# Frailty and Bleeding After Percutaneous Coronary Intervention

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**The aim of this study was to evaluate the predictive ability of frailty for bleeding after percutaneous coronary intervention (PCI). In 2439 patients who underwent their PCI, frailty was prospectively assessed according to the Canadian Study of Health and Aging clinical frailty scale (CFS). Patients were divided into three groups according to the CFS: low (CFS levels 1 to 3; 1748 patients, 71.7%), intermediate (CFS levels 4 to 6; 519 patients, 21.3%), and high CFS groups (CFS levels 7 to 9; 172 patients, 7.1%). Academic Research Consortium High Bleeding Risk (ARC-HBR) was present in 47.3% in the low CFS group, in 83.2% in the intermediate CFS group and in 89.0% in the high CFS group (p <0.001). Patients in the intermediate and high CFS groups were associated with higher 1-year major bleeding risk after PCI in the overall cohort (HR 3.82, 95% CI 2.65 to 5.51, p <0.001, and HR 7.81, 95% CI 5.07 to 12.0, p <0.001, respectively). Patients in the high CFS group were also associated with higher 1-year major bleeding risk regardless of having the high bleeding risk (HBR) according to ARC-HBR. In conclusion, the association of frailty with 1-year major bleeding was consistently observed in patients with and without HBR, indicating that frailty *per se* might be a predictor for major bleeding after PCI on top of HBR criteria.**  **(Am J Cardiol 2021;148:22−29)**

Frailty is a geriatric syndrome that is defined as a state of reduced physiological reserve against pathological or iatrogenic stressors due to age-related impairments.[1] Since frail patients are likely to be excluded from clinical studies due to those factors including an unwillingness of the patients to participate, the physician's decisions, and/or perceptions for poor prognosis,[2] the causative role of frailty for the long-term bleeding risk after percutaneous coronary intervention (PCI) remains unclear.[3−6] Moreover, none of the currently available bleeding risk scores included frailty as a potential predictor for bleeding events; in the consensus from the Academic Research Consortium for HBR (ARC-HBR) criteria, frailty *per se* was not included as a criterion, although advanced age and coexisting ARC-HBR criteria may account for frailty at least to some degree.[7] To address these issues, we sought to evaluate the impact of frailty on 1-year bleeding events in patients who underwent PCI in an all-comer registry from a single-center.

## Methods

From February 24, 2016, to December 4, 2017, a total of consecutive 2439 patients underwent their PCI in Kokura Memorial Hospital, Kitakyushu, Japan. Written informed consents from the patients were waived, because we retrospectively enrolled the patients. No patients refused to participate in the study when contacted for follow-up. This opt-out consent strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare. The institutional review board of Kokura Memorial Hospital approved the protocol of this observational study. Moreover, the study was conducted following the Declaration of Helsinki. The objectives and detailed design are provided on the University Hospital Medical Information Network (UMIN000042266).

Frailty was routinely assessed for all patients by healthcare professionals in the cardiovascular center, according to the clinical frailty scale (CFS) derived from Canadian Study of Health and Aging (Supplemental Table 1).[8,9] Frailty was defined as a score ≥4 on the Clinical Frailty Scale. Patients were divided into three groups according to the CFS: low (CFS levels 1 to 3), intermediate (CFS levels 4 to 6), and high CFS groups (CFS levels 7 to 9) to assess the impact of frailty on clinical outcomes. We further subclassified clinical frailty according to the original CFS in patients within the intermediate and high CFS group (CFS levels 4 to 9), while clinical frailty was not subclassified in patients within the low CFS group (i.e., CFS levels 1 to 3).

Bleeding risk was assessed using the ARC-HBR criteria,[10] the JCS-HBR (Japanese Circulation Society High Bleeding Risk) criteria,[11] the PRECISE-DAPT (Predicting

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Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score,[12] the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens In Stented Patients) bleeding score,[13] and the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) bleeding score.[14] HBR was regarded as present in patients with at least one major or two minor ARC-HBR criteria, at least one major or two minor JCS-HBR criteria, a PRECISE-DAPT score of 25 or higher, a PARIS bleeding score of 8 or higher, or a CREDO-Kyoto bleeding score of 3 or higher. The variables for each bleeding risk score/criteria were shown in the Supplemental Table 2.

We obtained clinical follow-up information from the medical records, patients' referral documents, and telephone interviews with the patients, their families, or their family doctors. As the main outcome measures, we assessed all-cause death and major bleeding at 1-year (Bleeding Academic Research Consortium [BARC] type 3 or 5 bleeding).[15] We also assessed cardiovascular death, non-cardiovascular death, myocardial infarction, stroke, ischemic stroke, hemorrhagic stroke, target vessel revascularization, target lesion revascularization, and definite stent thrombosis according to the Academic Research Consortium (ARC) criteria.[16]

Continuous variables were expressed as mean ± standard deviations or as medians (interquartile ranges) and were compared using Kruskal-Wallis test. Categorical variables were presented as values and percentages and were compared using the $\chi^2$ test. Kaplan-Meier curves were used to estimate the cumulative incidence of clinical events. Gray method was used to account for the competing risk for all-cause death. Hazard ratios and their 95% confidence intervals were calculated using Cox proportional hazards model. Because we consider frailty as stand-alone predictor summarizing many risk factors of patients, we did not construct multivariable models to adjust such risk factors. Instead, patients were stratified into those with or without HBR according to each bleeding risk score/criteria to explore the discriminative ability of frailty on bleeding risk in patients with and without HBR, separately. We assessed the interaction between the presence or absence of HBR and the effect of frailty on the risk of 1-year major bleeding, as well as the interaction between the presence or absence of each HBR criterion and the effect of frailty on the risk of 1-year major bleeding. Moreover, since data on the impact of frailty on clinical outcomes in non-ACS patients and in cardiogenic shock patients are scarce, we stratified patients according to the ACS presentation and according to cardiogenic shock as exploratory analyses. A two-sided P-value of less than 0.05 was considered statistically significant for all tests. All analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and JMP version 14.3.0 (SAS Institute Incorporated, Cary, NC, USA).

## Results

The CFS level was low (1 to 3) in 1748 (71.7%) patients, intermediate (4 to 6) in 519 (21.3%) patients, and high (7 to 9) in 172 (7.1%) patients (Figure 1). The baseline clinical characteristics, according to the CFS groups, are summarized in Table 1. Frailer patients were older and had more comorbidities, such as renal failure and anemia. All risk scores successfully stratified the risk for 1-year major bleeding, while the prevalence of high bleeding risk was different largely according to each risk score (Supplemental Figure 1).

Frailer patients were more often regarded as having HBR according to the ARC-HBR criteria (at least one major or two minor criteria; low CFS: 47.3%, intermediate CFS: 83.2%, and high CFS: 89.0%; p <0.001), the JCS-HBR criteria (at least one major or two minor criteria; 55.2%, 89.0%, and 93.0%; p <0.001), the PRECISE-DAPT score (≥25; 37.0%, 80.2%, and 85.5%; p <0.001), the PARIS bleeding score (≥8; 31.1%, 67.6%, and 81.4%; p <0.001), and the CREDO-Kyoto bleeding score (≥3; 11.7%, 31.1%, and 37.8%; p <0.001). Meanwhile, majority of patients who were regarded as not having HBR had low CFS levels (1-3) (the ARC-HBR criteria: 89.8%, the JCS-HBR criteria: 92.0%, PRECISE-DAPT score: 89.7%, the PARIS bleeding

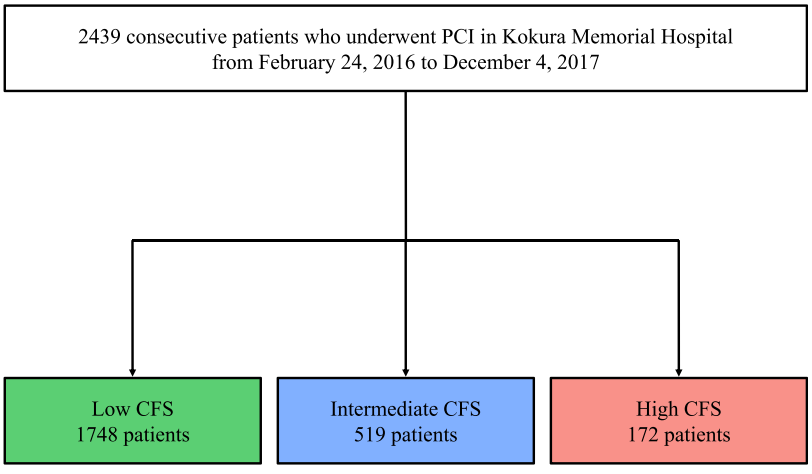



Figure 1. Study patient flow.
CFS was derived from Canadian Study of Health and Aging.
PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CFS = clinical frailty scale.

Table 1
Baseline characteristics according to the clinical frailty scale groups

| | Overall (N = 2439) | Clinical frailty scale groups | | | p values |
|---|---|---|---|---|---|
| | | Low (1-3) N = 1748 | Intermediate (4-6) N = 519 | High (7-9) N = 172 | |
| Variable | | | | | |
| Age (years) | 71.9±10.1 | 69.3±10.2 | 77.9±9.9 | 80.5±9.9 | <0.001 |
| Age ≥75 | 1072 (44.0%) | 583 (33.4%) | 359 (69.2%) | 130 (75.6%) | <0.001 |
| Men | 1772 (72.7%) | 1399 (80.0%) | 297 (57.2%) | 76 (44.2%) | <0.001 |
| Body mass index (kg/m$^2$) | 23.8±3.5 | 24.3±3.4 | 23.1±3.7 | 21.3±3.9 | <0.001 |
| Low body weight <55 kg (men)/ <50 kg (women) | 569 (23.4%) | 262 (15.0%) | 203 (39.1%) | 104 (60.5%) | <0.001 |
| Acute coronary syndrome at presentation | 698 (28.6%) | 473 (27.1%) | 143 (27.6%) | 82 (47.7%) | <0.001 |
| Cardiogenic shock | 53 (2.2%) | 20 (1.1%) | 16 (3.1%) | 17 (9.9%) | <0.001 |
| Prior myocardial infarction | 462 (18.9%) | 349 (20.0%) | 87 (16.8%) | 26 (15.1%) | 0.10 |
| Hypertension | 1968 (80.7%) | 1399 (80.0%) | 425 (81.9%) | 144 (83.7%) | 0.36 |
| Diabetes mellitus | 1057 (43.3%) | 727 (41.6%) | 260 (50.1%) | 70 (40.7%) | 0.002 |
| Dyslipidemia | 1251 (71.6%) | 295 (56.8%) | 295 (56.8%) | 73 (42.2%) | <0.001 |
| Current smoker | 359 (14.7%) | 286 (16.4%) | 55 (10.6%) | 18 (10.5%) | 0.07 |
| Renal failure | | | | | |
| eGFR <30 mL/min per 1.73m$^2$ or dialysis | 343 (14.1%) | 146 (8.4%) | 138 (26.6%) | 59 (34.3%) | <0.001 |
| eGFR 30-59 mL/min per 1.73m$^2$ | 859 (35.2%) | 583 (33.4%) | 213 (41.0%) | 63 (36.6%) | 0.006 |
| Chronic obstructive pulmonary disease | 52 (2.1%) | 31 (1.7%) | 19 (3.7%) | 2 (1.2%) | 0.03 |
| Peripheral artery disease | 282 (11.6%) | 149 (8.5%) | 102 (19.7%) | 31 (18.0%) | <0.001 |
| Atrial fibrillation | 301 (12.3%) | 177 (10.1%) | 79 (15.2%) | 45 (26.2%) | <0.001 |
| Prior heart failure | 236 (9.7%) | 103 (5.9%) | 85 (16.4%) | 48 (27.9%) | <0.001 |
| Liver cirrhosis with portal hypertension | 11 (0.5%) | 5 (0.3%) | 6 (1.2%) | 0 (0%) | 0.03 |
| Prior spontaneous major bleeding* | | | | | |
| in the past 6 months or at any time if recurrent | 20 (0.8%) | 12 (0.7%) | 4 (0.8%) | 4 (2.3%) | 0.16 |
| in the past 6-12 months and not recurrent | 3 (0.1%) | 1 (0.1%) | 2 (0.4%) | 0 (0%) | 0.22 |
| Prior spontaneous intracranial hemorrhage | 49 (2.0%) | 22 (1.3%) | 20 (3.9%) | 7 (4.1%) | <0.001 |
| Prior ischemic stroke | | | | | |
| moderate or severe stroke within 6 months† | 14 (0.6%) | 4 (0.2%) | 8 (1.5%) | 2 (1.2%) | 0.003 |
| mild stroke within 6 months or any stroke > 6 months | 237 (9.7%) | 130 (7.4%) | 72 (13.9%) | 35 (20.4%) | <0.001 |
| Recent major surgery or major trauma within 30 days | 7 (0.3%) | 4 (0.2%) | 2 (0.4%) | 1 (0.6%) | 0.68 |
| Non-deferrable major surgery on dual antiplatelet therapy | 3 (0.1%) | 0 (0%) | 1 (0.2%) | 2 (1.2%) | 0.007 |
| Active malignancy | 107 (4.4%) | 71 (4.1%) | 25 (4.8%) | 11 (6.4%) | 0.34 |
| White blood cell count, × 10$^6$/L | 68.2±26.5 | 67.6±24.3 | 66.4±25.1 | 79.9±45.1 | 0.003 |
| Anemia | | | | | |
| Hemoglobin <11g/dl | 429 (17.6%) | 169 (9.7%) | 177 (34.1%) | 83 (48.3%) | <0.001 |
| Hemoglobin 11-12.9g/dl (men) / 11-11.9g/dl (women) | 573 (23.5%) | 388 (22.2%) | 141 (27.2%) | 44 (25.6%) | 0.054 |
| Thrombocytopenia (Platelet<100 × 10$^9$/L) | 73 (3.0%) | 32 (1.8%) | 27 (5.2%) | 14 (8.1%) | <0.001 |
| ARC-HBR | 1411 (57.9%) | 826 (47.3%) | 432 (83.2%) | 153 (89.0%) | <0.001 |
| JCS-HBR | 1586 (65.0%) | 964 (55.2%) | 462 (89.0%) | 160 (93.0%) | <0.001 |
| PRECISE DAPT score | 24 (15-34) | 21 (13-28) | 35 (26-44) | 43 (33-51) | <0.001 |
| PRECISE DAPT score ≥25 | 1210 (49.6%) | 647 (37.0%) | 416 (80.2%) | 147 (85.5%) | <0.001 |
| PARIS bleeding score | 7 (4-10) | 6 (4-8) | 9 (7-11) | 10.5 (8-11) | <0.001 |
| PARIS bleeding score ≥8 | 1034 (42.4%) | 543 (31.1%) | 351 (67.6%) | 140 (81.4%) | <0.001 |
| CREDO-Kyoto bleeding score | 1 (0-2) | 0 (0-1) | 2 (0-3) | 2 (1-4) | <0.001 |
| CREDO-Kyoto bleeding score ≥3 | 431 (17.7%) | 205 (11.7%) | 161 (31.1%) | 65 (37.8%) | <0.001 |
| Medication at discharge | | | | | |
| P2Y$_{12}$ inhibitors | 2348 (96.3%) | 1690(96.7%) | 496 (95.6%) | 162 (94.2%) | 0.19 |
| Clopidogrel | 2224 (91.2%) | 1589 (90.9%) | 480 (92.5%) | 155 (90.1%) | 0.46 |
| Prasugrel | 114 (4.7%) | 88 (5.0%) | 18 (3.5%) | 8 (4.7%) | 0.31 |
| Aspirin | 2266 (98.5%) | 899 (98.9%) | 267 (97.8%) | 118 (98.5%) | 0.28 |
| Oral anticoagulant | 313 (12.8%) | 171 (9.8%) | 97 (18.7%) | 45 (26.2%) | <0.001 |
| Nonsteroidal anti-inflammatory drugs or steroids | 143 (5.8%) | 87 (5.0%) | 46 (8.9%) | 10 (5.8%) | 0.007 |
| Proton pump inhibitor | 1756 (72.0%) | 1222 (69.9%) | 399 (76.9%) | 135 (78.5%) | 0.001 |

eGFR = estimated glomerular filtration rate; ARC-HBR = Academic Research Consortium high bleeding risk; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; PARIS = Patterns of Non-Adherence to Antiplatelet Regimens In Stented Patients; CREDO-Kyoto = Coronary Revascularization Demonstrating Outcome Study in Kyoto.

Continuous variables are given as mean ± standard deviation or median (interquartile range). Categorical variables are given as number (%). In evaluating ARC-HBR, chronic bleeding diathesis, prior traumatic intracranial hemorrhage within 12 months, and brain arteriovenous malformation were regarded as not present in any patient. HBR was regarded as present in patients with at least one major or two minor ARC-HBR criteria.

* Bleeding requiring hospitalization or transfusion.

† National Institutes of Health Stroke Scale score ≥5.

Table 2
Clinical outcomes at 1-year according to the clinical frailty scale groups

| | Overall (N = 2439) | Clinical frailty scale groups | | | p values |
|---|---|---|---|---|---|
| | | Low (1-3) N = 1748 | Intermediate (4-6) N = 519 | High (7-9) N = 172 | |
| All-cause death | 112 (4.7%) | 26 (1.5%) | 37 (7.3%) | 49 (30.0%) | <0.001 |
| Cardiovascular death | 66 (2.8%) | 17 (1.0%/1.0%) | 20 (4.0%/3.9%) | 29 (19.0%/17.7%) | <0.001/<0.001 |
| Non-cardiovascular death | 46 (2.0%) | 9 (0.5%/0.5%) | 17 (3.4%/3.3%) | 20 (13.6%/12.3%) | <0.001/<0.001 |
| Myocardial infarction | 27 (1.1%) | 16 (0.9%/0.9%) | 9 (1.8%/1.9%) | 2 (1.8%/1.3%) | 0.26/0.16 |
| Stroke | 47 (2.0%) | 25 (1.5%/1.6%) | 13 (2.6%/2.5%) | 9 (5.6%/5.3%) | <0.001/0.002 |
| Ischemic stroke | 36 (1.5%) | 21 (1.3%/1.3%) | 9 (1.8%/1.8%) | 6 (3.8%/3.6%) | 0.01/0.06 |
| Hemorrhagic stroke | 16 (0.7%) | 8 (0.5%/0.5%) | 4 (0.8%/0.8%) | 4 (2.4%/2.3%) | 0.006/0.01 |
| Target lesion revascularization | 100 (4.3%) | 71 (4.2%/4.1%) | 25 (5.1%/4.9%) | 4 (3.4%/2.6%) | 0.55/0.41 |
| Target vessel revascularization | 151 (6.5%) | 106 (6.2%/6.1%) | 38 (7.8%/7.5%) | 7 (5.5%/4.4%) | 0.43/0.55 |
| Definite stent thrombosis | 7 (0.3%) | 4 (0.2%/0.2%) | 2 (0.4%/0.4%) | 1 (1.1%/1.1%) | 0.57/0.59 |
| Bleeding | | | | | |
| Major bleeding (BARC type 3 or 5) | 147 (6.1%) | 55 (3.2%/3.2%) | 59 (11.7%/11.5%) | 33 (20.9%/19.7%) | <0.001/<0.001 |
| Procedure related bleeding | 23 (0.9%) | 7 (0.4%/0.4%) | 10 (1.9%/1.9%) | 6 (3.5%/3.5%) | <0.001/<0.001 |
| Non-procedure related bleeding | 124 (5.1%) | 48 (2.8%/2.8%) | 49 (9.7%/9.5%) | 27 (17.4%/16.2%) | <0.001/<0.001 |
| Spontaneous bleeding | 80 (3.4%) | 35 (2.0%/2.0%) | 30 (6.0%/5.8%) | 15 (9.5%/8.9%) | <0.001/<0.001 |
| Iatrogenic bleeding | 38 (1.6%) | 13 (0.7%/0.7%) | 15 (3.0%/2.9%) | 10 (6.5%/6.0%) | <0.001/<0.001 |
| Traumatic bleeding | 6 (0.3%) | 0 (0%/0%) | 4 (0.8%/0.8%) | 2 (1.6%/1.3%) | <0.001/<0.001 |
| Bleeding (BARC type 2, 3 or 5) | 267 (11.1%) | 126 (7.4%/7.3%) | 95 (18.9%/18.6%) | 46 (29.7%/27.7%) | <0.001/<0.001 |
| BARC type 5 bleeding | 11 (0.5%) | 5 (0.3%/0.3%) | 5 (1.1%/1.1%) | 1 (0.8%/0.6%) | 0.08/0.10 |
| BARC type 3 bleeding | 136 (5.7%) | 50 (2.9%/2.9%) | 54 (10.7%/10.5%) | 32 (20.4%/19.1%) | <0.001/<0.001 |
| BARC type 2 bleeding | 120 (5.0%) | 71 (4.1%/4.1%) | 36 (7.1%/7.0%) | 13 (8.8%/7.8%) | 0.001/0.005 |

BARC = Bleeding Academic Research Consortium.

Data are presented as number of patients with event (cumulative 1-year incidence).

Procedure-related bleeding was defined as puncture site bleeding or PCI procedure-related bleeding. Iatrogenic bleeding was defined as any bleeding related to medical activities.

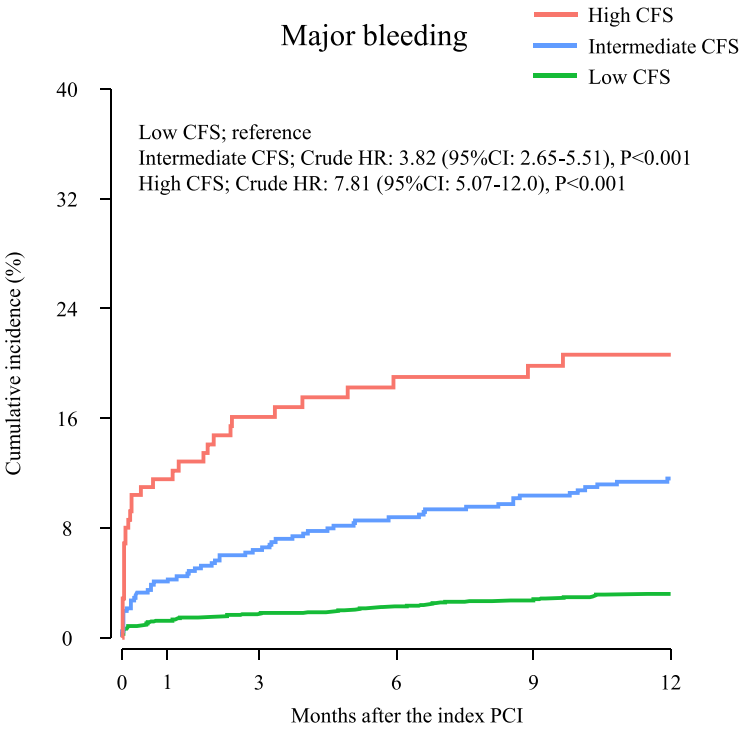
score: 85.8%, and the CREDO-Kyoto bleeding score: 76.9%, respectively). Among 691 frail patients, 84.8% were regarded as having HBR according to the ARC-HBR criteria, while among 1028 patients who were regarded not having HBR, 89.8% were not frail according to the CFS.

The follow-up rates of 1-year clinical information were 97.5%. The cumulative incidence of cessation of at least one antiplatelet drug was significantly lower in the high CFS group than low and intermediate CFS groups (at 1-year: 38.3%, 43.3%, and 49.1%, P=0.006) (Supplemental Figure 2). In the entire cohort, 145 (5.9%) patients suffered from major bleeding and 112 (4.8%) patients suffered from death during 1-year follow-up period.

Clinical outcomes are summarized in Table 2. The cumulative 1-year incidence of major bleeding (3.1%, 11.7%, and 20.9%, p <0.001) was higher in frailer patients (Figure 2 and Table 2). Compared with CFS level 1-3, the risk for major bleeding was incrementally higher among patients with CFS level 4-9 (Supplemental Table 3). The significant association between frailty and bleeding events was consistently noted for major or minor bleeding, and for the types of bleeding such as procedure related bleeding, non-procedure related bleeding, spontaneous bleeding, and iatrogenic bleeding. Among the group differences taking competing risks into account were in line with the main analyses (Table 2).

CFS successfully stratified the risk for 1-year major bleeding regardless of HBR according to clinical risk scores (Figure 3). It was of note that patients in the high CFS group was associated with markedly higher risk for major bleeding even in patients who were regarded as not having HBR according to the ARC-HBR criteria, JCS-HBR criteria, PRECISE-DAPT score, PRAIS bleeding score, and CREDO-Kyoto bleeding score. There also was significant association between frailty and 1-year risk of major bleeding in patients who did not have each of the HBR criterion of ARC-HBR and JCS-HBR (Supplemental Table 4). Notably, while the prevalence of frail patients was low in the younger stratum (<75 years, intermediate: 11.6% and high: 1.8%), frailty remained associated with higher risk for 1-year major bleeding (intermediate CFS group: HR, 2.92; 95% CI, 1.58 to 5.40; p <0.001; high CFS group: HR; 8.29, 95% CI; 4.00 to 17.2; p <0.001, reference: low CFS group) (Supplemental Table 4). Meanwhile, HBR patients in the high CFS group were associated with substantially higher risk for major bleeding compared with HBR patients in the low CFS group (Supplemental Table 4). The cumulative 1-year incidence of major bleeding was numerically higher in patients with ACS presentation or cardiogenic shock than in patients without. However, the association of frailty with major bleeding was consistently seen regardless of the presence of ACS presentation or cardiogenic shock without significant interaction (Supplemental Table 5).

The cumulative 1-year incidence of all-cause death was also higher in frailer patients (low CFS group: 1.5%, intermediate CFS group: 7.3%, and high CFS group: 30.0%, p <0.001) (Table 2). The cumulative 1-year incidence of stroke was substantially higher in patients in the high CFS group (1.5%, 2.6%, and 5.6%, p <0.001), while the cumulative 1-year incidence of myocardial infarction was not




| CFS | Months | 0 | 1 | 3 | 6 | 12 |
|---|---|---|---|---|---|---|
| High (N=172) | N of patient at risk | 172 | 142 | 118 | 109 | 89 |
| | N of patients with event | 0 | 20 | 27 | 31 | 33 |
| | Cumulative incidence | 0% | 11.8% | 16.3% | 19.3% | 20.9% |
| Intermediate (N=519) | N of patient at risk | 519 | 494 | 475 | 457 | 421 |
| | N of patients with event | 0 | 22 | 33 | 45 | 59 |
| | Cumulative incidence | 0% | 4.3% | 6.4% | 8.8% | 11.7% |
| Low (N=1748) | N of patient at risk | 1748 | 1717 | 1701 | 1687 | 1651 |
| | N of patients with event | 0 | 21 | 30 | 39 | 53 |
| | Cumulative incidence | 0% | 1.2% | 1.7% | 2.2% | 3.1% |

Figure 2. Kaplan-Meier curves for major bleeding according to the CFS groups.
CFS = clinical frailty scale.

significantly different across the 3 groups (0.9%, 1.8%, and 1.8%, p = 0.26).

## Discussion

The salient findings of this study are as follows;

1. In an all-comer, single-center PCI registry with a mean age of 71.9 ± 10.1 years, 29.4% of the patients were regarded as frail according to the CFS (high: 7.3% and intermediate: 22.1%). Frailer patients more often suffered major bleeding during the 1-year follow-up period after PCI.
2. Among 691 frail patients, 84.8% were regarded as having HBR according to the ARC-HBR criteria, while among 1028 patients who were regarded not having HBR, 89.8% were not frail according to the CFS. CFS was a simple tool that enabled us to identify HBR patients without assessing respective HBR criteria. Moreover, the risk of 1-year major bleeding was profound in patients who had both frailty and HBR.
3. Among patients who did not have HBR, there also was a significant association between frailty and 1-year risk of major bleeding, although the prevalence of frailty was low in non-HBR patients. Of note, frailty remained associated with higher risk for 1-year major bleeding even in the younger patients (<75 years).

Frailty is an increasingly recognized metric that was reportedly associated with in-hospital cardiovascular events after PCI for ACS, while the prevalence of frail patients widely varied depending on the definitions of frailty used and study cohorts, ranging from 16.4% to 48.5%.[4–6] In our study including all-comer patients with a mean age of 71.9 ± 10.1 years, 29.4% of patients were regarded as frail using a simple tool of CFS (high: 7.3% and intermediate: 22.1%), and more often suffered 1-year major bleeding than those without frailty. The association of frailty with bleeding was consistently observed regardless of severity of bleeding or

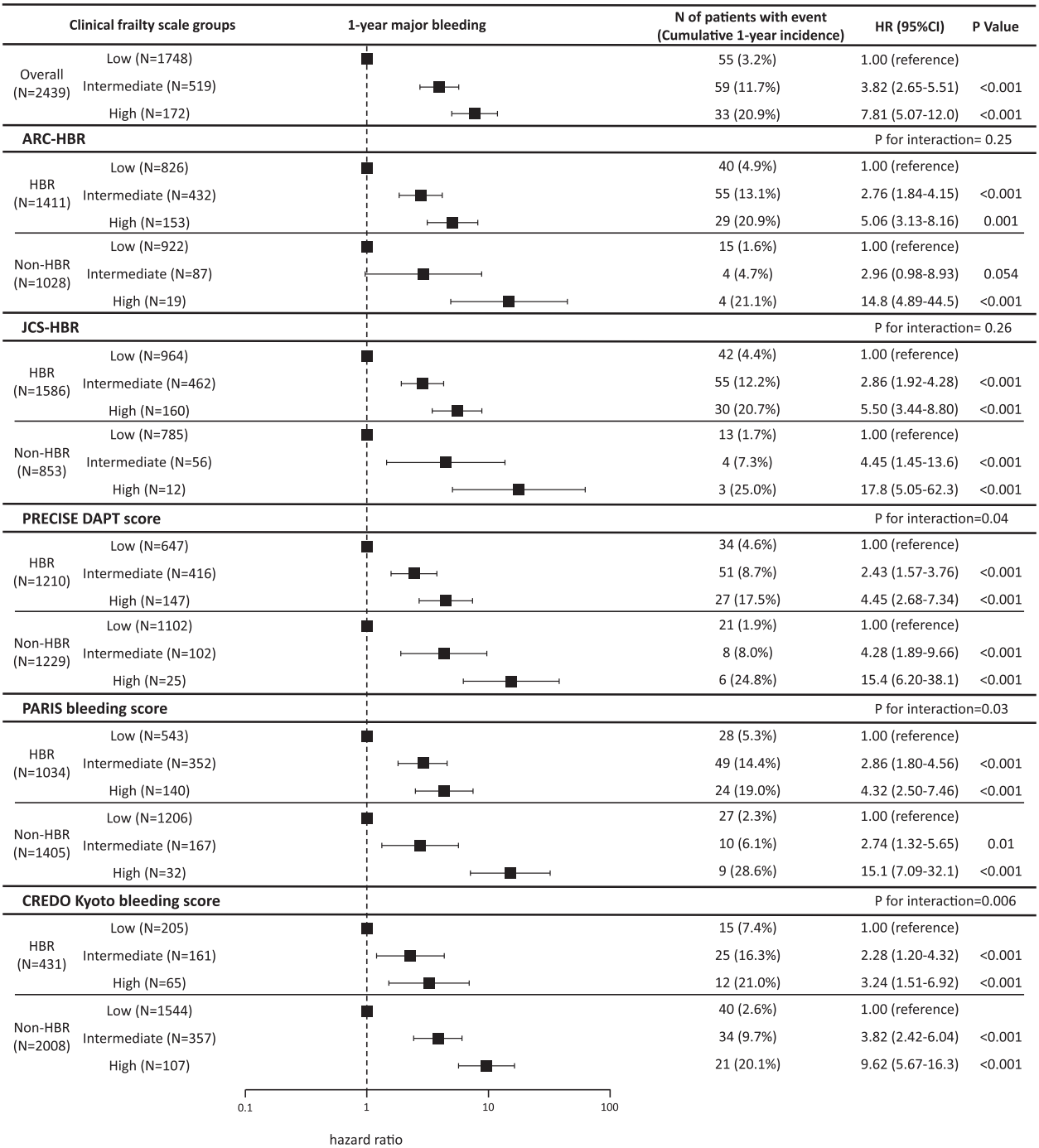



Figure 3. Subgroup analyses for the effects of CFS on 1-year major bleeding stratified by high bleeding risk according to the ARC-HBR criteria, JCS-HBR criteria, PRECISE-DAPT score, PARIS bleeding score, and CREDO-Kyoto bleeding score.
HR = hazard ration; CI = confidence interval; ARC-HBR = Academic Research Consortium for high bleeding risk; JCS-HBR = Japan Circulation Society high bleeding risk; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; PARIS = Patterns of Non-Adherence to Antiplatelet Regimens In Stented Patients; CREDO-Kyoto = Coronary Revascularization Demonstrating Outcome Study in Kyoto.

types of bleeding, which supported the hypothesis that frailty plays an important role for bleeding events after PCI. Moreover, while ACS presentation and cardiogenic shock were well-known predictors for post-PCI adverse events,[17-19] there remained an association of frailty with major bleeding irrespective of the presence or absence of ACS presentation or cardiogenic shock.

Since frailer patients were older and had more comorbidities, frail patients in the present study often had HBR according to the ARC-HBR criteria, JCS-HBR criteria,

PRECISE-DAPT score, PARIS bleeding score, and CREDO-Kyoto bleeding score. While each bleeding risk score have high accuracy in discriminating patients with high bleeding risk, the prevalence of high bleeding risk was different largely according to each risk score. The observed discrepancy might be driven by sensitivity and specificity of each assessment tool. Among 691 frail patients, most of patients were regarded as having HBR according to the respective criteria or scores, while among patients who were regarded not having HBR, almost all of those were not frail according to the CFS. Patients with frailty, which was assessed according to CFS, had large overlap with patients with HBR, and therefore, high bleeding risk of frail patients could be predicted in large part by the HBR criteria or bleeding risk scores. It should be noted that CFS was a simple tool that enabled us to identify HBR patients without assessing respective HBR criteria.

Recently, ARC-HBR criteria has been proposed as a world-wide consensus for determining the patients with HBR;[7] however, frailty *per se* was not included as a criterion, since there is a scarcity of data on the causative role of frailty for the long-term bleeding risk after PCI. Despite there was a substantial overlap between HBR according to the ARC-HBR criteria and frailty assessed by CFS, our findings shed light on the clinical relevance of frailty to identify HBR patients. Compared with patients without frailty, frail patients more often suffered 1-year major bleeding in those with HBR according to ARC-HBR (4.9% versus 15.1%, p <0.001), and in those without HBR (1.6% versus 7.7%, p <0.001), suggesting frailty has a predicting ability for 1-year major bleeding on top of ARC-HBR criteria. HBR criteria or scores have been developed to identify patients who receive benefit from short-term DAPT.[11,20,21] Kaplan-Meier curves among CFS groups diverged early within six months, suggesting there may be a potential benefit of short-term (1 to 6 months) DAPT in frail patients. Since frail patients were often excluded from clinical studies, larger-scale, all-comer multicenter studies are needed to confirm our observations and to clarify the optimal DAPT duration after PCI for frail patients.

In the previous studies addressing the impact of frailty on clinical outcomes after PCI, the study cohorts were limited to patients who were older than certain cutoff age of around 65 to 75 years.[4-6] In our all-comer cohort, it was intriguing that not few patients (intermediate: 11.6% and high: 1.8%) were regarded as frail in the younger patients with <75 years of age. Indeed, these younger patients with frailty more often suffered major bleeding within 1-year compared with those without frailty. This indicates that not only biological age but also a reduced physiological reserve is an essential factor for adverse events. Although frailty-related factors such as alterations in response to antiplatelet drugs, reduced pharmacokinetics, and vascular fragility might explain the higher risk of bleeding in frail patients, its underlying mechanisms remain largely unclear. Furthermore, it cannot be explicitly stated whether improvement of frailty (by implementing exercise and improving overall nutrition status) can reduce the risk of bleeding. Notwithstanding these uncertainties, CFS would be a simple and reliable decision-making tool to identify HBR patients in daily clinical practice.

There were several limitations to this study. First, it is uncertain whether the results are generalizable due to a single-center design. Second, CFS is a semiquantitative scale of frailty. Although medical professionals have assessed the CFS, its reproducibility has not been evaluated. Third, original 9-level CFS was concatenated into 3 CFS groups due to a lack of data for CFS level 1 to 3, and the relatively small patient cohort. Finally, since there were no patients who did not undergo PCI in our cohort, we could not assess the excessive risk for bleeding in patients who underwent PCI compared with those who did not undergo PCI.

In conclusions, among 691 frail patients, 84.8% were regarded as having HBR according to the ARC-HBR criteria, while among 1028 patients who were regarded not having HBR, 89.8% were not frail according to the CFS. The association of frailty with 1-year major bleeding was consistently observed in patients with and without HBR, indicating that frailty *per se* might be a predictor for major bleeding after PCI on top of HBR criteria.

## Author Contribution

Kenji Kanenawa: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft

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Hiroaki Tashiro: Data Curation

Takeshi Morimoto: Writing - Review & Editing, Supervision

Takashi Hiromasa: Supervision

Masaomi Hayashi: Supervision

Seiichi Hiramori: Supervision

Yusuke Tomoi: Supervision

Shoichi Kuramitsu: Supervision

Takenori Domei: Supervision

Makoto Hyodo: Supervision

Kenji Ando: Supervision

Takeshi Kimura: Writing - Review & Editing, Supervision

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.041.

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;381:752–762.
2. Kanenawa K, Yamaji K, Tashiro H, Domei T, Ando K, Watanabe H, Kimura T. Patient selection and clinical outcomes in the STOPDAPT-2 trial. *Circ Cardiovasc Interv* 2021;14(2):e010007. https://doi.org/10.1161/CIRCINTERVENTIONS.120.010007.
3. Kanenawa K, Isotani A, Yamaji K, Nakamura M, Tanaka Y, Hirose-Inui K, Fujioka S, Mori S, Yano M, Ito S, Morinaga T, Fukunaga M, Hyodo M, Ando K. The impact of frailty according to clinical frailty

scale on clinical outcome in patients with heart failure. *ESC Heart Fail* 2021. https://doi.org/10.1002/ehf2.13254.
4. Ekerstad N, Swahn E, Janzon M, Alfredsson J, Löfmark R, Lindenberger M, Carlsson P. Frailty is independently associated with short-term outcomes for elderly patients with non−ST-segment elevation myocardial infarction. *Circulation* 2011;124:2397–2404.
5. Dodson JA, Hochman JS, Roe MT, Chen AY, Chaudhry SI, Katz S, Zhong H, Radford MJ, Udell JA, Bagai A, Fonarow GC, Gulati M, Enriquez JR, Garratt KN, Alexander KP. The association of frailty with in-hospital bleeding among older adults with acute myocardial infarction. *JACC: Cardiovasc Interv* 2018;11:2287–2296.
6. Matsuzawa Y, Konishi M, Akiyama E, Suzuki H, Nakayama N, Kiyokuni M, Sumita S, Ebina T, Kosuge M, Hibi K, Tsukahara K, Iwahashi N, Endo M, Maejima N, Saka K, Hashiba K, Okada K, Taguri M, Morita S, Sugiyama S, Ogawa H, Sashika H, Umemura S, Kimura K. Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol* 2013;61:1964–1972.
7. Urban P, Mehran R, Colleran 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 HS, 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 MC. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the academic research consortium for high bleeding risk. *Eur Heart J* 2019;40:2632–2653.
8. Rockwood K. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J* 2005;173:489–495.
9. Morley JE, Vellas B, Abellan Van Kan G, Anker SD, Bauer JM, Bernabei R, Cesari M, Chumlea WC, Doehner W, Evans J, Fried LP, Guralnik JM, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, Von Haehling S, Vandewoude MF, Walston J. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013;14:392–397.
10. Urban P, Mehran R, Colleran 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.
11. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, Kosuge M, Shinke T, Nakagawa Y, Natsuaki M, Yasuda S, Akasaka T, Kohsaka S, Haze K, Hirayama A. JCS 2020 Guideline focused update on antithrombotic therapy in patients with coronary artery disease. *Circ J* 2020;84:831–865.
12. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-K, Kim H-S, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. 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;389:1025–1034.
13. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;67:2224–2234.
14. Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, Nakagawa Y, Furukawa Y, Kadota K, Ando K, Akasaka T, Hanaoka KI, Kozuma K, Tanabe K, Morino Y, Muramatsu T, Kimura T. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto thrombotic and bleeding risk scores. *J Am Heart Assoc* 2018;7:e008708.
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. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW. Serruys PW and academic research C. clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
17. Nikolsky E, Stone GW, Kirtane AJ, Dangas GD, Lansky AJ, McLaurin B, Lincoff AM, Feit F, Moses JW, Fahy M, Manoukian SV, White HD, Ohman EM, Bertrand ME, Cox DA, Mehran R. Gastrointestinal bleeding in patients with acute coronary syndromes: incidence, predictors, and clinical implications. *J Am Coll Cardiol* 2009;54:1293–1302.
18. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, Bassand JP, De Caterina R, Eikelboom JA, Gulba D, Hamon M, Helft G, Fox KAA, Kristensen SD, Rao SV, Verheugt FWA, Widimsky P, Zeymer U, Collet JP. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the working group on thrombosis of the European society of cardiology. *Eur Heart J* 2011;32:1854–1864.
19. Kawaji T, Shiomi H, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Ando K, Mizoguchi T, Abe M, Takahashi M, Kimura T, Investigators C-KA. Long-term clinical outcomes in patients with ST-segment elevation acute myocardial infarction complicated by cardiogenic shock ue to acute pump failure. *Eur Heart J Acute Cardiovasc Care* 2018;7:743–754.
20. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *J Am Coll Cardiol* 2009;68:1082–1115.
21. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, Badimon L, Vranckx P, Agewall S, Andreotti F, Antman E, Barbato E, Bassand J-P, Bugiardini R, Cikirikcioglu M, Cuisset T, De Bonis M, Delgado V, Fitzsimons D, Gaemperli O, Galiè N, Gilard M, Hamm CW, Ibanez B, Iung B, James S, Knuuti J, Landmesser U, Leclercq C, Lettino M, Lip G, Piepoli MF, Pierard L, Schwerzmann M, Sechtem U, Simpson IA, Uva MS, Stabile E, Storey RF, Tendera M, Van De Werf F, Verheugt F, Aboyans V, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Roithinger FX, Aliyev F, Stelmashok V, Desmet W, Postadzhiyan A, Georghiou GP, Motovska Z, Grove EL, Marandi T, Kiviniemi T, Kedev S, Gilard M, Massberg S, Alexopoulos D, Kiss RG, Gudmundsdottir IJ, McFadden EP, Lev E, De Luca L, Sugraliyev A, Haliti E, Mirrakhimov E, Latkovskis G, Petrauskiene B, Huijnen S, Magri CJ, Cherradi R, Ten Berg JM, Eritsland J, Budaj A, Aguiar CT, Duplyakov D, Zavatta M, Antonijevic NM, Motovska Z, Fras Z, Montoliu AT, Varenhorst C, Tsakiris D, Addad F, Aydogdu S, Parkhomenko A, Kinnaird T. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;39:213–260.