



Original article

Bleeding and ischemic events during dual antiplatelet therapy after second-generation drug-eluting stent implantation in hemodialysis patients



Akiyoshi Shimizu (MD), Shinjo Sonoda (MD, PhD, FJCC)*, Yoshitaka Muraoka (MD, PhD), Koshi Setoyama (MD), Konosuke Inoue (MD), Toshiya Miura (MD), Reo Anai (MD), Yoshinori Sanuki (MD, PhD), Tetsu Miyamoto (MD, PhD), Yasushi Oginosawa (MD, PhD), Yuki Tsuda (MD, PhD), Masaru Araki (MD, PhD), Yutaka Otsuji (MD, PhD, FJCC)

Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan

ARTICLE INFO

Article history:

Received 20 July 2018

Received in revised form 23 October 2018

Accepted 29 October 2018

Available online 24 December 2018

Keywords:

Drug-eluting stent

Hemodialysis

Dual-antiplatelet therapy

Bleeding event

Ischemic event

ABSTRACT

Background: Dual-antiplatelet therapy (DAPT) after second-generation drug-eluting stent (2nd-DES) implantation reduces the risk of stent thrombosis and subsequent ischemic events, with an increase in bleeding risk. Although chronic kidney disease patients have both high ischemic and bleeding events, little is known about both risks during DAPT in hemodialysis (HD) patients.

Methods: From July 2009 to March 2017, we retrospectively analyzed bleeding events and major adverse cardiac and cerebrovascular events (MACCE) in 644 consecutive patients who underwent successful percutaneous coronary intervention (PCI) with 2nd-DES implantation in our institution. We divided the patients into 2 groups [102 HD and 518 non-HD patients] after excluding 24 patients. The primary endpoint was bleeding events of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5. The secondary endpoint was MACCE. We also investigated potential bleeding risk factors in those patients. **Results:** At a median follow-up of 49 months, bleeding events occurred in 76 (12.3%) patients. Critical bleeding events of BARC type 3 or 5 occurred more frequently in HD (HD vs. non-HD: 16.7% vs. 7.1%; $p = 0.004$). Most events tended to occur within 6 months post PCI. Multivariate analysis demonstrated that HD [hazard ratio (HR) 2.50, 95% confidence interval (CI) 1.03–3.16; $p = 0.04$], body mass index (BMI) (HR 0.91, 95%CI 0.87–0.99, $p = 0.02$), and serum albumin (HR 0.35, 95%CI 0.34–0.96, $p = 0.03$) were independent predictors of bleeding events. MACCE also occurred more frequently in HD (HD vs. non-HD: 53.9% vs. 29.3%; $p < 0.001$). Multivariate analysis demonstrated that pre-dialysis systolic blood pressure (HR 1.03, 95%CI 1.00–1.06, $p = 0.02$) and high-sensitive C-reactive protein level (HR 1.76, 95%CI 1.06–2.72, $p = 0.03$) were independent predictors of bleeding events in HD.

Conclusions: HD displayed more adverse bleeding and ischemic events compared with non-HD. Therefore, practitioners should reconsider the current regimen of DAPT in this patient cohort to prevent critical bleeding complications and spates of ischemic events.

© 2018 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Dual-antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) is necessary to prevent stent thrombosis and subsequent ischemic events. Although the risk of stent thrombo-

sis and myocardial infarction (MI) are dramatically reduced in the era of second-generation drug-eluting stents (2nd-DES), DAPT is associated with an increased risk of bleeding unexpectedly [1–4]. Several trials have explored the safe reduction of DAPT duration to 3 to 6 months in patients with a high bleeding risk; on the other hand, other randomized trials have shown benefits of DAPT duration longer than 12 months [5,6]. To date, there has been no consensus on the optimal DAPT duration, although the importance of balancing the risks and benefits of prescribing DAPT after 2nd-DES implantation has been recognized. Therefore,

* Corresponding author at: Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan.

E-mail address: s-sonoda@med.uoeh-u.ac.jp (S. Sonoda).

it is imperative to optimize DAPT duration to patients' characteristics [7–11].

Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular morbidity and mortality. Furthermore, patients with CKD who are receiving anti-platelet therapy after PCI are also at an increased risk of both major adverse cardiac events and bleeding complications [12,13]. Several studies have also demonstrated that bleeding risk outweighs ischemic risk in the presence of moderate-to-severe CKD [14–16]. However, little is known about bleeding risk in hemodialysis (HD) during DAPT after PCI. This is because HD was less likely to be enrolled in various studies (including randomized controlled trials) of bleeding outcomes in CKD [15]. Therefore, the differences in the severity of bleeding events during DAPT between HD and non-hemodialysis (non-HD) need to be investigated.

HD is considered to have a higher ischemic risk and bleeding risk as compared with non-HD, and the DAPT regimen needs to be customized accordingly. Therefore, the aims of this study were to: (1) investigate whether HD is at an increased risk of post-discharge bleeding events such as Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 during DAPT and ischemic events after PCI compared with non-HD [17] [18]; and (2) investigate potential predictors of bleeding events during DAPT in HD.

Methods

Patient population

This study was a single-center, consecutive, and observational retrospective study conducted at the University of Occupational and Environmental Health, Kitakyushu, Japan. We evaluated 644 consecutive patients who underwent successful PCI treated with 2nd-DES implantation in our institution between July 2009 and March 2017. Patients lost to follow-up ($n = 20$) and those receiving peritoneal dialysis ($n = 4$) were excluded. As shown in Fig. 1, eventually 620 patients who underwent successful PCI with 2nd-DES were enrolled. At the time of discharge, more than 80% of all patients were prescribed DAPT, and the regimen included aspirin (100 mg/day) and a thienopyridine ($n = 551$) such as clopidogrel 75 mg/day ($n = 506$), ticlopidine 200 mg/day ($n = 22$), or prasugrel 3.75 mg/day ($n = 23$). The duration of DAPT was as per the attending physician's discretion. Follow-up was concluded on March 31, 2018. Data on post-discharge bleeding events and major adverse cardiac and cerebrovascular events (MACCE) were obtained from hospital charts and by telephonic interview. This study was approved by the ethics committee at the

institution and performed in accordance with the Declaration of Helsinki. Informed consents of all patients were obtained in the form of an opt-out option on our web-site.

Study objectives and definitions

The primary endpoint was the incidence of post-discharge adverse bleeding events, which were categorized according to BARC criteria [18]. The secondary endpoint was the incidence of MACCE, which was defined as cardiac death, non-fatal myocardial infarction (MI), target vessel revascularization (TVR), non-TVR, definite or probable stent thrombosis, and cerebral infarction. All causes of death were also recorded. We defined sudden cardiac death as an unexpected death in the previous 24 h who was known to have been well. In addition, both in-hospital bleeding and ischemic events were also recorded.

The following data were collected: age, sex, body mass index, coronary risk factors, MI, unstable angina, left ventricular ejection fraction (LVEF), medical history, prescribed medication, laboratory data to reflect baseline clinical characteristics, and procedural characteristics (Table 1). We defined each coronary risk factor as follows: hypertension, systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the current use of antihypertensive drugs; diabetes mellitus, fasting plasma glucose > 126 mg/dL, glycated hemoglobin concentration $\geq 6.5\%$, and requiring treatment with anti-diabetic agents or insulin; dyslipidemia, low-density lipoprotein cholesterol > 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL or requiring treatment with cholesterol-lowering agents; CKD, estimated glomerular filtration rates (eGFR) < 60 mL/min/1.73 m². Regarding systemic blood pressure, we collected systolic and diastolic blood pressure values during hospitalization in both HD and non-HD patients. In HD patients, pre-dialysis and post-dialysis systolic/diastolic blood pressure values were also averaged over the 3 months after PCI. Especially, in HD patients who experienced bleeding events during follow-up, the pre- and post-dialysis blood pressure values for 3 months before the events were averaged. In HD, HD duration was defined as the time from the initiation of HD until the time of PCI. The etiology of HD was investigated using the hospital charts.

Interventional procedures

PCI including stent implantation was performed according to standard techniques. The site of vascular access, type of guiding catheter, guide wire, and the medical therapy including the periprocedural antithrombotic regimen after PCI were as per the operator's discretion.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD) for normally distributed variables and as median values (interquartile range [IQR], 25th to 75th percentiles) for non-normally distributed variables. Categorical variables are expressed as numbers and percentages. Continuous variables were compared using two-tailed unpaired *t*-tests, and categorical variables were compared using the chi-squared test or Fisher's exact test. The cumulative incidences of bleeding events and MACCE between HD and non-HD was evaluated using the Kaplan–Meier method, and differences were evaluated using the log-rank test. All variables with a *p*-value of < 0.10 on univariate analysis were analyzed using the Cox hazards model to identify predictors of major bleeding events. For all analyses, a *p*-value of < 0.05 was considered as

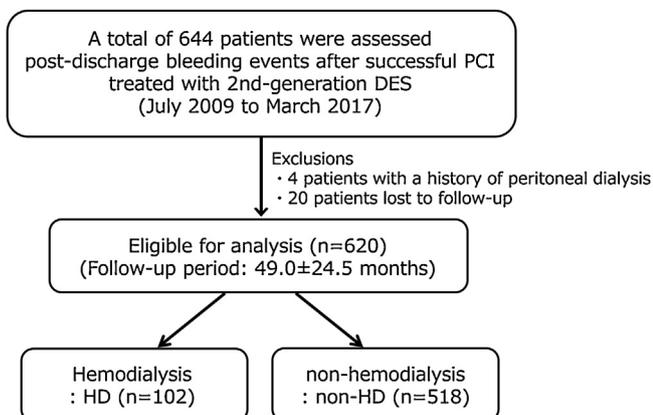


Fig. 1. Flow chart of the study design. DES, drug-eluting stent; PCI, percutaneous coronary intervention.

Table 1
Baseline clinical characteristics and procedural characteristics of study subjects (n = 620).

| Variables | Overall n = 620 | HD n = 102 | Non-HD n = 518 | p-Value |
|--|--------------------|------------------|-------------------|---------|
| Baseline clinical characteristics | | | | |
| Age (years) | 70.9 ± 10.5 | 68.4 ± 10.4 | 71.4 ± 10.5 | 0.01 |
| Sex, male, n (%) | 436 (70.3) | 66 (64.7) | 370 (71.4) | 0.18 |
| Body mass index | 23.4 ± 3.8 | 23.1 ± 4.5 | 23.4 ± 3.6 | 0.49 |
| Systolic blood pressure (mmHg) | 132.7 ± 22.6 | 145.0 ± 27.9 | 130.3 ± 20.6 | <0.001 |
| Diastolic blood pressure (mmHg) | 73.7 ± 15.3 | 75.2 ± 16.5 | 73.4 ± 15.1 | 0.29 |
| Hypertension, n (%) | 489 (78.9) | 93 (91.2) | 396 (76.5) | <0.001 |
| Diabetes mellitus, n (%) | 321 (51.8) | 73 (71.6) | 248 (47.9) | <0.001 |
| Dyslipidemia, n (%) | 579 (93.3) | 90 (88.2) | 489 (94.4) | 0.04 |
| Current smoker, n (%) | 154 (24.8) | 28 (27.5) | 126 (24.3) | 0.51 |
| Peripheral arterial disease, n (%) | 110 (17.7) | 36 (35.3) | 74 (14.3) | <0.001 |
| Acute myocardial infarction, n (%) | 124 (20.0) | 8 (7.8) | 116 (22.4) | <0.001 |
| Unstable angina, n (%) | 91 (14.7) | 12 (11.8) | 79 (15.3) | 0.35 |
| Prior PCI, n (%) | 108 (17.4) | 19 (18.6) | 89 (17.2) | 0.73 |
| Prior CABG, n (%) | 46 (7.4) | 12 (11.8) | 34 (6.6) | 0.08 |
| Old myocardial infarction, n (%) | 111 (17.9) | 17 (16.6) | 94 (18.2) | 0.72 |
| History of cerebral infarction, n (%) | 90 (14.5) | 16 (15.7) | 74 (14.3) | 0.72 |
| History of bleeding, n (%) | 48 (7.7) | 15 (14.7) | 33 (6.4) | 0.008 |
| History of malignancy, n (%) | 124 (20.0) | 21 (20.6) | 104 (20.1) | 0.87 |
| Atrial fibrillation, n (%) | 76 (12.3) | 14 (13.7) | 62 (12.0) | 0.63 |
| LVEF (%) | 49.8 ± 9.0 | 47.6 ± 9.8 | 50.2 ± 8.8 | 0.007 |
| Aspirin + Oral anticoagulant, n (%) | 1 (0.2) | 0 (0) | 1 (0.2) | 0.55 |
| Aspirin + Thienopyridine, n (%) | 551 (88.9) | 86 (84.3) | 465 (89.7) | 0.12 |
| Aspirin + Cilostazol, n (%) | 68 (11.0) | 16 (15.7) | 52 (10.0) | 0.11 |
| Triple therapy, n (%) | 79 (12.7) | 11 (10.8) | 68 (13.1) | 0.51 |
| DAPT duration (>1year), n (%) | 255 (41.1) | 44 (43.1) | 211 (40.7) | 0.65 |
| ACE-I/ARB, n (%) | 452 (72.9) | 75 (73.5) | 377 (72.8) | 0.88 |
| β-Blocker, n (%) | 339 (54.7) | 58 (56.9) | 281 (54.3) | 0.63 |
| Ca channel blocker, n (%) | 293 (47.3) | 65 (67.3) | 228 (44.0) | <0.001 |
| Statins, n (%) | 556 (89.7) | 86 (84.3) | 470 (90.7) | 0.06 |
| PPI, n (%) | 356 (57.4) | 59 (57.8) | 297 (57.8) | 0.92 |
| White blood cell (×10 ³ /μL) | 6.2 (4.9–7.6) | 5.8 (4.4–7.1) | 6.2 (4.9–7.7) | 0.047 |
| Hemoglobin (g/dL) | 12.7 (11.2–14.1) | 10.9 (9.8–12.1) | 12.9 (11.6–14.1) | <0.001 |
| Serum albumin (g/dL) | 3.9 (3.6–4.2) | 3.5 (3.3–3.8) | 3.9 (3.6–4.2) | <0.001 |
| Serum creatinine (mg/dL) | 0.92 (0.74–1.4) | 6.8 (5.64–8.41) | 0.86 (0.71–1.08) | <0.001 |
| High sensitivity CRP (mg/dL) | 0.12 (0.05–0.38) | 0.27 (0.10–0.69) | 0.11 (0.04–0.30) | <0.001 |
| Creatinine clearance (mL/min) | 55.8 (32.0–76.7) | 7.83 (5.99–9.85) | 62.2 (45.5–79.9) | <0.001 |
| Procedural characteristics | | | | |
| Vascular access site | | | | |
| Radial artery, n (%) | 412 (66.4) | 2 (2.0) | 410 (79.2) | <0.001 |
| Brachial artery, n (%) | 32 (5.2) | 9 (8.8) | 23 (4.4) | 0.09 |
| Femoral artery, n (%) | 176 (28.4) | 91 (89.2) | 85 (16.4) | <0.001 |
| Sheath size | | | | |
| 6Fr, n (%) | 559 (90.2) | 86 (84.3) | 473 (91.3) | 0.04 |
| 7Fr, n (%) | 61 (9.8) | 16 (15.7) | 45 (8.7) | 0.04 |
| Number of follow-up angiography, n (%) | 545 (87.9) | 84 (82.3) | 461 (89.0) | 0.07 |

Values are n (%), median (IQR), mean ± SD.
ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting-enzyme inhibitor; Ca, calcium; CABG, coronary artery bypass grafting; CI, confidence intervals; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; HD, hemodialysis; Non-HD, non-hemodialysis; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

statistically significant. Statistical analysis was performed using JMP 13 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

A total of 620 patients were evaluated for bleeding events and MACCE after successful PCI treated with 2nd-DES implantation. The mean clinical follow-up duration was 49.0 ± 24.5 months. The patient baseline characteristics and procedural characteristics are shown in Table 1. Mean age was 70.9 ± 10.5 years, and 70.3% of the study subjects were male. Overall, there were 102 HD (16.5%) and 518 non-HD (83.5%). Among a total of 518 non-HD, there were 223 (43.0%) patients with CKD. Due to multicollinearity, we did not include CKD in baseline characteristics of Table 1. The median DAPT duration was 12 months (IQR, 8–22). DAPT was prescribed in over 80% of all patients. Anticoagulant

therapy such as warfarin or a direct oral anticoagulant was prescribed in 12.7% of all patients. A high prevalence of cardiovascular risk factors such as hypertension (78.9%), dyslipidemia (93.3%), and diabetes mellitus (51.8%) was observed in this study population. As compared with non-HD, prevalence of hypertension (HD vs. non-HD: 91.2% vs. 76.5%; $p < 0.001$), diabetes mellitus (HD vs. non-HD: 71.6% vs. 47.9%; $p < 0.001$), and peripheral artery disease (HD vs. non-HD: 35.3% vs. 14.3%; $p < 0.001$) were significantly higher in HD. In laboratory data, white blood cell count, hemoglobin level, serum albumin level, and creatinine clearance were significantly lower and serum creatinine level and hs-CRP level were significantly higher in HD. Regarding procedural characteristics, femoral artery approach (HD vs. non-HD: 89.2% vs. 16.4%; $p < 0.001$) and 7Fr sheath size (HD vs. non-HD: 15.7% vs. 8.7%; $p = 0.04$) were significantly higher in HD than non-HD (Table 1). In addition, there were no significant differences in indications for PCI and the number of follow-up angiography between HD and non-HD.

Clinical outcomes

As shown in Table 2A, we collected all-cause mortality, bleeding events, and MACCE at post-discharge. All-cause mortality was significantly higher in HD than in non-HD [hazard ratio (HR) 2.61, 95% confidence interval (CI) 1.79–3.75, $p < 0.001$]. In total, bleeding events occurred in 76 (12.3%) patients. BARC type 2, 3, and 5 bleeding events occurred in 21 (3.4%), 46 (7.4%), and 9 (1.5%) patients, respectively. Adverse bleeding events of BARC type 2, 3, or 5 were significantly higher in HD than in non-HD (HR 2.50, 95% CI 1.49–4.06; $p < 0.001$). Regarding BARC type 3 or 5, the HR increased in HD (HR 2.83, 95% CI 1.55–4.95; $p = 0.001$) (Table 2A). Major bleeding events were intracranial bleeding (HD vs. non-HD: 36.4% vs. 37.0%) and gastrointestinal bleeding (HD vs. non-HD: 50.0% vs. 44.4%). There was no significant difference in the occurrence of both complications between HD and non-HD (Fig. 2). DAPT duration was not associated with bleeding events in this cohort. In addition, DAPT with oral anticoagulant therapy was not associated with bleeding events (Table 3A). Among thienopyridine antiplatelet drugs, prasugrel did not show any significant difference in post-discharge bleeding events compared with others. Multivariate analysis demonstrated that HD (HR 1.83, 95%CI 1.03–3.16, $p = 0.04$), body mass index (BMI) (HR 0.91, 95%CI 0.87–0.99, $p = 0.02$), and serum albumin (HR 0.35, 95%CI 0.34–0.96, $p = 0.03$) were independent predictors of bleeding events (Table 3B). In total, MACCE occurred significantly more frequently in HD than in non-HD (HD vs. non-HD: 53.9% vs. 29.3%; $p < 0.001$). The incidences of cardiac death (HR 6.20, 95%CI 3.18–12.1; $p < 0.001$) and TVR (HR 2.60, 95%CI 1.48–4.36; $p = 0.001$) were significantly higher in HD than in non-HD (Table 2A). The rate of sudden cardiac death was included in approximately 25% of cardiac

deaths. As shown in Table 2B, both in-hospital bleeding events and MACCE rate tended to be higher in HD than in non-HD, however, there were no statistically significant differences.

More than 25% of post-discharge bleeding events tended to occur within 6 months post-PCI in both groups (HD vs. non-HD: 27.3% vs. 26.0%, $p = 0.90$) (Fig. 3A and B). The PRECISE-DAPT score, which can predict bleeding risk at 12 months post-PCI, showed almost all HD patients were above 25 points (high bleeding risk) [8]. Cumulative incidences of both bleeding events (HD vs. non-HD: 8.1% vs. 4.5%) and MACCE (HD vs. non-HD: 29.2% vs. 16.2%) at 12 months post-PCI were higher in HD than in non-HD (Fig. 4).

The baseline characteristics in HD are shown in Table 4A. In HD, the bleeding group had a significantly higher level of pre-dialysis SBP (bleeding vs. non-bleeding: 163.6 ± 17.8 vs. 150.8 ± 22.8 ; $p = 0.02$) and hs-CRP [bleeding vs. non-bleeding: 0.59 (0.25–0.96) vs. 0.24 (0.09–0.72); $p = 0.02$] than those in the non-bleeding group (Table 4A). Multivariate analysis demonstrated that both pre-dialysis SBP (HR, 1.03; 95% CI 1.00–1.06; $p = 0.02$) and hs-CRP (HR, 1.76; 95% CI 1.06–2.72; $p = 0.03$) were independent predictors of bleeding events in HD (Table 4B). A pre-dialysis SBP of 145 mmHg or higher was associated with bleeding events in HD, as evidenced by results of the receiver operating characteristic curve analysis.

Discussion

The main findings of this study are as follows: (1) compared with non-HD, HD was significantly more likely to have adverse bleeding events after 2nd-DES implantation; (2) as a whole, HD, BMI, and serum albumin level were independent predictors of bleeding events in this cohort; and (3) in HD, serum hs-CRP level

Table 2A
All-cause mortality, bleeding events, and major adverse cardiac and cerebrovascular events at post-discharge.

| Variables | HD <i>n</i> = 102 | Non-HD <i>n</i> = 518 | Univariable analysis | | |
|-----------------------------------|----------------------|--------------------------|----------------------|------------|-----------------|
| | | | HR | 95% CI | <i>p</i> -Value |
| All-cause mortality, <i>n</i> (%) | 41 (40.2) | 94 (18.2) | 2.61 | 1.79–3.75 | <0.001 |
| Primary endpoint | | | | | |
| BARC classification | | | | | |
| Type 2, 3 or 5, <i>n</i> (%) | 22 (21.6) | 54 (10.4) | 2.50 | 1.49–4.06 | <0.001 |
| Type 3 or 5, <i>n</i> (%) | 17 (16.7) | 37 (7.1) | 2.83 | 1.55–4.95 | 0.001 |
| Secondary endpoint | | | | | |
| MACCE, <i>n</i> (%) | 55 (53.9) | 152 (29.3) | 2.40 | 1.75–3.25 | <0.001 |
| Cardiac death, <i>n</i> (%) | 18 (17.7) | 17 (3.3) | 6.20 | 3.18–12.1 | <0.001 |
| TVR, <i>n</i> (%) | 19 (18.6) | 46 (8.9) | 2.60 | 1.48–4.36 | 0.001 |
| Non-TVR, <i>n</i> (%) | 15 (14.7) | 62 (12.0) | 1.61 | 0.88–2.75 | 0.12 |
| MI, <i>n</i> (%) | 2 (2.0) | 6 (1.2) | 2.19 | 0.32–9.54 | 0.37 |
| Stent thrombosis, <i>n</i> (%) | 1 (1.0) | 1 (0.2) | 6.98 | 0.27–181.4 | 0.20 |
| Cerebral infarction, <i>n</i> (%) | 5 (4.9) | 22 (4.3) | 1.60 | 0.53–3.91 | 0.37 |

Values are *n*.
BARC, Bleeding Academic Research Consortium; CI, confidence intervals; HD, hemodialysis; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; Non-HD, non-hemodialysis; TVR, target vessel revascularization.

Table 2B
In-hospital bleeding and ischemic events in patients with or without hemodialysis.

| Variables | HD <i>n</i> = 102 | Non-HD <i>n</i> = 518 | Univariable analysis | | |
|---------------------------------------|----------------------|--------------------------|----------------------|-----------|-----------------|
| | | | OR | 95% CI | <i>p</i> -Value |
| Bleeding events | | | | | |
| BARC Type 2 or 3, <i>n</i> (%) | 8 (7.8) | 20 (3.9) | 2.12 | 0.91–4.95 | 0.10 |
| Ischemic events | | | | | |
| MACCE, <i>n</i> (%) | 2 (2.0) | 4 (0.8) | 2.57 | 0.46–14.2 | 0.31 |
| New MI, <i>n</i> (%) | 1 (1.0) | 0 (0) | – | – | – |
| New cerebral infarction, <i>n</i> (%) | 1 (1.0) | 4 (0.8) | 1.27 | 0.14–11.5 | 0.83 |
| New stent thrombosis, <i>n</i> (%) | 0 (0) | 0 (0) | – | – | – |

Values are *n*.
BARC, Bleeding Academic Research Consortium; CI, confidence intervals; HD, hemodialysis; OR, odds ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; Non-HD, non-hemodialysis.

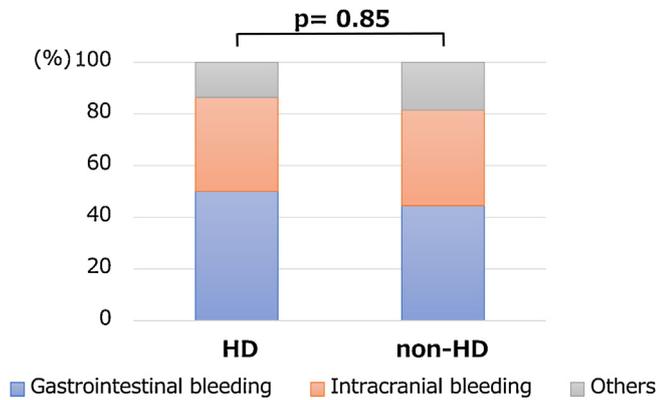


Fig. 2. Causes of bleeding events by hemodialysis status. Comparison of causes of bleeding events in hemodialysis (HD) and non-hemodialysis (non-HD).

and pre-dialysis SBP were independent predictors of adverse bleeding events.

This is the first study to demonstrate that HD was an independent predictor of adverse bleeding events during DAPT after PCI. Furthermore, both serum hs-CRP level and pre-dialysis SBP were independent bleeding predictors in HD.

A previous study confirmed that CKD was a risk factor for both ischemic and bleeding events [12,17]. In patients with moderate-to-severe CKD, DAPT had a higher reduction in the rates of stent thrombosis and subsequent ischemic events with an increased risk

of bleeding compared with those with mild or no CKD [16]. However, evidence in patients with HD is limited. While HD has been thought to be more likely to cause bleeding events compared with non-HD, the current PCI guidelines did not provide a detailed DAPT regimen for HD patients. Accordingly, we evaluated the bleeding risk in patients with HD after PCI.

Two recent studies focused on bleeding events in patients with HD during DAPT after PCI. A large retrospective cohort study by Chen et al. investigated the efficacy and safety of optimal DAPT duration between 6 months and 12 months [13]. This study showed clinical utility of a 6-month course of DAPT in HD. In another retrospective observational study, Asami et al. examined the occurrence of bleeding events up to one year after PCI in the 1st-generation DES era [19]. However, there were no data regarding both severity and timing of bleeding events during DAPT after PCI comparing HD and non-HD. In the current study, we conducted a comparative study of adverse bleeding events between HD and non-HD after 2nd-DES implantation.

In the current study, HD accounted for approximately 17% of all patients, allowing us to compare adverse events between HD and non-HD. Our results revealed a higher likelihood of fatal bleeding events such as BARC type 3 or 5 in HD compared with those in non-HD. HD was one of the independent predictors of bleeding events. BMI and serum albumin level were also important predictors of bleeding events in this cohort.

Regarding the timing of bleeding events, more than 25% of those tended to occur within 6 months post-PCI in both HD and non-HD;

Table 3A

Baseline characteristics comparing patients with bleeding events and those without.

| Variables | Bleeding (+) n = 76 | Bleeding (-) n = 544 | p-Value |
|---|------------------------|-------------------------|---------|
| Age (years) | 72.0 ± 10.7 | 70.7 ± 10.5 | 0.32 |
| Sex, male, n (%) | 48 (63.2) | 388 (71.3) | 0.15 |
| Body mass index | 22.5 ± 3.7 | 23.5 ± 3.8 | 0.02 |
| Systolic blood pressure (mmHg) | 135.9 ± 24.2 | 132.3 ± 22.4 | 0.19 |
| Diastolic blood pressure (mmHg) | 76.3 ± 16.2 | 73.3 ± 15.2 | 0.11 |
| Hypertension, n (%) | 63 (82.9) | 426 (78.3) | 0.35 |
| Diabetes mellitus, n (%) | 47 (61.8) | 274 (50.4) | 0.06 |
| Dyslipidemia, n (%) | 69 (90.8) | 510 (93.8) | 0.35 |
| Current smoker, n (%) | 15 (19.7) | 139 (25.6) | 0.26 |
| Hemodialysis, n (%) | 22 (29.0) | 80 (14.7) | 0.003 |
| Peripheral arterial disease, n (%) | 14 (18.4) | 96 (17.7) | 0.87 |
| Acute myocardial infarction, n (%) | 16 (21.1) | 108 (19.9) | 0.81 |
| Unstable angina, n (%) | 12 (15.8) | 79 (14.5) | 0.77 |
| Prior PCI, n (%) | 14 (18.4) | 94 (17.3) | 0.81 |
| Prior CABG, n (%) | 6 (7.9) | 40 (7.4) | 0.87 |
| Old myocardial infarction, n (%) | 11 (14.5) | 100 (18.4) | 0.39 |
| History of cerebral infarction, n (%) | 14 (18.4) | 76 (14.0) | 0.32 |
| History of bleeding, n (%) | 7 (9.2) | 41 (7.5) | 0.62 |
| History of malignancy, n (%) | 20 (26.3) | 104 (19.1) | 0.15 |
| Atrial fibrillation, n (%) | 12 (15.8) | 64 (11.8) | 0.63 |
| LVEF (%) | 48.1 ± 9.8 | 50.0 ± 8.9 | 0.11 |
| Aspirin + Oral anticoagulant, n (%) | 0 (0) | 1 (0.2) | 0.61 |
| Aspirin + Thienopyridine, n (%) | 71 (93.4) | 480 (88.2) | 0.15 |
| Aspirin + Cilostazol, n (%) | 5 (6.6) | 63 (11.6) | 0.17 |
| Triple therapy, n (%) | 13 (17.1) | 66 (12.1) | 0.24 |
| DAPT duration (>1 year), n (%) | 34 (44.7) | 221 (40.6) | 0.50 |
| ACE-I/ARB, n (%) | 58 (76.3) | 394 (72.4) | 0.47 |
| β-Blocker, n (%) | 43 (56.6) | 296 (54.4) | 0.72 |
| Ca channel blocker, n (%) | 39 (51.3) | 254 (46.7) | 0.45 |
| Statins, n (%) | 64 (84.2) | 492 (90.4) | 0.11 |
| PPI, n (%) | 44 (57.9) | 312 (57.4) | 0.93 |
| White blood cell (×10 ³ /μL) | 5.8 (4.6–7.8) | 6.2 (4.9–7.6) | 0.37 |
| Hemoglobin (g/dL) | 11.9 (10.4–13.5) | 12.7 (11.2–14.1) | 0.002 |
| Serum albumin (g/dL) | 3.7 (3.3–4.0) | 3.9 (3.6–4.2) | 0.001 |
| High sensitivity CRP (mg/dL) | 0.25 (0.09–0.78) | 0.12 (0.05–0.35) | 0.002 |

Values are n (%), median (IQR), mean ± SD.

ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting-enzyme inhibitor; Ca, calcium; CABG, coronary artery bypass grafting; CI, confidence intervals; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

Table 3B
Predictors of bleeding events.

| Variables | Univariable analysis | | | Multivariable analysis | | |
|----------------------|----------------------|-----------|---------|------------------------|-----------|---------|
| | HR | 95% CI | p-Value | HR | 95% CI | p-Value |
| Body mass index | 0.91 | 0.85–0.97 | 0.01 | 0.93 | 0.87–0.99 | 0.02 |
| Diabetes mellitus | 1.62 | 1.02–2.60 | 0.04 | 1.29 | 0.78–2.15 | 0.33 |
| Hemodialysis | 2.50 | 1.49–4.06 | <0.001 | 1.83 | 1.03–3.16 | 0.04 |
| LVEF | 0.97 | 0.95–0.99 | 0.02 | 0.99 | 0.97–1.01 | 0.42 |
| Statins | 0.52 | 0.29–1.01 | 0.05 | 0.70 | 0.39–1.37 | 0.28 |
| Serum albumin | 0.35 | 0.24–0.53 | <0.001 | 0.57 | 0.34–0.96 | 0.03 |
| Hemoglobin | 0.82 | 0.74–0.92 | <0.001 | 0.98 | 0.86–1.13 | 0.82 |
| High sensitivity CRP | 1.31 | 1.10–1.50 | 0.004 | 1.18 | 0.96–1.40 | 0.11 |

CI, confidence intervals; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction.

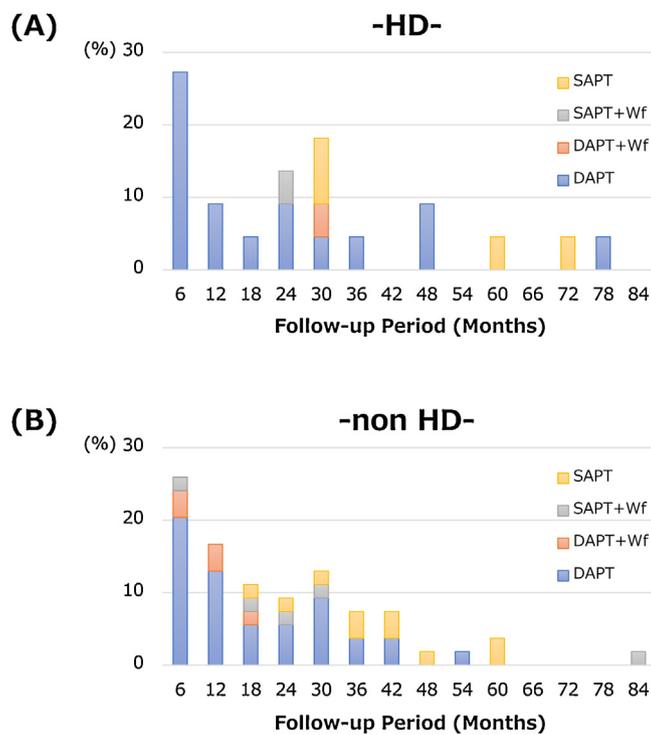


Fig. 3. Timing of the occurrence of hemorrhagic events and the antiplatelet therapy at the events. (A) Hemodialysis patients. (B) Non-hemodialysis patients. SAPT, single antiplatelet therapy; Wf, warfarin; DAPT, dual antiplatelet therapy.

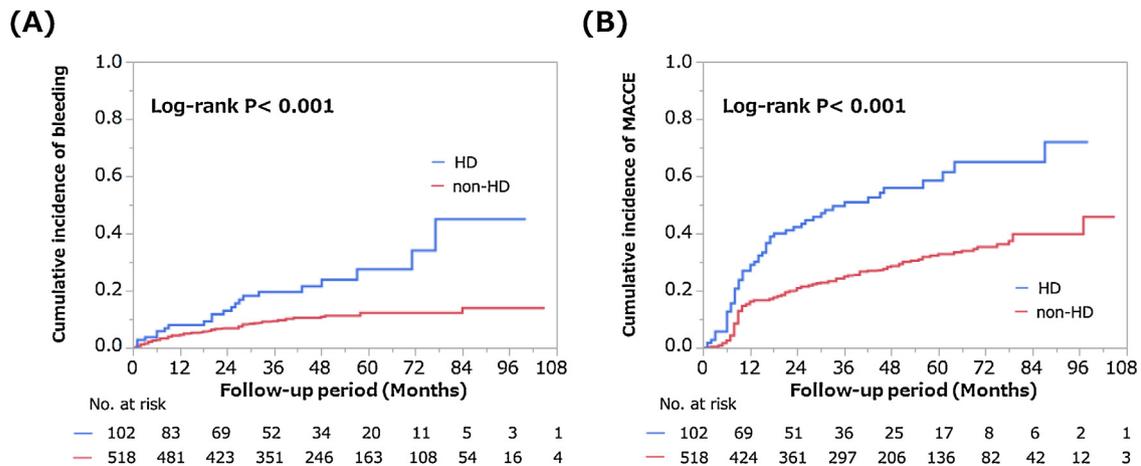


Fig. 4. Kaplan–Meier curves for primary and secondary endpoints. (A) Cumulative incidence of bleeding events. (B) Cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE).

Table 4A

Baseline clinical characteristics of hemodialysis patients comparing patients with bleeding events and those without.

| Variables | Bleeding (+) n = 22 | Bleeding (-) n = 80 | p-Value |
|---|------------------------|------------------------|---------|
| Age (years) | 68.6 ± 9.0 | 68.4 ± 10.8 | 0.92 |
| Sex, male, n (%) | 15 (68.2) | 51 (63.8) | 0.70 |
| Body mass index | 22.7 ± 3.9 | 23.3 ± 4.6 | 0.57 |
| Pre-dialysis SBP (mmHg) | 163.6 ± 17.8 | 150.8 ± 22.8 | 0.02 |
| Pre-dialysis DBP (mmHg) | 79.2 ± 9.6 | 75.5 ± 10.6 | 0.15 |
| Post-dialysis SBP (mmHg) | 149.3 ± 16.5 | 142.5 ± 19.7 | 0.14 |
| Post-dialysis DBP (mmHg) | 75.3 ± 8.2 | 73.3 ± 9.8 | 0.39 |
| Hypertension, n (%) | 21 (95.5) | 772 (90.0) | 0.39 |
| Diabetes mellitus, n (%) | 18 (81.8) | 555 (68.8) | 0.21 |
| Dyslipidemia, n (%) | 19 (86.4) | 71 (88.8) | 0.76 |
| Current smoker, n (%) | 6 (27.3) | 22 (27.4) | 0.98 |
| Peripheral arterial disease, n (%) | 5 (22.7) | 31 (38.7) | 0.15 |
| Acute myocardial infarction, n (%) | 2 (9.1) | 6 (7.5) | 0.81 |
| Prior PCI, n (%) | 2 (9.1) | 17 (21.3) | 0.17 |
| Prior CABG, n (%) | 3 (13.6) | 9 (11.3) | 0.76 |
| Old myocardial infarction, n (%) | 2 (9.1) | 15 (18.8) | 0.25 |
| History of cerebral infarction, n (%) | 5 (22.7) | 11 (13.8) | 0.32 |
| History of bleeding, n (%) | 1 (4.6) | 14 (17.5) | 0.09 |
| History of malignancy, n (%) | 4 (18.2) | 17 (21.3) | 0.75 |
| Atrial fibrillation, n (%) | 3 (13.6) | 11 (13.8) | 0.99 |
| LVEF (%) | 45.7 ± 8.9 | 48.1 ± 10.0 | 0.30 |
| Aspirin + Thienopyridine, n (%) | 21 (95.5) | 65 (81.3) | 0.07 |
| Aspirin + Cilostazol, n (%) | 1 (4.6) | 15 (18.8) | 0.07 |
| Triple therapy, n (%) | 2 (9.1) | 9 (11.3) | 0.83 |
| DAPT duration (>1 year), n (%) | 11 (50.0) | 33 (41.3) | 0.46 |
| ACE-I/ARB, n (%) | 18 (81.8) | 57 (71.3) | 0.31 |
| β-Blocker, n (%) | 10 (45.5) | 48 (60.0) | 0.22 |
| Ca channel blocker, n (%) | 13 (59.1) | 52 (65.0) | 0.61 |
| Statins, n (%) | 17 (77.3) | 69 (86.3) | 0.32 |
| PPI, n (%) | 11 (50.0) | 48 (60.0) | 0.40 |
| White blood cell (×10 ³ /μL) | 5.7 (4.0–7.5) | 5.9 (4.5–7.1) | 0.91 |
| Hemoglobin (g/dL) | 11.5 (10.3–12.1) | 10.9 (9.8–12.1) | 0.36 |
| Serum albumin (g/dL) | 3.6 (3.2–3.8) | 3.6 (3.3–3.8) | 0.93 |
| High sensitivity CRP (mg/dL) | 0.59 (0.25–0.96) | 0.24 (0.09–0.72) | 0.02 |
| HD duration (months) | 45.2 ± 19.6 | 79.6 ± 10.0 | 0.06 |

Values are n (%), median (IQR), mean ± SD.

ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting-enzyme inhibitor; Ca, calcium; CABG, coronary artery bypass grafting; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; HD, hemodialysis; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SBP, systolic blood pressure.

Table 4B

Predictors of bleeding events in hemodialysis patients.

| Variables | Univariable analysis | | | Multivariable analysis | | |
|----------------------|----------------------|-----------|---------|------------------------|-----------|---------|
| | HR | 95% CI | p-Value | HR | 95% CI | p-Value |
| Pre-dialysis SBP | 1.03 | 1.00–1.05 | 0.02 | 1.03 | 1.00–1.06 | 0.02 |
| LVEF | 0.96 | 0.92–1.00 | 0.08 | 0.97 | 0.93–1.01 | 0.11 |
| High sensitivity CRP | 1.79 | 1.09–2.72 | 0.03 | 1.76 | 1.06–2.72 | 0.03 |

SBP, systolic blood pressure; CI, confidence intervals; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction.

this observation may imply a probable limitation of the current regimens for DAPT (stable angina: 6 months, MI: 12 months). For HD patients with a high bleeding risk, a short DAPT regimen within 6 months might be implemented. In addition, intracranial bleeding and gastrointestinal bleeding were the most frequent identifiable sources, and there was no significant difference in the distribution of bleeding events between HD and non-HD. As shown in previous studies conducted in Western countries, gastrointestinal bleeding was the most common bleeding event after PCI regardless of the presence or absence of HD [14]. Although the overall tendency of bleeding events was similar, the event rate of intracranial bleeding in both HD and non-HD was about 5 times higher than that in Western countries, which may be explained by the fact that the Japanese population is more susceptible to antithrombotic therapy-related intracranial bleeding events [20]. We did not observe a correlation between the regimen of triple antithrombo-

tic therapy including warfarin and bleeding events in this study, which may due to small sample size of HD.

As shown in Fig. 4, the event rate of MACCE at 12 months in non-HD (16.2%) was higher than those previously reported in non-HD. This may be explained by the higher rate of CKD patients (approximately 43%) and the number of elderly patients over the age of 75 years (approximately 45%) in non-HD in this study. Indeed, CKD and advanced age are associated with MACCE [12,21].

Interpretation of bleeding risk factors

At present, bleeding risk factors in HD prescribed DAPT after PCI have not been clarified. Thus, we evaluated potential bleeding risk factors in our study. As a result, serum hs-CRP level and pre-dialysis SBP were identified as risk factors of bleeding events in HD.

In general, the hs-CRP level has been reported as a risk factor for cardiovascular events [22,23]. However, the mechanism connecting bleeding risk to hs-CRP level is not clear. According to the previous study, combined effects of inflammation, inappropriate protein and caloric intake cause hypoalbuminemia [24]. Since decreased serum albumin is known as a bleeding risk factor on antiplatelet therapy after PCI, we speculated that combination of hs-CRP as a marker of inflammation, malnutrition (low-BMI), and hypoalbuminemia might be associated with bleeding risks during DAPT [25,26].

In our study, pre-dialysis SBP was also found to be associated with bleeding risk in HD. A previous study revealed the relationship between hemorrhagic stroke accompanying DAPT and elevated SBP more than 140 mmHg after PCI [27].

The most recent European Society of Cardiology (ESC) guidelines recommend a 3–6-month course of DAPT after DES implantation in patients with a high bleeding risk [28]. In HD, it may be necessary to shorten the DAPT regimen as much as possible in addition to implementing strict blood pressure management. Currently, the Short and Optimal duration of Dual AntiPlatelet Therapy-2 (STOPDAPT2) study (UMIN00019948) is being conducted with a protocol to evaluate the safety of reducing DAPT duration to 1 month after implantation of the everolimus-eluting cobalt-chromium stent [29]. Since HD is associated with not only bleeding risk but ischemic risk such as stent thrombosis or additional ischemic events, single antiplatelet therapy (SAPT) by potent P2Y12 antagonist monotherapy will be strongly recommended following short DAPT. At present, the Prasugrel monotherapy after Drug-eluting stent deployment as a Management Of patients who are unsuitable for long-term dual antiplatelet therapy (-PENDULUM mono-) trial (UMIN00028023) is investigating the efficacy and safety regarding whether prasugrel is clinically viable for SAPT [30]. Combining newly potent P2Y12 monotherapy following 1-month DAPT might be effective in HD.

Limitations

There are several limitations in this study. First, this was a single-center, consecutive and observational retrospective study with a small sample size. Second, we assessed the laboratory data and medication details only once at baseline. The choice of DAPT and the duration of DAPT were as per the attending physician's discretion. Third, we did not analyze the cut-off values for hs-CRP to unconfound the results of this study. Further studies are necessary to consider the significance and the cut-off value of hs-CRP. Fourth, due to the existence of multicollinearity between serum creatinine and HD, we did not include serum creatinine and/or creatinine clearance as one of the predictors of bleeding events. Lastly, the results may not necessarily be adaptable to a non-Japanese population, because all the study patients were of Japanese origin.

Conclusion

HD displayed more adverse bleeding and ischemic events compared with non-HD. Therefore, we need to reconsider the current regimen of DAPT in this patient cohort to prevent critical bleeding complications and spates of ischemic events.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors declare that there is no conflict of interest.

References

- Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (Prolonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study). *JACC Cardiovasc Interv* 2014;7:20–8.
- Gada H, Kirtane AJ, Newman W, Sanz M, Hermiller JB, Mahaffey KW, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 2013;6:1263–6.
- Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. *Circulation* 2009;119:987–95.
- Tsuchida K, Ikegami R, Sato M, Shobugawa Y, Okubo T, Yano T, et al. Primary percutaneous coronary intervention and bleeding risk in the era of drug-eluting stent: a long-term cohort study. *Cardiovasc Interv Ther* 2015;30:216–26.
- Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A critical appraisal of aspirin in secondary prevention: is less more? *Circulation* 2016;134:1881–906.
- Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155–66.
- Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735–49.
- Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025–34.
- Valgimigli M, Gargiulo G. DAPT duration after drug-eluting stent implantation: no news is good news. *JACC Cardiovasc Interv* 2017;10:1211–4.
- Nakamura M, Kougame N, Iijima R, Ono T, Ikeda N, Tokue M, et al. Individualized antiplatelet therapy after drug-eluting stent deployment: Implication of clinical trials of different durations of dual antiplatelet therapy. *J Cardiol* 2017;70:511–7.
- Lugo LM, Ferreiro JL. Dual antiplatelet therapy after coronary stent implantation: Individualizing the optimal duration. *J Cardiol* 2018;72:94–104.
- Kaya E, Cuneo A, Hochadel M, Junger C, Stepper W, Bramlage P, et al. Impact of chronic kidney disease on the prognosis of patients undergoing percutaneous coronary interventions using drug-eluting stents. *Clin Res Cardiol* 2011;100:1103–9.
- Chen YT, Chen HT, Hsu CY, Chao PW, Kuo SC, Ou SM, et al. Dual antiplatelet therapy and clinical outcomes after coronary drug-eluting stent implantation in patients on hemodialysis. *Clin J Am Soc Nephrol* 2017;12:262–71.
- Généreux P, Giustino G, Witzensbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol* 2015;66:1036–45.
- Honda Y, Yamawaki M, Mori S, Shirai S, Makino K, Tokuda T, et al. Frequency and predictors of bleeding events after 2nd generation drug-eluting stent implantation differ depending on time after implantation. *J Cardiol* 2017;69:632–9.
- Gargiulo G, Santucci A, Piccolo R, Franzone A, Ariotti S, Baldo A, et al. Impact of chronic kidney disease on 2-year clinical outcomes in patients treated with 6-month or 24-month DAPT duration: An analysis from the PRODIGY trial. *Catheter Cardiovasc Interv* 2017;90:E73–84.
- Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;156:445–59.
- Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–47.
- Asami M, Aoki J, Sato T, Tanimoto S, Watanabe M, Horiuchi Y, et al. Impact of stent type and prolonged dual antiplatelet therapy on long-term clinical outcomes in hemodialysis patients with coronary artery disease. *Cardiovasc Interv Ther* 2018;33:84–94.
- Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M, et al. Incidence of stroke in Shibata, Japan: 1976–1978. *Stroke* 1981;12:460–6.
- Stähli BE, Wischnowsky MB, Jakob P, Klingenberg R, Obeid S, Heg D, et al. Gender and age differences in outcomes of patients with acute coronary syndromes referred for coronary angiography. *Catheter Cardiovasc Interv* 2018. <http://dx.doi.org/10.1002/ccd.27712>.

- [22] Wang A, Liu J, Li C, Gao J, Li X, Chen S, et al. Cumulative exposure to high-sensitivity C-reactive protein predicts the risk of cardiovascular disease. *J Am Heart Assoc* 2017;6:e005610.
- [23] Stenvinkel P, Lindholm B. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation* 2006;114:281–8.
- [24] Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial* 2004;17:432–7.
- [25] Tatami Y, Ishii H, Aoki T, Harada K, Hirayama K, Shibata Y, et al. Decreased serum albumin predicts bleeding events in patients on antiplatelet therapy after percutaneous coronary intervention. *Circ J* 2017;81:999–1005.
- [26] Wirth R, Streicher M, Smoliner C, Kolb C, Hiesmayr M, Thiem U, et al. The impact of weight loss and low BMI on mortality of nursing home residents - Results from the nutritionDay in nursing homes. *Clin Nutr* 2016;35:900–6.
- [27] Kai H, Kohro T, Fukuda K, Yamazaki T, Nagai R. Impact of systolic blood pressure on hemorrhagic stroke in patients with coronary artery disease during antiplatelet therapy: The Japanese Coronary Artery Disease (JCAD) study. *Int J Cardiol* 2016;224:112–3.
- [28] Jeppsson A, Petricevic M, Kolh P, Valgimigli M. 2017 European Society of Cardiology (ESC) focused update on dual antiplatelet therapy in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2018;53:3–4.
- [29] UMIN Clinical Trial Registry. www.umin.ac.jp/ctr/. Identifier: UMIN000019948.
- [30] UMIN Clinical Trial Registry. www.umin.ac.jp/ctr/. Identifier: UMIN000028023.