a *P*-value of <0.05 was considered statistically significant.

## Results

### Baseline characteristics

Baseline clinical characteristics of the 335 patients with AMICS are shown in Table 1. The overall mean age was 71.3 ± 13.6 years, 95 (28.4%) were female, and 299 (89.3%) patients had ST-segment elevation myocardial infarction. Three hundred and seventeen (94.6%) and 57 (17.0%) patients were treated with dual antiplatelet therapy and oral anticoagulants, respectively. Among patients treated with clopidogrel, 43.2% received a 300 mg loading dose and 93.5% received a 75 mg maintenance dose. Among patients treated with prasugrel, 79.4% received a 20 mg loading dose and 96.8% received a 3.75 mg maintenance dose. No patients received thrombolytic therapy in this study. The PCI success rate, defined as final Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, was 84.5%.

Overall, major in-hospital bleeding (BARC type 3 and 5) occurred in 14.6% of patients with AMICS (Table 1). Of the patients who experienced major in-hospital bleeding, the proportion of BARC type 5 was 16.3%, and periprocedural bleeding within 48 hours after PCI occurred in 73.5%. In-hospital ischaemic events including non-fatal myocardial infarction, non-fatal stroke, and cardiac death occurred in 27.2% in the overall population, 55.1% in the major bleeding group, and 22.4% in the non-major bleeding group, respectively. In-hospital mortality was 28.7% in the overall population, 59.2% in the major bleeding group, and 23.4% in the non-major bleeding group, respectively.

Compared to patients without major in-hospital bleeding, those with major in-hospital bleeding were older and more likely to be female, had a lower estimated glomerular filtration rate, and higher rates of intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) support and left main coronary artery culprit lesion. Radial artery access for PCI was less common in patients with major in-hospital bleeding than in those without it. Door-to-device time was longer and the proportion of patients achieving a door-to-device time of <90 min was lower in the major bleeding group. Prasugrel was less common and switching between

**Table 1** Patient characteristics

|  | Overall, <i>n</i> = 335 | Non-major bleeding,<br><i>n</i> = 286 (85.4%) | Major bleeding,<br><i>n</i> = 49 (14.6%) | <i>P</i> -value |
|--|-------------------------|---|--|-----------------|
| <b>Baseline characteristics</b>                                |                         |   |  |                 |
| Age, years   | 71.3 ± 13.6             | 70.6 ± 13.8                                   | 75.3 ± 11.8                              | 0.026           |
| Age ≥75 years, <i>n</i> (%)                                    | 146 (43.6)              | 117 (40.9)                                    | 29 (59.2)                                | 0.017           |
| Female sex, <i>n</i> (%)                                       | 95 (28.4)               | 75 (26.2)                                     | 20 (40.8)                                | 0.036           |
| Body weight ≤50 kg ( <i>n</i> = 301), <i>n</i> (%)             | 78 (25.9)               | 65 (25.0)                                     | 13 (31.7)                                | 0.362           |
| Ambulance use, <i>n</i> (%)                                    | 316 (94.3)              | 271 (94.8)                                    | 45 (91.8)                                | 0.499           |
| Hypertension, <i>n</i> (%)                                     | 209 (62.4)              | 178 (62.2)                                    | 31 (63.3)                                | 0.891           |
| Diabetes mellitus, <i>n</i> (%)                                | 130 (38.8)              | 110 (38.5)                                    | 20 (40.8)                                | 0.755           |
| Dyslipidaemia, <i>n</i> (%)                                    | 229 (68.4)              | 197 (68.9)                                    | 32 (65.3)                                | 0.619           |
| Previous myocardial infarction or PCI, <i>n</i> (%)            | 53 (15.8)               | 45 (15.7)                                     | 8 (16.3)                                 | 0.916           |
| Previous stroke, <i>n</i> (%)                                  | 48 (14.3)               | 42 (14.7)                                     | 6 (12.2)                                 | 0.652           |
| Peripheral artery disease, <i>n</i> (%)                        | 19 (5.7)                | 14 (4.9)                                      | 5 (10.2)                                 | 0.138           |
| eGFR, mL/min/1.73 m <sup>2</sup>                               | 48.00 ± 21.0            | 49.8 ± 20.1                                   | 37.6 ± 23.3                              | <0.001          |
| eGFR <30 mL/min/1.73 m <sup>2</sup> , <i>n</i> (%)             | 68 (20.3)               | 49 (17.1)                                     | 19 (38.8)                                | <0.001          |
| Peak CPK, IU/L   | 2857 (1283–6567)        | 2864 (1283–6167)                              | 2704 (1467–8740)                         | 0.241           |
| Peak CK-MB, IU/L ( <i>n</i> = 279)                             | 295 (119–569)           | 288 (123–537)                                 | 394 (117–763)                            | 0.221           |
| <b>Presentation</b>  |                         |   |  |                 |
| STEMI, <i>n</i> (%)  | 299 (89.3)              | 256 (89.5)                                    | 43 (87.8)                                | 0.714           |
| Out-of-hospital cardiac arrest, <i>n</i> (%) ( <i>n</i> = 329) | 62 (18.8)               | 57 (20.3)                                     | 5 (10.4)                                 | 0.115           |
| Heart rate, beats/min  | 80 (57–103)             | 79 (57–103)                                   | 84 (64–110)                              | 0.312           |
| Systolic blood pressure, mmHg                                  | 90 (73–121)             | 90 (72–119)                                   | 106 (83–124)                             | 0.101           |
| <b>Angiographic and procedural characteristics</b>             |                         |   |  |                 |
| Radial access, <i>n</i> (%)                                    | 98 (29.3)               | 90 (31.5)                                     | 8 (16.3)                                 | 0.031           |
| IABP or ECMO support, <i>n</i> (%)                             | 193 (57.6)              | 154 (53.9)                                    | 39 (79.6)                                | <0.001          |
| IABP support, <i>n</i> (%)                                     | 190 (56.7)              | 153 (53.5)                                    | 37 (75.5)                                | 0.004           |
| ECMO support, <i>n</i> (%)                                     | 49 (14.6)               | 29 (10.1)                                     | 20 (40.8)                                | <0.001          |
| <b>Infarct-related artery location</b>                         |                         |   |  |                 |
| Right coronary artery, <i>n</i> (%)                            | 139 (41.5)              | 124 (43.4)                                    | 15 (30.6)                                | 0.094           |
| Left main coronary artery, <i>n</i> (%)                        | 30 (9.0)                | 20 (7.0)                                      | 10 (20.4)                                | 0.002           |
| Left anterior descending artery, <i>n</i> (%)                  | 158 (47.2)              | 132 (46.2)                                    | 26 (53.1)                                | 0.371           |
| Left circumflex, <i>n</i> (%)                                  | 36 (10.8)               | 34 (11.9)                                     | 2 (4.1)                                  | 0.134           |
| Bypass graft or unknown, <i>n</i> (%)                          | 3 (1.0)                 | 2 (0.7)                                       | 1 (2.0)                                  | 0.379           |
| Multivessel disease, <i>n</i> (%)                              | 187 (55.8)              | 160 (55.9)                                    | 27 (55.1)                                | 0.913           |
| Stent use, <i>n</i> (%)  | 304 (90.8)              | 261 (91.3)                                    | 43 (87.8)                                | 0.426           |
| Final TIMI flow grade 3, <i>n</i> (%)                          | 283 (84.5)              | 243 (85.0)                                    | 40 (81.6)                                | 0.552           |
| Onset-to-device time, min ( <i>n</i> = 305)                    | 175 (122–287)           | 169 (121–276)                                 | 230 (136–364)                            | 0.063           |
| Door-to-device time, min                                       | 76 (56–110)             | 73 (53–104)                                   | 95 (70–145)                              | <0.001          |
| Door-to-device time <90 min, <i>n</i> (%)                      | 204 (60.9)              | 181 (63.3)                                    | 23 (46.9)                                | 0.030           |
| <b>Drugs during hospitalization</b>                            |                         |   |  |                 |
| Aspirin, <i>n</i> (%)  | 322 (96.1)              | 276 (96.5)                                    | 46 (93.9)                                | 0.415           |
| P2Y <sub>12</sub> inhibitor                                    |                         |   |  | 0.016           |
| Clopidogrel, <i>n</i> (%)                                      | 46 (13.7)               | 37 (12.9)                                     | 9 (18.4)                                 |                 |
| Prasugrel, <i>n</i> (%)  | 252 (75.2)              | 223 (78.0)                                    | 29 (59.2)                                |                 |
| Switching between prasugrel and clopidogrel, <i>n</i> (%)      | 22 (6.6)                | 15 (5.2)                                      | 7 (14.3)                                 |                 |
| None, <i>n</i> (%)   | 15 (4.5)                | 11 (3.9)                                      | 4 (8.2)                                  |                 |
| Dual antiplatelet therapy, <i>n</i> (%)                        | 317 (94.6)              | 273 (95.5)                                    | 44 (89.8)                                | 0.159           |
| Oral anticoagulant use, <i>n</i> (%)                           | 57 (17.0)               | 48 (16.8)                                     | 9 (18.4)                                 | 0.785           |
| Duration of hospitalization, days                              | 16 (9–29)               | 16 (10–28)                                    | 15 (2–38)                                | 0.409           |

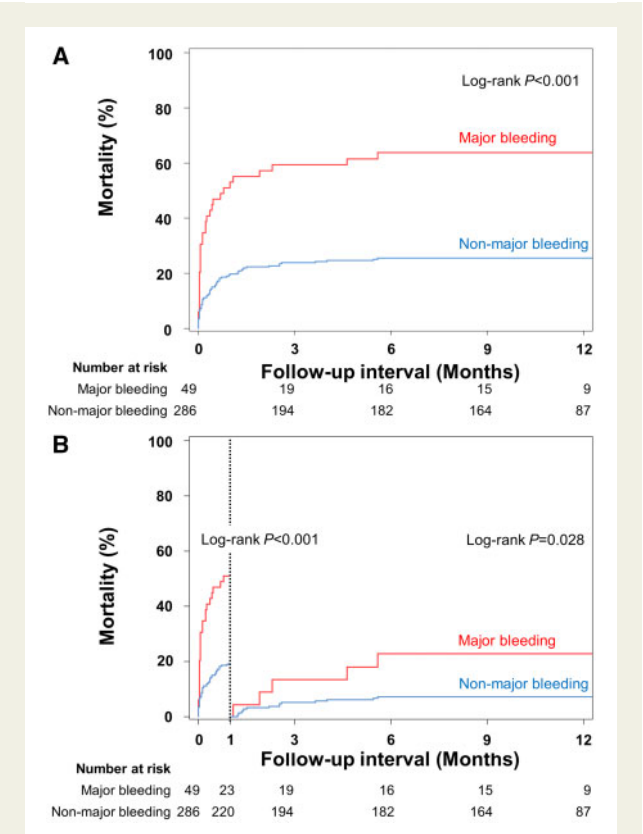
Data are expressed as means ± SD, *n* (%), or medians (interquartile range).

CK-MB, creatine kinase–myocardial band; CPK, creatine phosphokinase; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

**Table 2** Predictors of major in-hospital bleeding in patients with AMICS undergoing PCI

|   | OR (95% CI)       | P-value |
|---|-------------------|---------|
| Age ≥75 years   | 1.89 (0.87–4.11)  | 0.109   |
| Female sex  | 1.36 (0.61–3.03)  | 0.448   |
| eGFR <30 mL/min/1.73 m <sup>2</sup>                         | 2.59 (1.11–6.04)  | 0.027   |
| Radial access   | 0.44 (0.15–1.28)  | 0.131   |
| IABP or ECMO support  | 2.63 (1.07–6.47)  | 0.035   |
| Left main coronary artery culprit lesion                    | 3.06 (1.10–8.52)  | 0.032   |
| Right coronary artery culprit lesion                        | 1.21 (0.52–2.84)  | 0.658   |
| Longer onset-to-device time <sup>a</sup>                    | 1.05 (0.48–2.27)  | 0.909   |
| Longer door-to-device time <sup>a</sup>                     | 2.41 (1.09–5.35)  | 0.030   |
| Clopidogrel (vs. prasugrel)                                 | 1.44 (0.56–3.75)  | 0.451   |
| Switching between prasugrel and Clopidogrel (vs. prasugrel) | 4.89 (1.41–16.98) | 0.013   |
| Non-P2Y12 inhibitor (vs. prasugrel)                         | 1.35 (0.33–5.57)  | 0.679   |

The multivariate logistic regression model was adjusted for variables with a *P*-value <0.1 in univariate analyses. AMICS, acute myocardial infarction complicated by cardiogenic shock; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; OR, odds ratio; PCI, percutaneous coronary intervention. <sup>a</sup>Longer onset-to-device time and door-to-device time were defined as longer than the median time (onset-to-device time, 175 min; door-to-device time, 76 min).



**Figure 2** Kaplan-Meier curves for all-cause mortality. (A) Cumulative incidence curves for all-cause mortality in acute myocardial infarction complicated by cardiogenic shock patients with and without major in-hospital bleeding. (B) Cumulative incidence curves for all-cause mortality within and beyond 1 month. Major in-hospital bleeding was defined as BARC types 3 and 5. AMICS, acute myocardial infarction complicated by cardiogenic shock; BARC, Bleeding Academic Research Consortium.

prasugrel and clopidogrel was more frequent in the major bleeding group, but the use of aspirin and oral anticoagulants did not differ between the two groups (Table 1). In multivariate logistic regression analysis, estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> (OR 2.59; 95% CI 1.11–6.04), IABP or ECMO support (OR 2.63; 95% CI 1.07–6.47), left main coronary artery culprit lesion (OR 3.06; 95% CI 1.10–8.52), longer door-to-device time (OR 2.41; 95% CI 1.09–5.35) and switching between prasugrel and clopidogrel (OR 4.89; 95% CI 1.41–16.98) were independently associated with major in-hospital bleeding (Table 2).

### All-cause mortality

All-cause mortality at 1 year was 30.2% in the overall population, 63.8% in patients with major in-hospital bleeding, and 25.5% in those without it, respectively. Kaplan-Meier analysis showed that the cumulative incidence of all-cause mortality was significantly higher in the major bleeding group compared to the non-major bleeding group (log-rank *P* < 0.001) (Figure 2A). Landmark analysis at 1-month also showed the higher all-cause mortality in the major bleeding group both from 0 to 1 month and beyond 1 month (Figure 2B). Multivariate Cox proportional hazards analysis identified major in-hospital bleeding (HR 1.70; 95% CI 1.08–2.69) as being significantly associated with higher all-cause mortality, as was age ≥75 years (HR 1.81; 95% CI 1.19–2.74), estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> (HR 1.89; 95% CI 1.21–2.96), IABP or ECMO support (HR 1.75; 95% CI 1.08–2.83), left main coronary artery culprit lesion (HR 3.10; 95% CI 1.75–5.46), multivessel disease (HR 1.73; 95% CI 1.09–2.75), final TIMI flow grade <3 (HR 1.90; 95% CI 1.14–3.19), and longer door-to-device time (HR 1.73; 95% CI 1.14–2.64), whereas dual antiplatelet therapy (HR 0.27; 95% CI 0.15–0.51) was associated with lower all-cause mortality. Even after adjusting for age and sex, major in-hospital bleeding (HR 3.05; 95% CI 1.98–4.71) was significantly associated with all-cause mortality (Table 3). Also, the cumulative incidence of cardiac death was significantly higher in the major bleeding group

**Table 3** Cox proportional hazards analysis of all-cause mortality in patients with AMICS undergoing PCI

|  | Univariate analysis |         | Age, sex-adjusted analysis |         | Fully adjusted analysis <sup>a</sup> |         |
|--|---------------------|---------|----------------------------|---------|--------------------------------------|---------|
|  | HR (95% CI)         | P-value | HR (95% CI)                | P-value | HR (95% CI)                          | P-value |
| Major in-hospital bleeding <sup>b</sup>                  | 3.29 (2.16–5.02)    | <0.001  | 3.05 (1.98–4.71)           | <0.001  | 1.70 (1.08–2.69)                     | 0.023   |
| Age ≥ 75 years   | 2.21 (1.50–3.28)    | <0.001  | 2.20 (1.46–3.32)           | <0.001  | 1.81 (1.19–2.74)                     | 0.005   |
| Female sex   | 0.82 (0.53–1.28)    | 0.379   | 0.54 (0.34–0.86)           | 0.010   |                                      |         |
| Diabetes mellitus  | 1.10 (0.74–1.62)    | 0.643   |                            |         |                                      |         |
| Previous myocardial infarction or PCI                    | 0.90 (0.48–1.67)    | 0.727   |                            |         |                                      |         |
| Previous stroke  | 1.29 (0.77–2.18)    | 0.332   |                            |         |                                      |         |
| eGFR <30 mL/min/1.73 m <sup>2</sup>                      | 2.41 (1.60–3.63)    | <0.001  |                            |         | 1.89 (1.21–2.96)                     | 0.005   |
| Large infarct size estimated using peak CPK <sup>c</sup> | 1.42 (0.96–2.10)    | 0.076   |                            |         | 1.22 (0.80–1.85)                     | 0.353   |
| STEMI  | 0.63 (0.37–1.07)    | 0.089   |                            |         | 0.93 (0.52–1.65)                     | 0.805   |
| IABP or ECMO support                                     | 2.53 (1.62–3.95)    | <0.001  |                            |         | 1.75 (1.08–2.83)                     | 0.023   |
| Left main coronary artery culprit lesion                 | 3.28 (2.01–5.35)    | <0.001  |                            |         | 3.10 (1.75–5.46)                     | <0.001  |
| Multivessel disease                                      | 1.75 (1.16–2.64)    | 0.007   |                            |         | 1.73 (1.09–2.75)                     | 0.020   |
| Final TIMI flow grade <3                                 | 1.74 (1.09–2.79)    | 0.021   |                            |         | 1.90 (1.14–3.19)                     | 0.014   |
| Longer door-to-device time <sup>d</sup>                  | 2.01 (1.35–3.01)    | <0.001  |                            |         | 1.73 (1.14–2.64)                     | 0.010   |
| Dual antiplatelet therapy                                | 0.39 (0.16–0.95)    | 0.039   |                            |         | 0.27 (0.15–0.51)                     | <0.001  |

AMICS, acute myocardial infarction complicated by cardiogenic shock; CI, confidence interval; CPK, creatine phosphokinase; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

<sup>a</sup>Adjusted for variables with a *P*-value <0.1 in univariate analyses.

<sup>b</sup>Major in-hospital bleeding was defined as Bleeding Academic Research Consortium types 3 and 5.

<sup>c</sup>Large infarct size estimated using peak CPK was defined by peak CPK higher than the median peak CPK (2.857 IU/L).

<sup>d</sup>Longer door-to-device time was defined as longer than the median time (76 min).

compared to the non-major bleeding group (log-rank *P* < 0.001; adjusted HR 2.74; 95% CI 1.68–4.47) (Figure 3A).

And then, Kaplan–Meier analysis and multivariate Cox proportional hazards analysis showed that all-cause mortality of patients with major in-hospital bleeding within 48 h was numerically higher than that of patients with major in-hospital bleeding after 48 h, although the difference was not significant (log-rank *P* = 0.051; adjusted HR 2.31; 95% CI 0.93–5.74) (Figure 3B). As a sub-analysis, we also evaluated 2,747 non-CS patients. Major in-hospital bleeding was associated with all-cause mortality even in the non-CS group (log-rank *P* < 0.001; adjusted HR 4.90; 95% CI 2.78–8.62) (Supplementary material online, Figure S1).

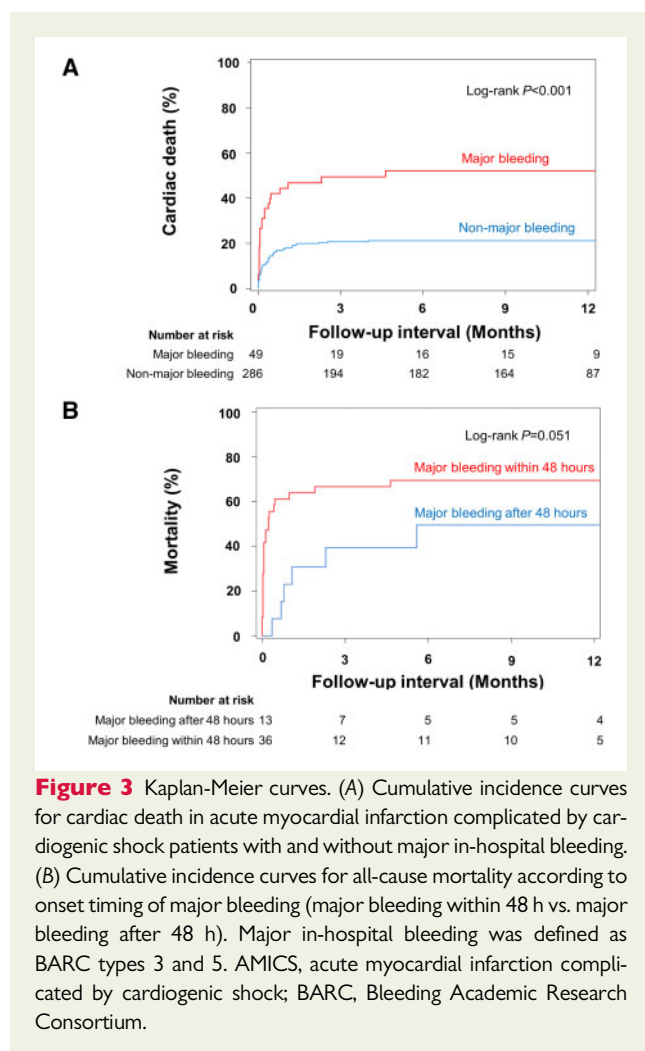
## Discussion

The major findings of this study following 1-year outcomes were as follows: (i) among these with AMICS who underwent PCI, the PCI success rate, major in-hospital bleeding rate, and in-hospital mortality were 84.5%, 14.6%, and 28.7%, respectively; (ii) lower estimated glomerular filtration rate, IABP or ECMO support, left main coronary artery culprit lesion, longer door-to-device time, and switching between prasugrel and clopidogrel were independent determinants of major in-hospital bleeding; and (iii) major in-hospital bleeding was associated with all-cause mortality.

CS is defined as a state of critical end-organ hypoperfusion and hypoxia due to reduced cardiac output, and is the leading cause of

death in patients with AMI.<sup>1,2</sup> The previous studies reported that CS occurs in 3–13% of patients with AMI.<sup>1,2</sup> Indeed, in this study, among 3082 patients with AMI who underwent PCI, 335 (10.9%) had CS as a complication. The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial demonstrated improved short- and long-term survival with early mechanical revascularization in patients with AMICS.<sup>17,18</sup> Emergency revascularization with either PCI or coronary artery bypass grafting irrespective of the time delay from symptom onset is a guideline-recommended therapy for patients with AMICS.<sup>1–4</sup> However, despite therapeutic advances, especially early revascularization, the mortality of AMICS remained high, in the range of 40–50%, during the last two decades.<sup>1,2</sup> In this study, the in-hospital mortality rate was as high as 28.7% in patients with AMICS, indicating that the management of patients with AMICS is still challenging even in the primary PCI era. Mechanical circulatory support devices for haemodynamic support failed to show an improvement in mortality in patients with AMICS.<sup>1,5,6,19</sup> In the IABP-SHOCK II trial, IABP could not reduce 30-day mortality in this population.<sup>5,19</sup> Also, recent retrospective studies could not demonstrate the superiority of Impella heart pump support on survival compared to IABP support.<sup>6,20,21</sup> It can be speculated that the haemodynamic effect provided by the Impella might be neutralized by the higher incidence of peripheral vascular complications, including severe or life-threatening bleeding.

In the recent study performed as a pre-defined sub-analysis of the randomized CULPRIT-SHOCK (PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock) trial, patients



**Figure 3** Kaplan-Meier curves. (A) Cumulative incidence curves for cardiac death in acute myocardial infarction complicated by cardiogenic shock patients with and without major in-hospital bleeding. (B) Cumulative incidence curves for all-cause mortality according to onset timing of major bleeding (major bleeding within 48 h vs. major bleeding after 48 h). Major in-hospital bleeding was defined as BARC types 3 and 5. AMICS, acute myocardial infarction complicated by cardiogenic shock; BARC, Bleeding Academic Research Consortium.

with any bleeding (BARC types 1–5) had a significantly higher probability of short-term mortality at 30 days.<sup>22</sup> However, there have been few reports evaluating the relationship between major in-hospital bleeding and 1-year mortality in patients with AMICS, which addressed in this study. The unique features of the real-world JAMIR study are that it provides detailed data on emergency care, including ambulance use, primary PCI and door-to-balloon time, and that it explores the impact of major in-hospital bleeding on 1-year all-cause mortality in patients with AMICS who underwent PCI. Indeed, compared to patients in the randomized CULPRIT SHOCK trial, those in the JAMIR were older, and had higher rates of comorbidities (e.g. diabetes mellitus, previous stroke and advanced stages of chronic kidney disease) and ST-segment elevation myocardial infarction.<sup>22</sup>

The present JAMIR study showed that major in-hospital bleeding, defined as BARC types 3 and 5 bleeding, occurred in 14.6% of patients with AMICS, and that renal dysfunction, IABP or ECMO support, left main coronary artery culprit lesion, door-to-device time, and switching between prasugrel and clopidogrel were associated with this adverse event. Moreover, this study also demonstrated that

major in-hospital bleeding was an independent predictor of all-cause mortality in this population. IABP and ECMO support require puncture of a femoral artery, insertion of a larger sheath and anticoagulant therapy, resulting in an increased risk of bleeding.<sup>5,22,23</sup> Additionally, impaired liver and renal function due to critical hypoperfusion affect drug metabolism and haemostasis, increasing bleeding in patients with AMICS.<sup>8</sup> We recently reported that door-to-device time was shorter in more serious and unstable left main coronary artery-related AMI patients.<sup>24</sup> The present study demonstrated that door-to-device time was longer in the major bleeding group than the non-major bleeding group. The delay in reperfusion therapy for patients with AMICS might have further exacerbated multi-organ damage, resulting in bleeding events. As a result, patients with major bleeding might require discontinuation of antiplatelet therapy and might experience adverse effects of transfusion, all of which can lead to increased all-cause mortality.<sup>15,16,25</sup> And then, switching between prasugrel and clopidogrel was associated with major in-hospital bleeding in this study. Bioavailability of these orally administered antiplatelet agents and of their active metabolites might be influenced owing to impaired gastrointestinal absorption and to decreased metabolism by an ischaemic liver in shock states.<sup>26</sup> Although there are no randomized data on the impact of access site in AMICS and although this variable was not significantly different according to the multivariate analysis in this study, several studies reported that radial access might reduce bleeding complications and improve early outcomes in patients with AMICS.<sup>27,28</sup> Our results, together with those of previous studies, suggest that major in-hospital bleeding considerably affects all-cause mortality, and efforts are needed to reduce bleeding complications, for instance by employing radial access during PCI in patients with AMICS and shortening the duration of ischaemia and hypoperfusion.

## Limitations

This study has several limitations. First, the number of participants in this study might have been too small to reach definitive conclusions. Second, this was an observational study, not a randomized controlled trial. Also, we could not perform a falsification analysis to evaluate the presence of any potential confounding, as appropriate falsification endpoints were unavailable within the dataset.<sup>29</sup> Since the study might involve selection bias and unmeasured confounders, further research is required to determine a causal relationship. Third, we did not compare outcomes between patients who initially underwent PCI of only the culprit lesion and those who underwent immediate multivessel PCI. Fourth, the JAMIR study did not include patients without return of spontaneous circulation on admission after out-of-hospital cardiac arrest. A recent study suggested that out-of-hospital cardiac arrest was associated with major bleeding.<sup>30</sup> Exclusion of these patients might affect the incidence of bleeding. Fifth, although all-cause mortality was not significantly different between patients with major in-hospital bleeding within 48 h and those with major in-hospital bleeding after 48 h, since the pathophysiology might differ depending on the timing of bleeding, further studies are needed to evaluate this in greater detail. Finally, endpoint adjudication by local

investigators, mixed follow-up periods, and lack of detailed causes of death were also limitations of this study.

## Conclusions

This real-world study of JAMIR following 1-year outcomes demonstrated that major in-hospital bleeding is associated with all-cause mortality in patients with AMICS who undergo PCI.

## Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

## Acknowledgements

The authors appreciate the support of the co-investigators participating in the JAMIR.

## Funding

The JAMIR is a project planned by the Japan Cardiovascular Research Foundation and is funded by Daiichi Sankyo Co., Ltd.

**Conflict of interest:** S.Y. reports remuneration for lectures from Takeda, Daiichi Sankyo, and Bristol-Myers Squibb, and trust research/joint research funds from Takeda and Daiichi Sankyo. M.T. reports lecture fees from Daiichi Sankyo. H.O. reports lecture fees and research grants from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer and Sanofi. The other authors have no conflicts of interest.

## Appendix

### JAMIR investigators

Hokkaido Medical Center: Takashi Takenaka; Hirosaki University: Hirofumi Tomita, Hiroaki Yokoyama; Iwate Medical University: Tomonori Ito, Masaru Ishida, Yorihiro Koeda; Yamagata University: Masafumi Watanabe, Tetsu Watanabe, Taku Toshima; Tohoku University: Hiroaki Shimokawa, Yasuhiko Sakata, Jun Takahashi, Kiyotaka Hao; Sakakibara Heart Institute: Tetsuya Sumiyoshi, Morimasa Takayama; Yokohama City University Hospital: Kazuo Kimura, Masami Kosuge, Toshiaki Ebina; Showa University Fujigaoka Hospital: Hiroshi Suzuki, Atsuo Maeda; Mie University Hospital: Masaaki Ito, Tairo Kurita, Jun Masuda; Matsuzaka Central General Hospital: Takashi Tanigawa; Ehime University Hospital: Jitsuo Higaki, Kazuhisa Nishimura; Oita University: Naohiko Takahashi, Hidefumi Akioka, Kyoko Kawano; Nagasaki University: Koji Maemura, Yuji Koide; Kumamoto University: Sunao Kojima, Kenichi Tsujita; National Cerebral and Cardiovascular Center: Hisao Ogawa, Satoshi Yasuda, Yasuhide Asaumi, Kensaku Nishihira, Yoshihiro Miyamoto, Misa Takegami, Satoshi Honda; Nagasaki Harbor Medical Center: Hiroshi Nakajima; Isahaya General Hospital: Kenji Yamaguchi; Sapporo City General Hospital: Takao Makino; Sapporo Cardiovascular Clinic: Daitarou Kanno; Teine Keijinkai Hospital: Yasuhiro Omoto; Hokkaido Cardiology Hospital: Daisuke Hotta; Sapporo Kosei General Hospital: Toshiya Sato; Nippon Medical School Musashi Kosugi Hospital: Naoki Sato, Arifumi Kikuchi, Michiko Sone, Koji Takagi; Ayase Heart Hospital: Imun Tei; Tokyo Metropolitan Hiroo General Hospital: Takashi Shibui, Sho Nagamine; Nippon Medical School Hospital: Wataru

Shimizu, Takeshi Yamamoto; Tokyo Saiseikai Central Hospital: Toshiyuki Takahashi; Tokyo Medical Center: Yukihiro Momiyama; St. Luke's International Hospital: Atsushi Mizuno; Edogawa Hospital: Hiroshi Ohira; Kyorin University Hospital: Hideaki Yoshino, Youhei Shigeta; Nihon University Itabashi Hospital: Atsushi Hirayama, Yasuo Okumura, Daisuke Fukamachi, Tadateru Takayama; Toho University Omori Medical Center: Hiroki Niikura, Hiroki Takenaka; Mitsui Memorial Hospital: Shuzo Tanimoto, Kazuyuki Yahagi; Tokyo Metropolitan Tama Medical Center: Hiroyuki Tanaka; Disaster Medical Center: Yasuhiro Sato, Ohno Masakazu; Musashino Red Cross Hospital: Takamichi Miyamoto, Nobuhiro Hara; NTT Medical Center: Mikio Kishi; Ome Municipal General Hospital: Shigeo Shimizu, Ken Kurihara; Ogikubo Hospital: Yasuhiro Ishii; Teikyo University Hospital: Ken Kozuma, Yusuke Watanabe; Fraternity Memorial Hospital: Yasuhiro Takahashi; Jikei University Hospital: Michihiro Yoshimura, Satoshi Morimoto; Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Yuichiro Minami; Tokyo Medical University Hospital: Jun Yamashita; Osaki Citizen Hospital: Kaoru Iwabuchi, Takeshi Yamauchi; Sendai Open Hospital: Atsushi Kato, Shigeto Namiuchi; Sendai Medical Center: Tsuyoshi Shinozaki, and Kesennuma City Hospital: Kazunori Ogata, Ryuji Tsuburaya.

## References

- Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J* 2019;**40**:2671–2683.
- van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017;**136**:e232–e268.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevinos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
- Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
- Werdan K, Gielen S, Ebel H, Hochman JS. Mechanical circulatory support in cardiogenic shock. *Eur Heart J* 2014;**35**:156–167.
- Schrage B, Ibrahim K, Loehn T, Werner N, Sinning J-M, Pappalardo F, Pieri M, Skurk C, Lauten A, Landmesser U, Westenfeld R, Horn P, Pauschinger M, Eckner D, Twerenbold R, Nordbeck P, Salinger T, Abel P, Empen K, Busch MC, Felix SB, Sieweke J-T, Möller JE, Pareek N, Hill J, MacCarthy P, Bergmann MW, Henriques JPS, Möbius-Winkler S, Schulze PC, Quarrak T, Zeymer U, Schneider S, Blankenberg S, Thiele H, Schäfer A, Westermann D. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation* 2019;**139**:1249–1258.
- Nishihira K, Watanabe N, Kuriyama N, Shibata Y. Clinical outcomes of nonagenarians with acute myocardial infarction who undergo percutaneous coronary intervention. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:488–495.
- Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim H-S, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice M-C. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation* 2019;**140**:240–261.

9. Honda S, Nishihira K, Kojima S, Takegami M, Asaumi Y, Suzuki M, Kosuge M, Takahashi J, Sakata Y, Takayama M, Sumiyoshi T, Ogawa H, Kimura K, Yasuda S; JAMIR investigators. Rationale, design, and baseline characteristics of the prospective Japan Acute Myocardial Infarction Registry (JAMIR). *Cardiovasc Drugs Ther* 2019;**33**:97–103.
10. Yasuda S, Honda S, Takegami M, Nishihira K, Kojima S, Asaumi Y, Suzuki M, Kosuge M, Takahashi J, Sakata Y, Takayama M, Sumiyoshi T, Ogawa H, Kimura K; JAMIR Investigators. Contemporary antiplatelet therapy and clinical outcomes of Japanese patients with acute myocardial infarction—results from the Prospective Japan Acute Myocardial Infarction Registry (JAMIR). *Circ J* 2019;**83**:1633–1643.
11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation* 2012;**126**:2020–2035.
12. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583–612.
13. Kawaji T, Shiomi H, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Ando K, Mizoguchi T, Abe M, Takahashi M, Kimura T; on behalf of the CREDO-Kyoto AMI investigators. Long-term clinical outcomes in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock due to acute pump failure. *Eur Heart J Acute Cardiovasc Care* 2018;**7**:743–754.
14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–2747.
16. Nishihira K, Yoshioka G, Kuriyama N, Ogata K, Kimura T, Matsuura H, Furugen M, Koiwaya H, Watanabe N, Shibata Y. Impact of frailty on outcomes in elderly patients with acute myocardial infarction who undergo percutaneous coronary intervention. *Eur Heart J Qual Care Clin Outcomes* 2020;doi: 10.1093/ehjqcco/qcaa018.
17. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, Picard MH, Menegus MA, Boland J, Dzavik V, Thompson CR, Wong SC, Steingart R, Forman R, Aylward PE, Godfrey E, Desvigne-Nickens P, Lejemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999;**341**:625–634.
18. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward P, Col J, White HD; SHOCK Investigators. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 2006;**295**:2511–2515.
19. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, Richardt G, Hennerdsdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebel H, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
20. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, Eitel I, Pöss J, Fuernau G, de Waha S. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Heart J* 2017;**38**:3523–3531.
21. Dhruva SS, Ross JS, Mortazavi BJ, Hurley NC, Krumholz HM, Curtis JP, Berkowitz A, Masoudi FA, Messenger JC, Parzynski CS, Ngufo C, Girotra S, Amin AP, Shah ND, Desai NR. Intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2020;**323**:734–745.
22. Freund A, Jobs A, Lurz P, Feistritz H-J, de Waha-Thiele S, Meyer-Saraei R, Montalescot G, Huber K, Noc M, Windecker S, Zeymer U, Ouarrak T, Schneider S, Thiele H, Desch S. Frequency and impact of bleeding on outcome in patients with cardiogenic shock. *JACC Cardiovasc Interv* 2020;**13**:1182–1193.
23. Davidavicius G, Godino C, Shannon J, Takagi K, Bertoldi L, Mussardo M, Chieffo A, Arioli F, Ielasi A, Montorfano M, Latib A, Colombo A. Incidence of overall bleeding in patients treated with intra-aortic balloon pump during percutaneous coronary intervention: 12-year Milan experience. *JACC Cardiovasc Interv* 2012;**5**:350–357.
24. Nishihira K, Kojima S, Takegami M, Honda S, Nakao YM, Takahashi J, Itoh T, Watanabe T, Takayama M, Shimokawa H, Sumiyoshi T, Kimura K, Yasuda S; on behalf of the JAMIR Investigators. Clinical characteristics and in-hospital mortality according to left main and non-left main culprit lesions—report from the Japan Acute Myocardial Infarction Registry (JAMIR). *Circ Rep* 2019;**1**:601–609.
25. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol* 2007;**49**:1362–1368.
26. Marquis-Gravel G, Zeitouni M, Kochar A, Jones WS, Sketch MH, Rao SV, Patel MR, Ohman EM. Technical consideration in acute myocardial infarction with cardiogenic shock: a review of antithrombotic and PCI therapies. *Catheter Cardiovasc Interv* 2020;**95**:924–931.
27. Romagnoli E, De Vita M, Burzotta F, Cortese B, Biondi-Zoccai G, Summaria F, Patrizi R, Lanzillo C, Lucci V, Cavazza C, Tarantino F, Sangiorgi GM, Liyo E, Crea F, Rao SV, Trani C. Radial versus femoral approach comparison in percutaneous coronary intervention with intraaortic balloon pump support: the RADIAL PUMP UP registry. *Am Heart J* 2013;**166**:1019–1026.
28. Guedeney P, Thiele H, Kerneis M, Barthélémy O, Baumann S, Sandri M, de Waha-Thiele S, Fuernau G, Rouanet S, Piek JJ, Landmesser U, Hauguel-Moreau M, Zeitouni M, Silvain J, Lattuza B, Windecker S, Collet J-P, Desch S, Zeymer U, Montalescot G, Akin I; CULPRIT-SHOCK Investigators. Radial versus femoral artery access for percutaneous coronary artery intervention in patients with acute myocardial infarction and multivessel disease complicated by cardiogenic shock: Subanalysis from the CULPRIT-SHOCK trial. *Am Heart J* 2020;**225**:60–68.
29. Kadakia MB, Rao SV, McCoy L, Choudhuri PS, Sherwood MW, Lilly S, Kobayashi T, Kolansky DM, Wilensky RL, Yeh RW, Giri J. Transradial versus transfemoral access in patients undergoing rescue percutaneous coronary intervention after fibrinolytic therapy. *JACC Cardiovasc Interv* 2015;**8**:1868–1876.
30. Picard F, Llitjos J-F, Diefenbronn M, Laghnam D, Seret G, Sokoloff A, Cariou A, Dumas F, Varenne O. The balance of thrombosis and hemorrhage in STEMI patients with or without associated cardiac arrest: an observational study. *Resuscitation* 2019;**145**:83–90.