Clinical Utility of the BIWACO Score for Patients With Atrial Fibrillation After Percutaneous Coronary Intervention

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Abstract

Background: No predictive clinical risk scores for net adverse clinical events (NACE) have been developed in patients with atrial fibrillation (AF) after percutaneous coronary intervention (PCI).

Methods: We evaluated the NACE in order to develop clinically applicable risk-stratification scores in the BIWACO study, a multicenter survey which enrolled a total of 7837 patients. We also investigated the current status and time trends for the use of antithrombotic drugs.

Results: A total of 188 AF patients who had received PCI were enrolled. At discharge, 65% of patients were prescribed a triple therapy (TT), 6% were prescribed a dual therapy, the remaining 29% of patients received dual-antiplatelet therapy. Over 3 years, the fraction of patients continuing TT decreased by 15%, whereas only 2% received oral anticoagulant alone. NACE developed in 20% of patients, resulting in the deaths of 5% patients, and 13% experiencing bleeding events. We developed risk scores for NACE comprising the five best predictive items, which we designated BIWACO scores. The area under the curve was 0.774 for NACE.

Conclusions: Our study explored the differences in treatment practices and guideline recommendations for antithrombotic therapy. We concluded that our BIWACO score is useful for predicting clinical outcomes in AF-patients after PCI.

Introduction

Atrial fibrillation (AF) is one of the major causes of stroke, heart failure (HF), sudden death, and cardiovascular morbidity. It requires oral anticoagulant (OAC) therapy to mitigate against thromboembolic events (1). Coronary artery disease is present in 20%-30% of patients with AF; approximately 5%-10% of patients requiring percutaneous coronary intervention (PCI) present with AF and so have an indication for chronic OAC (2–4). Because dual-antiplatelet therapy (DAPT) is recommended for all stent-implanted patients, those with AF undergoing PCI are at a substantially higher risk of serious bleeding resulting from the use of multiple antithrombotic drugs. It is very important to select which types of antithrombotic agents to use, after carefully considering the balance between safety and efficacy, despite the fact that 2nd generation drug-eluting stents (DES) cause a lower incidence of stent thrombosis compared to previous stents (5). A network meta-analysis of randomized controlled trials investigated the safety and efficacy of different antithrombotic regimens post–PCI for these high-risk patients with AF. This concluded that an antithrombotic regimen of a direct antagonist oral anticoagulant (DOAC) plus P2Y12 inhibitor results in less bleeding compared with a regime of vitamin K oral antagonist (VKA) plus DAPT (6). Therefore, current guidelines recommend a short period of triple therapy (TT) (i.e. an OAC plus aspirin and a P2Y12 inhibitor) followed by dual therapy (DT) comprising an OAC and one antiplatelet agent (7, 8). The general consensus is to continue oral anticoagulation and to modify antiplatelet drug intensity and duration as necessary. However, TT or DT are likely to be continued for longer periods in daily clinical practice reflecting physicians' concerns about safety. Thus, there seems to

be a disconnect between current antithrombotic regimens in practice and the recommendations in the guidelines. Little is known about trends in the actual use of the individualized antithrombotic therapies in patients with AF undergoing PCI (9). Several risk scores for thrombosis and bleeding have been proposed previously for patients with either PCI or AF (10–13), but no predictive clinical risk factor scores have been established for patients with AF and concomitant PCI. To this end, first, we evaluated the outcomes of antithrombotic therapy in terms of the rates of net adverse clinical events (NACE) and aimed to develop simple, clinically applicable risk-stratification scores in the BIWACO (**B**leeding and thrombotic risk evaluation **I**n patients **W**ith **A**trial fibrillation under **CO**ronary intervention) study cohorts. Second, we investigated the current status and trends over time for the use of DAPT and OAC. It had not previously been documented how long antithrombotic regimens had been applied to all AF patients after PCI. We evaluated the highly variable individual thrombotic and bleeding risks in clinical practice, while referring to the PARIS risk scores (10) in Japanese AF patients with stent placement. Because in the PARIS registry, patients post-PCI were evaluated not only for predicting bleeding but also for thrombotic risk.

Results

Study population.

A total of 7837 consecutive patients who received PCI with DES implantation was enrolled in the BIWACO study. The first registration begun from 1st, April, 2014 (the registration number 2014-001). Of these, only 219 (2.8%) had a medical history of AF at the time of hospitalization. We excluded 31 patients because they were treated by balloon angioplasty alone, leaving 188 patients in this analysis. The median follow-up period was 794 days (IQR, 504–1362 days). Baseline characteristics are listed in Table 1. Mean age was 74.2 years; 139 (73.9%) study participants were males. Second-generation DES were used in all patients, of whom 28.2% underwent PCI for acute coronary syndrome (ACS), and 14.9% had HF with reduced ejection fraction. A history of ischemic stroke or bleeding was present in 17.6% and 8.6% of patients, respectively.

Table 1
Baseline characteristics of the patients

Characteristics	
Patient number	188
Age, y	74.2 ± 9.7
Male, n (%)	139 (73.9)
BMI, kg/m^2	23.1 ± 4.0
Current smoker, n (%)	52 (27.7)
Hypertension, n (%)	160 (85.1)
Diabetes mellitus, n (%)	67 (35.8)
Permanent AF, n (%)	86 (46.0)
HFrEF, n (%)	28 (14.9)
BNP ≥ 200, n (%)	70 (37.2)
eGFR < 60, n (%)	112 (59.6)
ESRD on hemodialysis, n (%)	6 (3.2)
Anemia, n (%)	85 (45.2)
ACS, n (%)	53 (28.2)
Stent diameter, mm	3.04 ± 0.44
Stent length, mm	24 (18–40)
Prior myocardial infarction, n (%)	34 (18.1)
Prior PCI, n (%)	70 (37.2)
Prior CABG, n (%)	12 (6.4)
Prior ischemic stroke, n (%)	33 (17.6)
Prior major bleeding, n (%)	16 (8.6)
Prior hemorrhagic stroke, n (%)	3 (1.6)

Data given as n, mean ± SD, median (IQR) or n (%). BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Anemia, defined as hemoglobin level < 13 g/dl in men and < 12 g/dl in women; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

Clinical Outcomes By Nace

Overall characteristics of patients with NACE (n = 37, 19.7%) or without NACE (n = 151, 80.3%) at baseline are listed in Table 2. Over 3 years, 37 patients developed NACE, including 10 (5.3% of all patients) who died and two with thrombotic events; the remaining 25 (13.3%) experienced bleeding events as shown in Fig. 1. Causes of death of the 10 deceased patients were cardiac (n = 3), stroke (n = 4), systemic thrombosis (n = 1), and non-cardiovascular (n = 2). Major bleeding was observed in 25 patients including one intracranial hemorrhage and 13 patients with severe gastrointestinal bleeding. There were differences in the incidence of major bleeding between patients on TT, DT or DAPT (n = 15, 5, 5, respectively) but these differences are not statistically significant. Patients who experienced NACE were older, had lower body mass index (BMI) and had a higher prevalence of HF, previous ischemic stroke, renal dysfunction, and anemia relative to those without NACE.

Table 2
Overall Characteristics of patients with or without NACE.

Characteristics	All	NACE (−)	NACE (+)	P value
Patient number	188	151	37	
Age, y	74.2 ± 9.7	73.3 ± 9.8	77.9 ± 8.3	0.010
Male, n (%)	139 (73.9)	115 (76.2)	24 (64.9)	0.16
BMI, kg/m^2	23.1 ± 4.0	23.5 ± 4.0	21.4 ± 3.4	0.004
Permanent AF, n (%)	86 (46.0)	68 (45.3)	18 (48.7)	0.72
Risk factors				
Current smoker, n (%)	52 (28.1)	43 (28.9)	9 (25.0)	0.64
Hypertension, n (%)	160 (85.1)	126 (83.4)	34 (91.9)	0.20
Diabetes mellitus, n (%)	67 (35.8)	51 (34.0)	16 (43.2)	0.29
ACS, n (%)	53 (28.2)	42 (27.8)	11 (29.7)	0.82
HFrEF (LVEF < 40), n (%)	28 (14.9)	18 (11.9)	10 (27.0)	0.02
CKD (eGFR < 60), n (%)	112 (59.6)	83 (55.0)	29 (78.4)	0.009
ESRD on hemodialysis, n (%)	6 (3.2)	5 (3.3)	1 (2.7)	0.85
Anemia, n (%)	85 (45.2)	62 (41.1)	23 (62.2)	0.021
Prior myocardial infarction, n (%)	34 (18.1)	24 (15.9)	10 (27.0)	0.11
Prior PCI, n (%)	70 (37.2)	53 (35.1)	17 (46.0)	0.22
Prior CABG, n (%)	12 (6.4)	9(6.0)	3 (8.1)	0.63
Prior ischemic stroke, n (%)	33 (17.6)	20 (13.3)	13 (35.1)	0.002
Prior major bleeding, n (%)	16 (8.6)	11 (7.3)	5 (13.9)	0.20
Prior hemorrhagic stroke, n (%)	3 (1.6)	2 (1.3)	1 (2.7)	0.55
Laboratory examination				

Data given as n, mean ± SD, median (IQR) or n (%). NACE, net adverse clinical events; BMI, body mass index; ACS, acute coronary syndrome; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; ESRD, end-stage renal disease; Anemia, defined as hemoglobin level < 13 g/dl in men and < 12 g/dl in women; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LDL-C, low density lipoprotein cholesterol; PPIs, proton pump inhibitors; OACs, oral anticoagulants; VKA, vitamin K antagonist; DOACs, direct oral anticoagulants; DAPT, dual antiplatelet therapy.

Characteristics	All	NACE (−)	NACE (+)	P value
eGFR (ml/min/1.73 m^2)	55.0 ± 18.8	56.0 ± 19.0	50.7 ± 17.5	0.12
Hemoglobin (g/dL)	12.8 ± 2.0	13.0 ± 0.2	11.7 ± 0.3	< 0.001
Platelet count (×10^4/μL)	19.3 ± 5.7	19.3 ± 5.4	19.3 ± 6.7	0.97
BNP (pg/mL)	142.6 (54.6–283.5)	128.1 (52.5–255.3)	243.5 (84.8–396)	0.018
HbA1c (%)	6.4 ± 1.3	6.3 ± 1.4	6.4 ± 1.0	0.74
LDL-C (mg/dL)	98.7 ± 28.1	99.4 ± 27.8	96.1 ± 29.7	0.53
PCI lesion and procedure				
ACC/AHA type B2/C lesion, n (%)	134 (71.3)	104 (68.9)	30 (81.1)	0.14
Stent diameter, mm	3.04 ± 0.44	3.05 ± 0.46	3.00 ± 0.36	0.63
Stent length, mm	24 (18–40)	23 (16–41)	28 (18–38)	0.35
Medication at discharge				
ACEIs/ ARBs, n (%)	115 (61.2)	88 (58.3)	27 (73.0)	0.10
β-blockers, n (%)	96 (51.1)	73 (48.3)	23 (62.2)	0.13
Diuretics, n (%)	75 (40.0)	54 (35.8)	21 (56.8)	0.02
Statins, n (%)	100 (53.2)	83 (55.0)	17 (46.0)	0.32
PPIs, n (%)	122 (64.9)	98 (64.9)	24 (64.9)	0.99
OACs, n (%)	134 (71.3)	104 (68.9)	30 (81.1)	0.14
VKA, n (%)	57 (30.3)	38 (25.2)	19 (51.4)	0.002
DOACs, n (%)	77 (41.0)	66 (43.7)	11 (29.7)	0.12
Triple therapy, n (%)	122 (64.9)	95 (62.9)	27 (73.0)	0.25
Dual therapy, n (%)	12 (6.4)	9 (6.0)	3 (8.1)	0.16
DAPT without OAC, n (%)	54 (28.7)	47 (31.1)	7 (18.9)	0.25

Data given as n, mean ± SD, median (IQR) or n (%). NACE, net adverse clinical events; BMI, body mass index; ACS, acute coronary syndrome; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; ESRD, end-stage renal disease; Anemia, defined as hemoglobin level < 13 g/dl in men and < 12 g/dl in women; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LDL-C, low density lipoprotein cholesterol; PPIs, proton pump inhibitors; OACs, oral anticoagulants; VKA, vitamin K antagonist; DOACs, direct oral anticoagulants; DAPT, dual antiplatelet therapy.

Predictors Of Integer Risk Scores, The Biwaco Risk Score

As shown in Table 3, the BIWACO study included the following independent predictors of NACE: age, BMI, HF with reduced ejection fraction, previous ischemic stroke, chronic kidney disease (CKD), anemia, and prescription of VKA. From the multivariable model, we developed a simple, numerical risk score for NACE from the five strongest predictive items as follows: Brain infarction history; Impaired renal function (estimated glomerular filtration rate (eGFR) < 60 mg/dL/1.73 m^2); WArfarin use; Congestive HF (EF < 40%); and Older (age ≥ 78 years), yielding the acronym “BIWACO” scores from the BIWACO study (Fig. 2A). We assigned point values equally based on the log scale because of the magnitude of the modelling coefficient representing each variable’s association with NACE. After stratifying patients according to low (BIWACO score 0–2, n = 148) or high (BIWACO score 3 or greater, n = 40) categories, we constructed NACE-free curves of events stratified by the best cut-off value for the BIWACO score within each estimated risk group, as shown in Fig. 2B. Figure 3 presents a comparison of C-statistics (95% confidence intervals) for score discrimination of four different risk scoring systems, namely, the PARIS, PRECISE-DAPT, ORBIT, and HAS-BLED scores. Using this analytical approach, the AUC value of the BIWACO study was 0.774, indicating that our model showed the best discrimination, followed by the PRECISE-DAPT, the PARIS score, the ORBIT score and finally the HAS-BLED score.

Table 3
Univariate and Multivariate Analysis for NACE

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.06	1.02–1.10	0.005	collinearity with Age ≥ 78		
Age ≥ 78	2.69	1.40–5.35	0.003	2.16	1.01–4.79	0.048
Male	0.60	0.31–1.27	0.15	0.93	0.45–1.99	0.84
BMI	0.86	0.78–0.95	0.002	collinearity with BMI < 22		
BMI < 22	2.39	1.25–4.70	0.009	1.39	0.65–2.99	0.40
Current smoker	0.80	0.35–1.63	0.55			
Diabetes Mellitus	1.29	0.66–2.46	0.45			
Permanent AF	1.08	0.56–2.07	0.82			
HFrEF	2.47	1.14–4.95	0.024	2.64	1.18–5.49	0.020
Previous ischemic stroke	3.08	1.52–5.96	0.002	2.91	1.39–5.85	0.006
CKD	2.89	1.38–6.78	0.004	2.38	1.11–5.69	0.025
Anemia	2.29	1.19–4.57	0.013	1.10	0.51–2.42	0.82
Triple therapy	1.59	0.79–3.44	0.20			
VKA	2.53	1.32–4.86	0.005	2.31	1.16–4.65	0.018
DOACs	0.63	0.30–1.23	0.18			
PPIs	0.99	0.51–2.01	0.99			

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; Anemia, defined as hemoglobin level < 13 g/dl in men and < 12 g/dl in women; VKA, vitamin K antagonist; DOACs, direct oral anticoagulants; PPIs, proton pump inhibitors.

Stratification of patients according to the PARIS Thrombotic and Bleeding risk scores

Independent predictors in the PARIS scores for coronary thrombotic events (CTEs) included acute coronary syndrome, prior revascularization, diabetes mellitus, renal dysfunction, and current smoking. CTE scores ranged from 0 to 12, and patients were grouped according to low (0 to 2), intermediate (3 or 4), and high (≥ 5) thrombotic risk, as previously reported (10). Moreover, independent predictors of major bleeding (MB) included older age, BMI, TT at discharge, anemia, current smoking, and renal dysfunction. Analogously, the range of integer scores for MB was 0 to 15, with patients categorized as being at low (0 to 3), intermediate (4 to 7) and high (≥ 8) bleeding risk (10). The overall distribution of CTEs and MBs

according to the PARIS scores in our cohort is depicted in Fig. 4A and 4B. For CTE scores, the numbers of patients with low, intermediate, or high scores were 37%, 42%, and 21%, respectively and for the MB scores 4%, 38% and 58%, respectively. These data show that our patients were at higher risks of both CTE and MB than the PARIS study population.

Changes In Antithrombotic Treatment Regimen

Considering the proportion of patients at discharge, 65 % were prescribed TT (n = 122), while 6% were on DT (n = 12; comprising one OAC in combination with aspirin or a P2Y12 receptor inhibitor), and the remaining patients were on DAPT (n = 55, 29%), as shown in Fig. 5A. Warfarin was used as the OAC drug in 30.3% patients, whereas 40.4 % were treated with DOAC and 29.3% were not prescribed any OACs. The antiplatelet drugs used were aspirin (95.2%), clopidogrel (87.2%) and prasugrel (11.2%). During the follow-up period, 63% patients were switched to another drug within 24 months after PCI (Figs. 5B). The number of patients continuing TT decreased by 15%, DT increased by 51%, and DAPT decreased by 22%. Single antiplatelet therapy (SAPT) was used by 10% and OAC alone only by 2% of patients. Of the patients on TT at discharge, 66% were switched to DT, 6% to DAPT, and 5% to SAPT (5%); 23% of patients still continued TT therapy.

Discussion

In the present study, we surveyed the current clinical landscape concerning the administration of anticoagulant and antiplatelet therapy in Japanese patients with AF undergoing coronary stenting. This study explored the treatment practices and NACE outcomes achieved using several different antithrombotic regimens. First, we developed simple scores to predict risks for NACE. The resulting BIWACO score is a novel risk prediction model for AF patients undergoing PCI which we found enabled a moderately improved discrimination of events concordant with the previously reported DAPT or AF risk scales. We propose the use of BIWACO scores to identify the most at-risk AF-patients on multiple antithrombotic agents after PCI. Second, we summarized the distribution of bleeding and thrombotic risks in our population using the PARIS CTE and MB risk scores, and found that our patients had higher risks compared to those in the PARIS study. The proportion of patients on TT was higher and the use of aspirin was more common and for a longer duration; 15% of patients were still on TT at the end of the follow-up period.

In view of the requirement to arrive at a comprehensive judgment on DAPT duration, employing the PARIS score or the CREDO-Kyoto risk scores are useful predictors of clinical outcome in daily practice after PCI (10, 14). However, as AF, additional antiplatelet therapy and PCI themselves are strong characteristic risk factors, we selected patients with AF undergoing PCI and modeled predictive scores for NACE. CKD, HF, and higher age were found to be independent predictors of thrombosis and bleeding in our study. Among our clinical endpoints, bleeding occurred in 13.3% of patients as the most frequent clinical event. In the current study, 60% patients who experienced bleeding events were receiving TT. In the WOEST trial,

serious bleeding rates were similar to ours, and were also significantly lower in the DT than in the TT group (6.5% vs 12.7%; HR, 0.49) (15). A 2020 network meta-analysis of data from more than 11000 patients concluded that, compared with TT (as the reference), the odds ratios for TIMI major bleeding were 0.52 for DOAC plus P2Y12 inhibitor (16). The findings of this meta-analysis suggest that a regimen of DOAC plus P2Y12 inhibitor without aspirin has the best safety profile. Indeed, among the BIWACO scores, the use of warfarin was an independent predictor of NACE. Although the safety of using OAC alone 12 months after PCI is supported by the data in large registries (17), the early introduction of DOACs and their clinical testing in the PCI setting may encourage the shift towards safer antithrombotic strategies. The discriminatory power (AUC value) of the BIWACO risk scores for NACE was 0.774. Similar AUCs were reported in the PARIS, PRECISE-DAPT, ORBIT, HAS-BLED studies. Although no single score currently has a particularly accurate ability to predict NACE in patients with AF undergoing coronary stenting, our simple BIWACO scores have high C statistics and made it easy to identify patients who may come to harm by continuing their antithrombotic regimens. Compared with oral anticoagulation therapy alone, the addition of DAPT to OAC therapy results in at least a two- to threefold increase in bleeding complications (8). The best combinations and numbers of agents, as well as their duration of use for an optimal treatment strategy for patients with ACS and elective PCI and with coexisting AF are still under intensive investigation (18). Therefore, we secondly evaluated the risk status of our population concerning bleeding and thrombotic events. We assessed how the antithrombotic treatments changed after PCI therapy. According to the PARIS scores, we found that 21% and 58% of our population were assigned to high thrombotic and bleeding risk groups, respectively. BIWACO registry patients seemed to belong to quite high risk groups compared to the PARIS study population, probably because our registry had many elderly patients and those with low body weights. Serious bleeding events were more important than thrombotic risk in our population, as seen in other studies of antiplatelet therapy after PCI (14). In a Danish nation-wide registry, within 1 year, bleeding events were recorded in 6.3% of patients. Bleeding rates were 22.6, 20.3, and 14.3 events per 100 person-years for TT, DT and DAPT, respectively within 30 days. Both early and delayed bleeding risk on TT treatment relative to DT was increased with a hazard ratio of 1.47 and 1.36, respectively (19). It has been suggested that a DT regimen (oral anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor) instigated by the time of hospital discharge should be considered for most patients, whereas extending the use of aspirin beyond hospital discharge should be considered only for selected patients at high ischemic/thrombotic risk but low bleeding risk and for a limited period of time (20). After the release of DOAC, four randomized trials and meta-analyses using DOAC consistently showed a 20–40% reduction in bleeding events in the DOAC DT groups as compared with the TT groups, without increasing ischemic events (15, 21–23). The findings of RCTs engendered a paradigm shift from triple to dual therapy. TT should be given only for the periprocedural period within 2 weeks, followed by DT with a DOAC and clopidogrel, according to the Japanese guidelines (24). However, there were no “real-world” data regarding the timing of changes to the antithrombotic prescriptions after PCI procedures. In the current study, we evaluated the switching of drug prescriptions after discharge. At first, 65% of the patients were prescribed TT and 51% of patients were switched to DT in the follow-up period. Of the patients on the TT regimen, 66% were switched to DT, however, 15% of patients continued TT. These results suggested that there is still discordance between the guidelines and current clinical

practice. Even though in the era of 2nd generation stents, clinical trials have already shown that low-risk patients who receive contemporary stent technologies do not need prolonged DAPT to avoid stent thrombosis (25), some clinicians still seem likely to fear the occurrence of ischemic events after stent placement. This may explain why they did not try to change the treatment regimen unless major bleeding occurred. Next, we evaluated trends of timing the switch to a different anti-thrombotic therapy after discharge. We found that only 7% of patients had their regimens changed within one month of stent placement and 37% of patients were not changed at all. The SHINANO registry reported the same trend as our study in that OACs were administered to only 60% of the AF patients who underwent coronary stenting, and this had not still changed by one year after PCI, even in the second-generation DES era (26). This could be due to the fact that our cardiologists did not change their regimens in AF patients treated with DES because of concerns about thrombotic events associated with AF and stent placement (3). We also examined the percentage of patients taking various different anticoagulants at the time of enrollment in the registry. Whereas 30.3% of patients were warfarin users, a DOAC was used by 40.4%, the majority of whom used Xa inhibitors (29.2%) and 11.2% used thrombin inhibitors. A North American expert consensus recommends that a DOAC rather than a VKA should generally be preferred for most patients in the absence of any contraindications (20). As mentioned above, serious hemorrhages can occur very early after the beginning of treatment and this kind of risk persists over time.

Study Limitations

It has been reported that approximately 20% of patients with ACS and 5 ~ 10% of patients undergoing elective PCI have concomitant AF (2, 3, 18). One limitation of the current study is that in our registry, because in our 2nd generation DES recipients only 2.8% had AF, the prevalence was too low to evaluate any potential associations between different regimens and cardiovascular death and bleeding. A second limitation is that data on time spent in the therapeutic range of warfarin were only collected for patients at enrollment, and therefore we could not evaluate the appropriateness of warfarin therapy during the study.

Conclusions

We should change clinical practice to minimize the duration of TT as much as possible and take patient-by-patient decisions on antithrombotic therapy depending on the balance of the individual bleeding and ischemic risks. In these circumstances, our five-element BIWACO risk score can provide a simple tool to predict NACE in patients with AF undergoing PCI.

Methods

Study design

The BIWACO study was a prospective, multicenter, observational registry endeavor designed to provide up to 48 months of clinical follow-up to facilitate the evaluation of the different characteristics and

outcomes of antiplatelet and anticoagulant therapy after PCI in patients with AF. It took place in the Shiga prefecture where has the largest ancient lake Biwako in Japan from January 2014 to December 2017, during which time consecutive patients with PCI therapy for any coronary artery disease indication was enrolled from five institutions. AF in patients undergoing PCI was defined as either a history of AF or AF occurring during the hospital stay. The BIWACO study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR, no. UMIN 00002694, R000030644). The inclusion criterion for the registry were patients with AF and any coronary artery disease after 2nd generation coronary stent implantation. AF was documented on 12-lead electrocardiogram or Holter monitoring at any time. AF includes paroxysmal, persistent, or permanent AF. Patients with ≥ 20 years of age. Patients who are treated with an oral anticoagulant (warfarin or a DOAC; dabigatran, rivaroxaban, apixaban, and edoxaban) and antiplatelet agents (aspirin, clopidogrel and prasugrel). In patients receiving warfarin, international normalized ratio (INR) should be ≥ 1.6 at the time of study entry. Patients in whom written informed consent was obtained. Patients were excluded for the following reasons: cardiogenic shock or hypotension, defined as systolic blood pressure < 90 mm Hg; vulnerable ischemic stroke and any active bleeding, current HF hospitalization, a history of stent thrombosis, coexisting active tumor, poorly controlled hypertension, severe infections, severe liver injury, and pregnant women. Patients who are scheduled to undergo surgical procedures and plain balloon angioplasty alone. The participating institutions comprised five cardiovascular centers (Kusatsu General Hospital, Kotoh Memorial Hospital, Kohka Public Hospital, Nagahama Red Cross Hospital and Shiga Hospital JCHO). This study was carried out in accordance with the Declaration of Helsinki and the Ethics Committee of Kusatsu General Hospital approved the protocol (No. 2020-0004). Patients gave their informed consent before being enrolled. The interventional strategy and stent selection were left to the discretion of the operator in all procedures.

Status Of The Use Of Antithrombotic Drugs

Anticoagulant and antiplatelet status was assessed after PCI and followed until the end of the study. We defined OAC as warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Dose selection of each DOAC was evaluated based on the manufacturer labeling recommendations in Japan. Time in the therapeutic range was not incorporated into this analysis, because we checked INR only at enrollment and could not evaluate its lability. Antiplatelet drugs were aspirin, clopidogrel and prasugrel. The DAPT duration was left to the discretion of the operator and the family doctor. During the follow-up period, we noted any changes in the use of antithrombotic drugs.

Endpoints

The primary endpoints for this study were to investigate composite outcomes of NACE defined as the composite of all-cause death, thrombotic and bleeding events within four years of the PCI procedure. We also develop clinically applicable risk-stratification scores. An important secondary endpoint was to evaluate the current status and trends over time for the use of anticoagulant and antiplatelet therapy in

patients with AF after PCI. We also evaluated the status of the BIWACO study population referring to the PARIS risk scores (10).

Cardiac death included sudden death, progressive HF, and fatal myocardial infarction. HF was diagnosed if the patient had a history of hospitalization for HF or if the left ventricular ejection fraction was < 40%. CKD was diagnosed if there was persistent proteinuria or if the eGFR was < 60 mL/min/1.73 m^2. Bleeding was defined as the occurrence of Bleeding Academic Research Consortium type 2, 3 or 5 and complications thereof were defined as the requirement for blood transfusion or prolonged hospitalization owing to subcutaneous hematoma, gastrointestinal bleeding, or intracranial bleeding (27). Thrombotic events were defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and an acute vascular occlusion of a coronary and peripheral arteries confirmed by angiography. With respect to specific bleeding risk prediction, we compared the predictive performance of the BIWACO score to those of four previously existing bleeding scores, namely, PARIS (10), ORBIT (11), HAS-BLED (12) and PRECISE-DAPT (13).

Measurements.

Clinical baseline characteristics included age, sex, height, body weight, blood pressure, past medical history, smoking status, use of concomitant drugs and the information of PCI lesion, procedure and coronary stents. Red and white blood cell counts, hemoglobin, hematocrit, platelet count, aspartate transaminase, alanine aminotransferase, γ-glutamyl transpeptidase, creatine kinase, blood urea nitrogen, creatinine, blood glucose, hemoglobin $A1_C$ and brain natriuretic peptide were measured locally at baseline.

Statistical analysis

Continuous variables are reported as mean ± standard deviation. We compared baseline clinical characteristics by the presence or absence of NACE using Student t tests and chi-square tests for continuous and categorical variables, respectively. We constructed a multivariable Cox proportional hazards regression for time to first occurrence of NACE over 4 years of follow-up as the outcome. The observed event rate was calculated as a Kaplan-Meier estimate of time to first event and differences were assessed with the log-rank test. Candidate variables for the model were chosen from the list of variables remaining significant at a threshold p value of < 0.05. To create the simple BIWACO score, we retained five predictors from the full model with metrics of discrimination (Harrel's C statistic). Point values were assigned to each predictor equally. Discrimination was by calculating the area under the curve (AUC) and was expressed as the C statistic. A p value of < 0.05 was considered statistically significant in all analyses.

Abbreviations And Acronyms

OAC =oral anticoagulant

DAPT= dual-antiplatelet therapy

DOAC=direct antagonist oral anticoagulant

VKA =vitamin K oral antagonist

TT =triple therapy

DT =dual therapy

NACE=net adverse clinical events

CTE = coronary thrombotic events

MB = major bleeding

SAPT =Single antiplatelet therapy

Declarations

Acknowledgments

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Author contribution; T. T, T. D, Y.U and A.W contributed to the idea and design of the study. A.W drafted the initial the manuscript, T. T, and T. D revised the manuscript. T. T performed the presented analyses, had complete access to all the data and takes responsibility for the integrity and accuracy of the presented results. T.M, M.F, T. T, K.D, A.M, and H.M contributed to data acquisition and interpretation. All authors approved its submission for publication.

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Figures

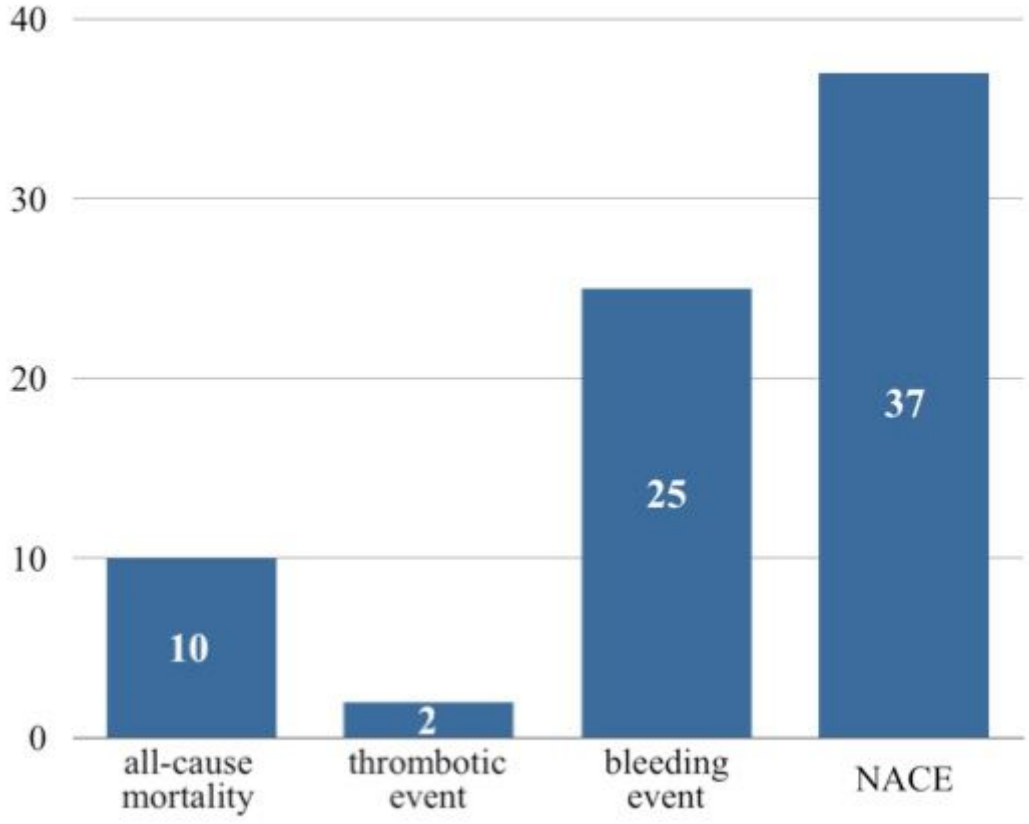


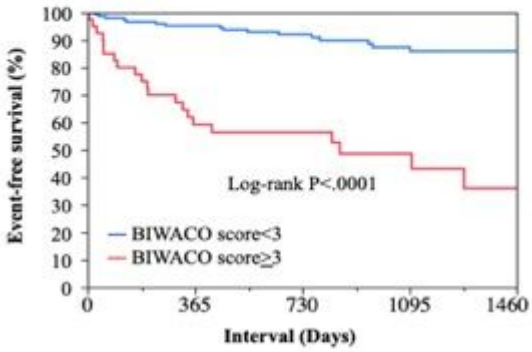
Figure 1

Incidence of NACEs. NACE; net adverse clinical events.

(A)

Variables	Point
B rain infarction history	1
I mpaired renal function	1
WA rfarin	1
C ongestive heart failure	1
O lder age (≥78 years)	1
Total score range	0-5

(B)



Interval	0 day	1 year	2 year	3 year	4 year
BIWACO score<3					
N of patients with event		7	11	15	16
N of patients at risk	148	133	88	59	30
Cumulative Incidence		5%	8%	13%	14%
BIWACO score≥3					
N of patients with event		16	17	19	21
N of patients at risk	40	22	16	9	3
Cumulative Incidence		41%	44%	51%	64%

Figure 2

The prediction scores for the composite of all-cause death, thrombotic events and major bleeding. A. Predictive risk scores for NACE (BIWACO scores). NACE; net adverse clinical events. B. Kaplan-Meier estimates of patients free of NACE among patients stratified by high (red line)-vs-low (blue line) BIWACO risk scores. NACE; net adverse clinical events.

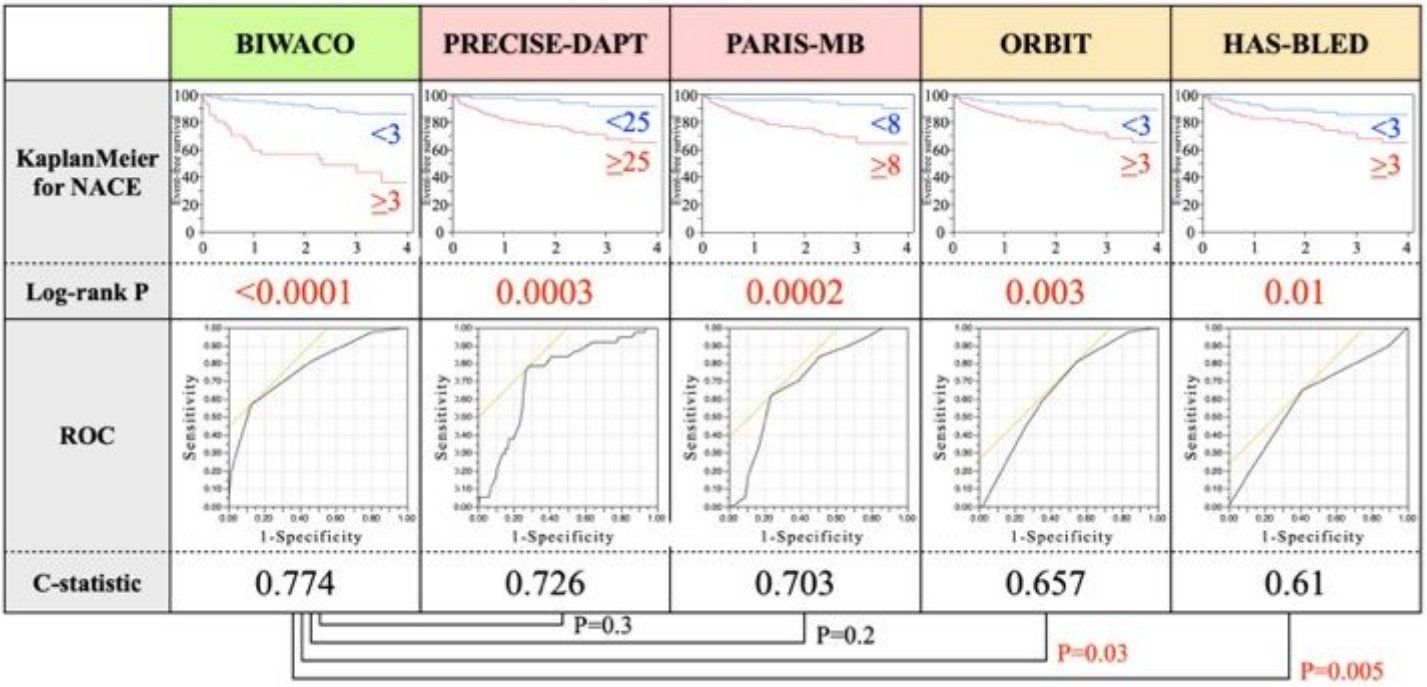


Figure 3

Comparison of Kaplan-Meier curves and AUC for predicting NACE among patients stratified according to BIWACO, PRECISE-DAPT, PARIS, ORBIT or HAS-BLED scores. AUC; area under the curve. NACE; net adverse clinical events.

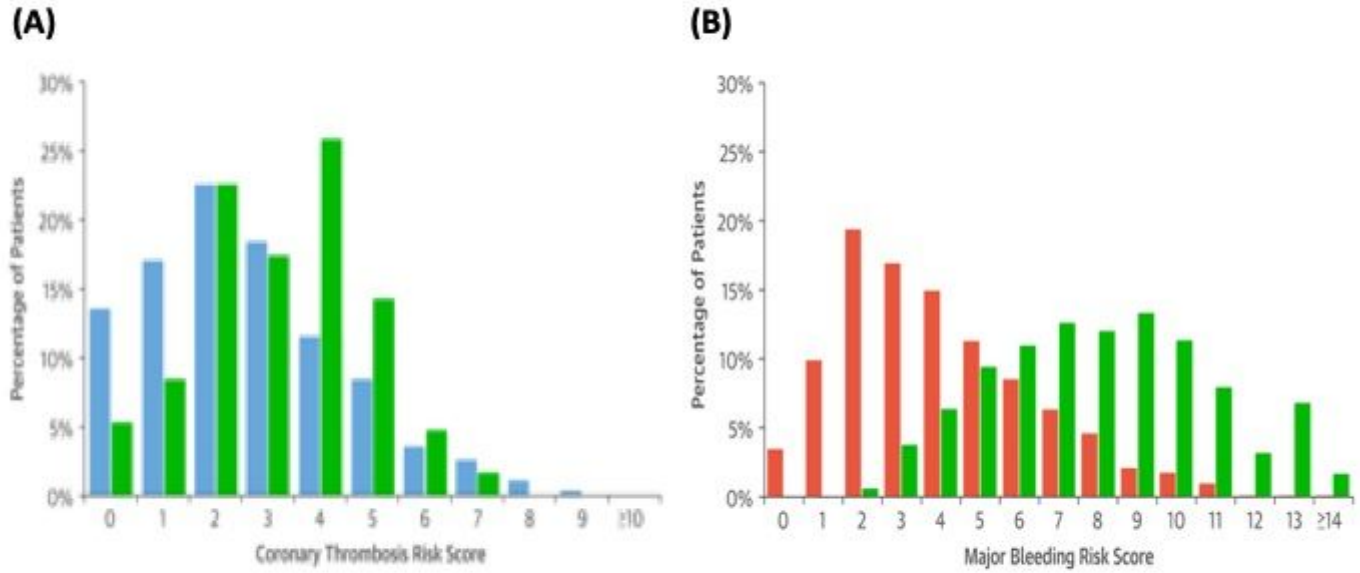


Figure 4

Overall prevalence of patients classified by coronary thrombotic events (A) and major bleeding (B) risk scores according to the PARIS scores. The blue and red bars show the number of thrombotic and bleeding event patients in the PARIS study (n= 4,190) and the green bar shows the BIWACO study (n=188) population, respectively.

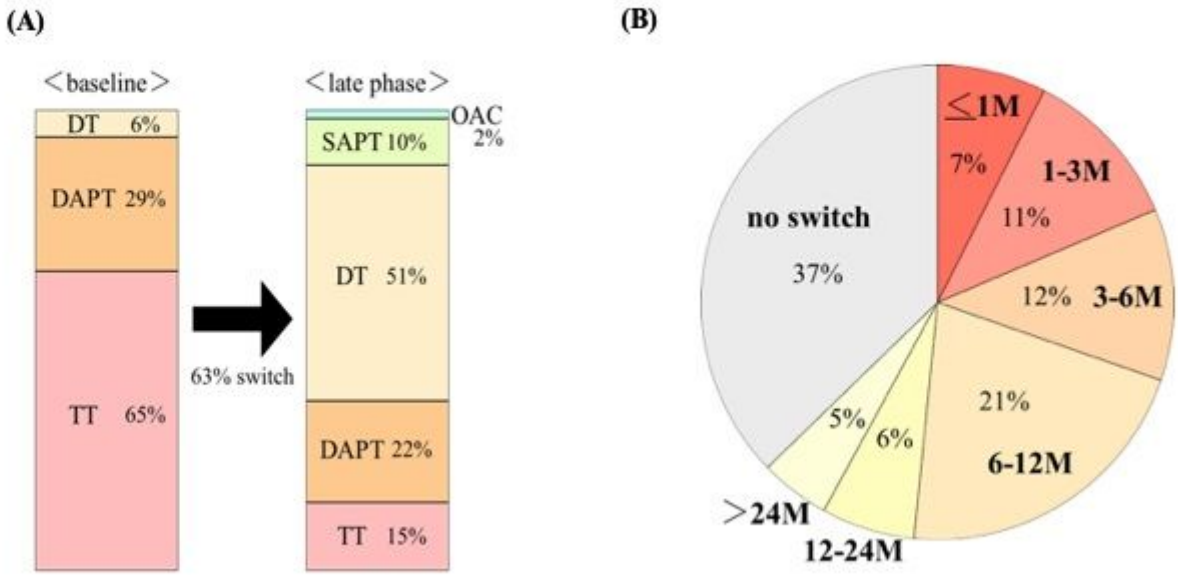


Figure 5

Antithrombotic drug prescriptions and switching regimens. A. Trends in prescriptions of antithrombotic regimens from baseline to the late phase. The figure shows the proportion of patients receiving single antiplatelet therapy (SPAT), oral anticoagulant alone (OAC), dual-therapy; OAC plus antiplatelet therapy (DT), dual antiplatelet therapy (DAPT)or triple therapy (TT). B. Timing of anti-thrombotic regimen switching