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ORIGINAL ARTICLE

Bleeding Risk Scores and Scales of Frailty for the Prediction of Haemorrhagic Events in Older Adults with Acute Coronary Syndrome: Insights from the FRASER study

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Abstract

Purpose Hitherto, no study has yielded important information on whether the scales of frailty may improve the ability to discriminate the risk of haemorrhages in older adults admitted to hospital for acute coronary syndrome (ACS). The aim of this study is to investigate whether frailty scales would predict the 1-year occurrence of haemorrhagic events and if they confer a significant incremental prognostic value over the bleeding risk scores.

Methods The present study involved 346 ACS patients aged ≥ 70 years enrolled in the FRASER study. Seven different scales of frailty and PARIS, PRECISE-DAPT and BleeMACS bleeding risk scores were available for each patient. The outcomes were the 1-year BARC 3-5 and 2 bleeding events.

Results Adherence to antiplatelet treatment at 1, 6 and 12 months was 98%, 87% and 78%, respectively. At 1-year, 14 (4%) and 30 (9%) patients presented BARC 3-5 and 2 bleedings, respectively. Bleeding risk scores and four scales of frailty (namely Short Physical Performance Battery, Columbia, Edmonton and Clinical Frailty Scale) significantly discriminated the occurrence of BARC 3-5 events. The addition of the scales of frailty to bleeding risk scores did not lead to a significant improvement in the ability to predict BARC 3-5 bleedings. Neither the bleeding risk scores nor the scales of frailty predicted BARC 2 bleedings.

Conclusions Both the bleeding risk scores and the scales of frailty predicted BARC 3-5 haemorrhages. However, integrating the scales of frailty with the bleeding risk scores did not improve their discriminative ability.

Clinical trial registration www.clinicaltrials.gov: NCT02386124

Keywords Acute coronary syndrome · Frailty · Bleeding · PRECISE-DAPT · PARIS · Elderly

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Abbreviations

ACS	Acute coronary syndrome
DAPT	Dual antiplatelet therapy
FRASER	Frailty in elderly patients receiving cardiac interventional procedures
BARC	Bleeding Academic Research Consortium
PRECISE-DAPT	Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy
PARIS	Patterns of Non-adherence to Anti-platelet Regimen in Stented Patients

BleeMACS	Bleeding complications in a multicentre registry of patients discharged with diagnosis of acute coronary syndrome
SPPB	Short Physical Performance Battery
CFS	Clinical Frailty Scale

Introduction

The combination of the dual antiplatelet therapy (DAPT) with aspirin and an inhibitor of the P2Y12 receptor has been found to give substantial and durable benefits in terms of reduction of ischemic adverse events after acute coronary syndromes (ACS) [1]. However, the DAPT has been undoubtedly associated with a higher risk of haemorrhagic events, which are a cause of morbidity and mortality [1]. Since advanced age is considered a strong independent predictor of both ischemic and bleeding complications [2], the current guidelines suggest an individualized approach based on ischemic versus (vs.) bleeding risk assessment [1]. For this purpose, several scores have been developed [3–6].

A large number of scores were validated for the prediction of haemorrhagic events occurring mainly during the hospital stay or early thereafter [3]. On the other hand, the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS), the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT), and the Bleeding Complications in a Multicenter Registry of Patients Discharged with Diagnosis of Acute Coronary Syndrome (BleeMACS) risk scores have been specifically designed to predict the out-of-hospital risk of haemorrhagic events [4–6]. These scores are based on widely diffused clinical and laboratory variables and showed a moderate-good ability to discriminate haemorrhagic events. However, several questions remain to be addressed. For instance, the role of these scores in older adults and whether combining them with scales of frailty or physical performance would enhance their prediction of bleeding risk.

Frailty in elderly patients receiving cardiac interventional procedures (FRASER) study [7, 8] investigated the role of different scales of frailty and/or physical performance in older adults admitted to hospital for ACS.

The purposes of the present analysis were (i) to verify the predictive value of PARIS, PRECISE-DAPT and BleeMACS scores in a sample of older frail patients admitted to hospital for ACS; (ii) to explore if indicators of frailty and/or physical performance would predict any bleeding risk in the same cohort of patients; (iii) to assess the incremental prognostic value of these scales over the PARIS, PRECISE-DAPT and BleeMACS bleeding risk scores in predicting 1-year occurrence of haemorrhagic events.

Methods

Study Design

The FRASER was a prospective, multicentre study involving patients aged ≥ 70 years and admitted to hospital with ACS diagnosis between December 2014 and October 2016 [7, 8]. The study was designed to assess the prognostic value of several scales of frailty and/or physical performance [7]. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committees of the participating centres independently approved the protocol, and all participants gave written informed consent. This study was registered at www.clinicaltrials.gov with the identifier NCT02386124.

Study Population

A detailed description of inclusion and exclusion criteria has been previously provided [7]. ACS diagnosis was performed in agreement with current guidelines [9, 10]. Patients were included if aged ≥ 70 years and with a hospital admission for ACS receiving coronary artery angiography ± percutaneous coronary intervention. Main exclusion criteria were short portable mental status questionnaire (SPMSQ) < 4, inability to stand upright, life expectancy < 3 months, surgical coronary revascularization and inability to be discharged to home [7]. The patient management, as well as the medical treatment during hospitalization and at discharge, was at the discretion of the attending physician and in accordance with the current guidelines [9, 10]. Similarly, the selection of P2Y12 inhibitors (clopidogrel vs. ticagrelor vs. prasugrel) was left to the physician. According to institutional protocols, DAPT regimen was prescribed for 12 months in all patients, except for those with clinical indication to oral anticoagulant therapy (OAT). For the present analysis, to avoid the bias related to OAT assumption on haemorrhagic events, the patients discharged with OAT were excluded.

Bleeding Risk Scores

The PARIS, PRECISE-DAPT and BleeMACS bleeding risk scores were calculated as reported previously [4–6]. The calculation was performed by an ad hoc team (ET, GB) blinded to the outcome and to the results of scales of frailty and/or physical performance. A patient was defined at high bleeding risk (HBR) if the bleeding scales scores were ≥ 8 (PARIS), ≥ 25(PRECISE-DAPT) and ≥ 26 (BleeMACS) points [4–6].

Scales of Frailty and/or Physical Performance

A large amount of clinical and management data, including demographics, previous medical history, comorbidities,

laboratory data and treatments, was collected [7, 8]. Seven tests of frailty or physical performance were compared: Fried's phenotype, handgrip strength, Short Physical Performance Battery (SPPB), Rockwood Clinical Frailty Scale (CFS), Columbia frailty index, Multidimensional Prognostic Index (MPI) and Edmonton Frail Scale [11–17]. Frailty assessment was performed after mobilization and before hospital discharge. It was performed by an ad hoc team including a study physician and a study assistant, both adequately trained to perform the tests following standardized protocols.

Clinical Follow-Up

All patients received follow-up visits at 1, 6 and 12 months. At each visit, information regarding single patients' drug adherence was collected and the on-treatment or off-treatment status was strictly monitored. Patients were examined and asked about the occurrence of adverse events [7, 8]. Source documentation regarding each adverse event was collected [7, 8].

Study Endpoints and Definitions

The objective of this analysis was the occurrence of haemorrhagic events, adjudicated according to Bleeding Academic Research Consortium (BARC) criteria [18]. The events of interest were BARC 3-5 and BARC 2 bleedings [18]. We decided to perform a separate analysis of BARC 3-5 vs. 2 bleedings, taking into account the different prognostic implication and relationship with long-term mortality [19, 20]. All haemorrhagic events were centrally adjudicated by the clinical events committee, whose members were unaware of the result of both bleeding scores and scales of frailty and/or physical performance.

Statistical Analysis

A detailed description of sample size calculation and of statistical analyses has been previously completed [7]. As stated above, to avoid the bias related to concomitant OAT, for the present analysis, we excluded patients discharged with anticoagulants. Continuous data were tested for normal distribution with the Kolmogorov–Smirnov test. Normally distributed values were presented as mean ± SD and compared by *t* test; otherwise, median value (interquartile range, IQR) and the Mann–Whitney *U* test were used.

Categorical variables were summarized in terms of counts and percentages and were compared by using the two-sided Pearson's chi-squared test or the Fisher's exact test, as appropriate. The performance of bleeding risk scores and scales of frailty or physical performance in the prediction of bleeding events was assessed using metrics of discrimination (Harrell's *C*-statistic).

In order to assess the incremental predictive value, each scale of frailty or physical performance able to predict bleeding events was added to the model generated with the bleeding risk score. The following indices were calculated: Δ *C*-statistic, Bayesian information criterion (BIC), integrated discrimination improvement (IDI) and net reclassification improvement (NRI) [21, 22].

Δ *C*-statistic represents the improvement in the discrimination ability of one score compared with another [21, 22]. The BIC measures the efficiency of the model in terms of predicting the data. More negative values indicate improved prediction, with a change of − 10 indicative of very strong evidence of improvement [22]. The IDI ranges between 0 and 1 and can be interpreted as equivalent to the increase in average sensitivity given no changes in specificity [22]. The NRI focuses on reclassification and is calculated by adding up two components: "event NRI", i.e. the net proportions of individuals with increase in predicted probability among those who will develop the event, and the "non-event NRI", i.e. the net proportions of individuals with a decrease in predicted probability among those who will not develop the event [22]. The NRI ranges from 0 to 2, with more positive values indicating greater improvement in predicting probabilities [22].

All tests are two-sided, and their statistical significance was defined as $p < 0.05$. All analyses were performed with Stata 13 (Stata Corp, College Station, TX) by the staff (EM) of the Center for Clinical Epidemiology of the School of Medicine at the University of Ferrara (Ferrara, Italy).

Results

The FRASER study population included 402 older adults. As reported in Table 1, 346 (85%) were discharged without indication to OAT and were considered for the present analysis. The median age was 77 [7 3-82] years. All patients underwent coronary artery angiography and 339 (98%) received a successful coronary revascularization. Overall, the DAPT regimen was prescribed at discharge in 340 (98%) patients. Adherence to antiplatelet treatment at 1, 6 and 12 months was 98%, 87% and 78%, respectively. The PARIS, PRECISE-DAPT and BleeMACS score distribution in the study population is shown in Fig. 1. The percentage of HBR patients were 34%, 73% and 65% as defined by PARIS score, PRECISE DAPT score BleeMACS score respectively (Fig. 1).

BARC 3-5

At 1-year, 14 (4%) patients presented BARC 3-5 bleedings, 1 (0.2%) of whom was a BARC 5 bleeding. The median time to the occurrence of the first event was 70 [16-109] days. The

Table 1 Baseline characteristics stratified according to the occurrence of bleedings

	Study population (without OAT) (n = 346)	Free from BARC 3-5 (n = 332)	Experiencing BARC 3-5 (n = 14)	$p1$	Free from BARC 2 (n = 316)	Experiencing BARC 2 (n = 30)	$p2$	Patients excluded (in OAT) (n = 56)
Age, (years)	78 ± 6	78 ± 6	79 ± 4	0.53	78 ± 6	78 ± 5	0.85	79 ± 6
Female sex, no. (%)	119 (34)	112 (34)	7 (50)	0.26	100 (31)	19 (63)	0.01	18 (32)
BMI, (Kg/m2)	26 ± 4	26 ± 4	26 ± 3	0.68	26 ± 4	26 ± 3	0.87	28 ± 4
CV risk factors, no. (%)								
Diabetes	107 (31)	104 (31)	3 (21)	0.53	100 (31)	7 (23)	0.42	13 (23)
Hypertension	287 (83)	274 (83)	13 (93)	0.91	262 (83)	25 (83)	0.93	50 (89)
Hyperlipidemia	185 (53)	166 (50)	6 (43)	0.87	156 (49)	16 (53)	0.71	30 (53)
Current smoker	97 (28)	91 (27)	6 (43)	0.34	86 (27)	11 (36)	0.36	18 (32)
Medical history, no. (%)								
MI	97 (28)	90 (27)	7 (50)	0.36	92 (29)	5 (17)	0.29	20 (36)
PCI	98 (28)	92 (28)	6 (43)	0.98	92 (29)	6 (20)	0.48	12 (21)
CABG	31 (9)	30 (9)	1 (7)	0.99	30 (9)	1 (3)	0.57	10 (18)
COPD	28 (7)	25 (7)	0 (0)	0.65	24 (7)	1 (3)	0.75	4 (7)
PAD	93 (27)	107 (32)	11 (78)	0.01	111 (35)	7 (23)	0.33	10 (18)
Dialysis	3 (0.8)	3 (1)	0 (0)	0.93	3 (1)	0 (0)	0.92	0 (0)
Clinical presentation, no. (%)								
STEMI	117 (34)	113 (34)	4 (28)	0.54	107 (34)	10 (33)		16 (29)
NSTEMI	145 (42)	137 (41)	8 (57)		130 (41)	15 (50)	0.52	35 (63)
UA	84 (24)	82 (25)	2 (15)		79 (25)	5 (17)		5 (9)
Killip class ≥ II	45 (13)	38 (11)	4 (28)	0.08	38 (12)	4 (14)	0.73	10 (18)
Laboratory data (at inclusion)								
White blood cells, (u/μL)	8 ± 2	8 ± 2	9 ± 2	0.18	8 ± 2	8 ± 2	0.51	8 ± 2
Haemoglobin, (g/dL)	12 ± 2	12.4 ± 2	10.8 ± 2	0.01	12.3 ± 2	12.6 ± 2	0.25	12 ± 2
Platelets, (u/μL)	208 (171–253)	205 (170–246)	266 (235–292)	0.33	208 (171–246)	221 [163–292]	0.96	209 (171–248)
CrCl, (mL/min)	54 (39–69)	56 (40–69)	36 (34–47)	0.02	54 (39–68)	67 (38–82)	0.47	55 (53–68)
Albumin, (g/dL)	3.6 (3.2–3.8)	3.6 (3.2–3.8)	3.7 (3–3.7)	0.63	3.6 (3.2–3.8)	3.7 (3.3–3.9)	0.78	3.7 (3.5–3.8)
Other data								
MVD, no (%)	253 (73)	250 (75)	13 (93)	0.22	243 (77)	20 (67)	0.35	38 (68)
PCI, no. (%)	339 (98)	326 (98)	13 (93)	0.36	309 (98)	30 (100)	0.34	53 (95)
Number of treated lesions	1 (1–2)	1 (1–2)	2 (1–2)	0.41	1 (1–2)	2 (1–2)	0.42	1 (1–2)
LVEF (%)	50 ± 10	50 ± 10	50 ± 10	0.97	50 ± 10	50 ± 10	0.93	49 ± 12
Antithrombotic drugs, no. (%)								
Aspirin	345 (99)	332 (100)	13 (93)	0.12	315 (99)	30 (100)	0.91	41 (73)
P2Y12 inhibitors	341 (98)	327 (98)	14 (100)	0.96	311 (98)	30 (100)	0.93	51 (91)
- Clopidogrel	204 (60)	196 (60)	8 (57)	0.82	183 (59)	21 (70)		51 (91)
- Ticagrelor	127 (37)	121 (37)	6 (43)		119 (38)	8 (27)	0.33	0 (0)
- Prasugrel	10 (3)	10 (3)	0 (0)		9 (3)	1 (3)		0 (0)
Dual antiplatelet therapy	340 (98)	327 (98)	13 (93)	0.28	310 (98)	30 (100)	0.91	38 (68)*
Proton pump inhibitors	335 (97)	322 (97)	13 (94)	0.8	307 (97)	28 (94)	0.7	52 (93)

p1: for the comparison between patients free from BARC 3-5 bleedings vs. those suffering from BARC 3-5 bleedings. p2: for the comparison between patients free from BARC 2 bleedings vs. those suffering from BARC 2 bleedings. *TIMI*, thrombolysis in myocardial infarction; *BMI*, body mass index; *CV*, cardiovascular; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *COPD*, chronic obstructive pulmonary disease; *PAD*, peripheral artery disease; *STEMI*, ST-segment elevation MI; *NSTEMI*, non ST-segment elevation MI; *UA*, unstable angina; *CrCl*, creatinine clearance; *MVD*, multi-vessel disease; *LVEF*, left ventricle ejection fraction

*DAPT on top of OAT for only 30 days

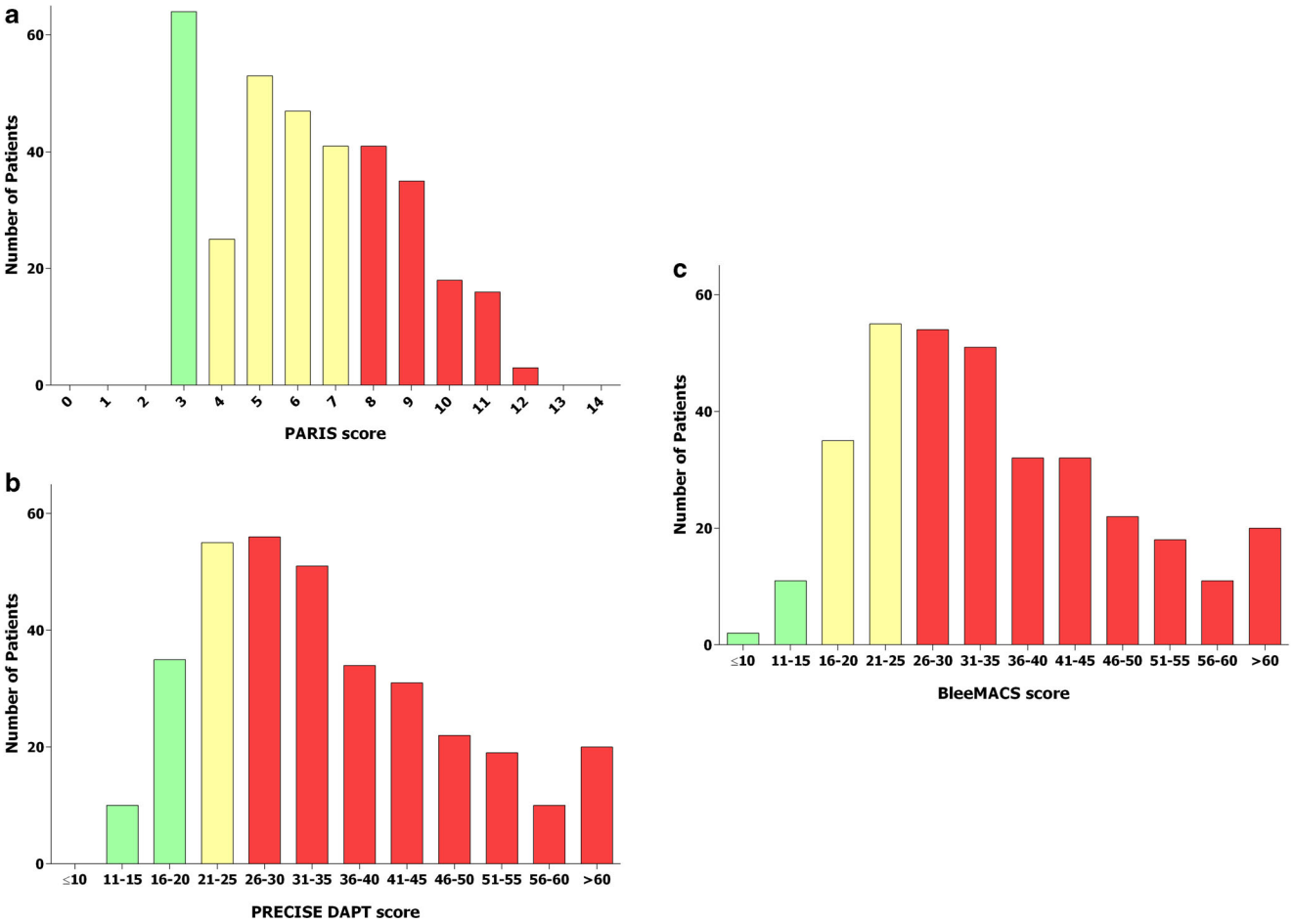

Fig. 1 Bleeding risk score distribution in the study population. **a** PARIS score. **b** PRECISE DAPT score. **c** BleeMACS score. Histograms refer to the number of patients for corresponding score points. Green bars refer to the low-risk group, yellow bars to the moderate risk and red bars to the high risk

bleeding occurred in the gastrointestinal site in 5 (36%) patients, in the genitourinary site in 3 (22%) patients and in the intracranial site in 1 (7%) patient. The other bleedings were from the lower airways (1, 7%), unknown (1, 7%), trauma-related (1, 7%) and after urgent surgery (2, 14%).

The baseline characteristics of the patients experiencing BARC 3-5 events are shown in Table 1 along with those of patients not experiencing them. Bleeding risk scores significantly discriminated the occurrence of BARC 3-5 haemorrhagic events (Table 2 and Fig. 2). Their ability to discriminate patients with bleedings did not significantly differ ($p = 0.4$). Among the scales of frailty or physical performance, SPPB, Columbia, Edmonton and CFS were the ones that predicted bleedings (Table 2 and Fig. 3). Among these four scales, we did not observe any significant differences in the discriminative ability ($p = 0.7$). Similarly, the predictive model based on frailty scales did not differ from the one based on bleeding risk scores.

The addition of these four scales with bleeding risk scores did not lead to significant increase in the probability to discriminate BARC 3-5 bleedings (Table 3). The *C*-statistics of the model considering only bleeding risk score did not differ from the ones of the model including both bleeding risk score and scale of frailty (Table 3). The BIC values did not show any strong evidence of improvement (Table 3). A slight and limited increase in sensitivity (IDI values) and reclassification (NRI values) was observable when adding the SPPB and Edmonton scales (Table 3).

BARC 2

At 1-year, 30 (9%) patients suffered of a BARC 2 bleeding. The median time to the occurrence of the first event of BARC 2 was 166 [6 7-312] days. Baseline characteristics stratified according to the occurrence or not of BARC 2 bleedings are shown in Table 1. The PARIS, PRECISE-DAPT and BleeMACS bleeding risk scores did not discriminate patients affected by BARC 2 bleedings (Table 2). Similar findings were obtained with the scales of frailty or physical performance (Table 2). None of them was associated with BARC 2 bleedings. We found that only female sex was significantly related to the occurrence of BARC 2 bleedings (OR 3.7, 95% CI 1.7–8.1, $p < 0.001$).

Table 2 Ability to discriminate haemorrhagic events of risk scores and scales of frailty or physical performance

	BARC 3-5		BARC 2	
	C-statistic (95% CI)	*p* value	*C*-statistic (95% CI)	*p* value
Risk scores				
PARIS	0.74 (0.61–0.86)	0.002	0.52 (0.46–0.57)	0.817
PRECISE-DAPT	0.79 (0.66–0.91)	< 0.001	0.55 (0.50–0.61)	0.332
BleeMACS	0.77 (0.60–0.93)	< 0.001	0.54 (0.50–0.60)	0.434
Scales of frailty/physical performance				
SPPB	0.75 (0.64–0.86)	0.002	0.53 (0.47–0.58)	0.632
Columbia	0.67 (0.54–0.80)	0.013	0.53 (0.48–0.59)	0.555
Edmonton	0.75 (0.62–0.89)	< 0.001	0.50 (0.44–0.55)	0.961
Grip strength, (Kg)	0.64 (0.53–0.76)	0.088	0.57 (0.51–0.62)	0.189
Fried	0.66 (0.55–0.78)	0.067	0.55 (0.50–0.61)	0.343
Rockwood CFS	0.71 (0.58–0.84)	0.005	0.57 (0.52–0.62)	0.225
MPI	0.60 (0.44–0.76)	0.243	0.56 (0.51–0.61)	0.267

PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; *PARIS*, Patterns of Non-adherence to Antiplatelet Regimen in Stented Patients; *BleeMACS*, Bleeding Complications in a Multicenter Registry of Patients Discharged with Diagnosis of Acute Coronary Syndrome; *SPPB*, Short Physical Performance Battery; *CFS*, Clinical Frailty Scale; *MPI*, Multidimensional Prognostic Index

Patients with Indication to OAT at Hospital Discharge

Due to atrial fibrillation (n = 54, 15%), mechanical valve prosthesis (n = 1, 0.2%) and history of pulmonary embolism (n = 1, 0.2%), OAT was prescribed at discharge in 56 (15%) patients (Table 1). Their main characteristics are described in Table 1. As expected, the rate of bleeding events was significantly higher in this subgroup of patients. BARC 3-5 bleedings occurred in 9 (16%) vs. 14 (4%) patients (p = 0.001), respectively. BARC 2 bleedings were 11 (19%) in patients with OAT vs. 30 (9%) in those without (p = 0.03), respectively.

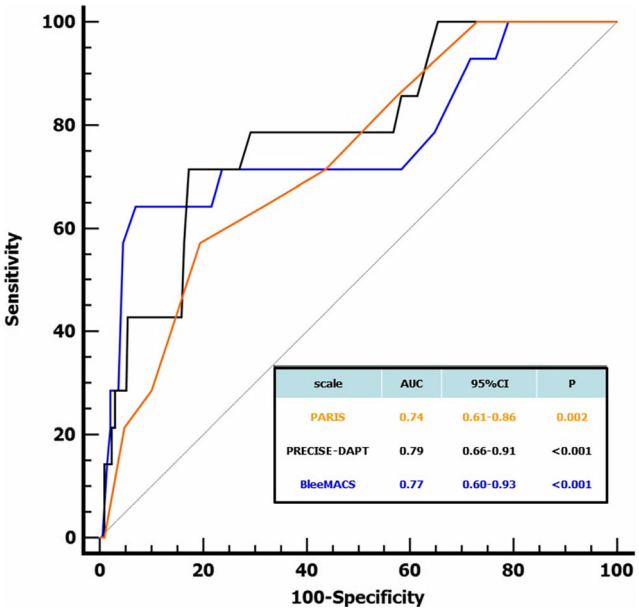

Fig. 2 Receiver operating characteristics (ROC) curves for the prediction of BARC 3-5 bleedings of the different bleeding risk scores. PARIS, Patterns of Non-adherence to Antiplatelet Regimen in Stented Patients; PRECISE DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; BleeMACS, Bleeding Complications in a Multicenter Registry of Patients Discharged with Diagnosis of Acute Coronary Syndrome; AUC, area under the curve; CI, confidence intervals

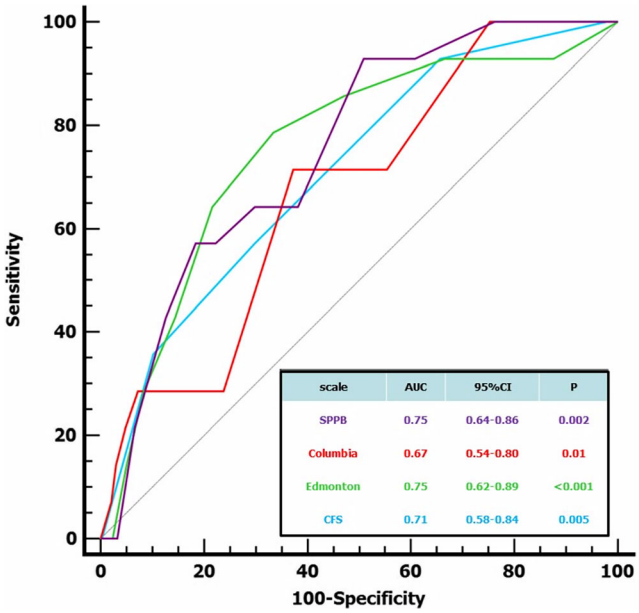

Fig. 3 Receiver operating characteristics (ROC) curves for the prediction of BARC 3-5 bleedings of the different scales of frailty or physical performance. SPPB, Short Physical Performance Battery; CFS, Clinical Frailty Scale; AUC, area under the curve; CI, confidence intervals

Table 3 Contribution of the scales of frailty or physical performance to bleeding risk score for the prediction of BARC 3-5 bleedings

	C-statistic (95% CI)	Δ *C*-statistic*	*p* value*	Δ BIC*	IDI*	*p* value*	NIR*	*p* value*
PARIS								
+ SPPB	0.78 (0.67–0.90)	0.050	0.138	− 0.82	0.031	0.009	0.443	0.103
+ Columbia	0.76 (0.64–0.89)	0.027	0.245	− 3.23	0.013	0.271	0.285	0.295
+ Edmonton	0.79 (0.70–0.88)	0.057	0.087	− 2.13	0.014	0.078	0.656	0.016
+ Rockwood CFS	0.78 (0.67–0.88)	0.043	0.254	− 2.83	0.011	0.167	0.343	0.208
PRECISE-DAPT								
+ SPPB	0.80 (0.67–0.92)	0.012	0.532	− 1.74	0.027	0.012	0.635	0.019
+ Columbia	0.79 (0.68–0.91)	0.008	0.580	− 4,54	0.007	0.449	0.176	0.518
+ Edmonton	0.80 (0.68–0.92)	0.011	0.669	− 3.56	0.014	0.110	0.665	0.014
+ Rockwood CFS	0.80 (0.66–0.93)	0.008	0.571	− 4.68	0.007	0.281	0.379	0.163
BleeMACS								
+ SPPB	0.80 (0.61–0.93)	0.031	0.257	− 2.09	0.030	0.027	0.617	0.024
+ Columbia	0.77 (0.62–0.93)	0.008	0.527	− 4.74	0.006	0.596	0.289	0.314
+ Edmonton	0.79 (0.64–0.94)	0.022	0.327	− 4.59	0.006	0.405	0.498	0.067
+ Rockwood CFS	0.77 (0.61–0.93)	0.002	0.768	− 5.69	0.001	0.707	0.197	0.470

*The values are referred for the comparison between the bleeding risk score alone vs. the model including bleeding risk score and the scale of frailty or physical performance

BIC, Bayesian information criterion; *IDI*, integrated discrimination improvement; *NRI*, net reclassification improvement; *SPPB*, Short Physical Performance Battery; *CFS*, Clinical Frailty Scale; *MPI*, Multidimensional Prognostic Index; *PRECISE-DAPT*, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; *PARIS*, Patterns of Non-adherence to Antiplatelet Regimen in Stented Patients; *BleeMACS*, Bleeding Complications in a Multicenter Registry of Patients Discharged with Diagnosis of Acute Coronary Syndrome

Discussion

The number of older adults affected by ACS and undergoing percutaneous coronary revascularization is increasing worldwide [23]. Since these patients are subjected to a higher risk of recurrences after the first event, a long-term DAPT regimen can minimize this heightened ischemic risk [23]. Unfortunately, several studies showed that also bleeding complications during DAPT treatment tend to be more frequent in older patients, with negative prognostic implications [2]. Advanced age is a variable that should be taken into consideration in bleeding risk predictions [3–6].

Available bleeding risk scores were generated starting from large databases including several anamnestic, clinical and laboratory variables [3–6]. These databases were mainly obtained from studies designed and conducted with different aims [3–6]. Therefore, it is not surprising that data regarding frailty or physical performance were missing. Nevertheless, it is well established that a significant discrepancy between chronological and biological age occurs in older adults [2, 23]. Whether the assessment of the "biological age" and its integration in the available bleeding risk scores may contribute to individualize the best antithrombotic regimen is unknown.

The present sub-analysis of the FRASER study [7, 8] started from the premise that there could be a relationship between bleeding risk scores, scales of frailty or physical performance and the 1-year occurrence of haemorrhagic events in older (≥ 70 years) adults treated with DAPT after ACS.

The major strengths of the present analysis were a study population of older ACS patients receiving evidence-based treatments in terms of invasive management and medical therapy; the concomitant assessment with seven different scales of frailty or physical performance; a head to head comparison of three different bleeding risk scores; the blinded adjudications of haemorrhagic events according to current and validate standards.

Our main findings can be summarized as follows:

i. The 1-year occurrence of BARC 3-5 bleeding was 4% (95% CI 2.2–6.7%), whereas BARC 2 bleedings rate was 9% (95% CI 6–12%);
ii. The available bleeding risk scores predicted BARC 3-5 bleedings with a good discriminative ability;
iii. Some scales of frailty (namely Columbia, Edmonton, CFS) or physical performance (namely SPPB) predicted BARC 3-5 bleedings with a discriminative ability comparable with the one of bleeding risk scores;
iv. The addition of the scales of frailty on top of bleeding risk scores did not improve the ability to discriminate BARC 3-5 bleedings;
v. Neither the bleeding risk scores nor the scales of frailty or physical performance predicted BARC 2 bleedings.

We observed a significant 1-year rate of BARC 3-5 bleedings. This result is higher than what was observed in all-comer trials or registries (e.g. 2% in the GLOBAL LEADERS and PRODIGY trials, 3% and 2.5% in the PARIS and the Bern PCI registries, respectively [5, 6, 24, 25]), highlighting the impact of advanced age on the risk of bleeding complications during DAPT treatment. Despite the derivation cohorts of the PARIS, PRECISE DAPT and BleeMACS scores [4–6] were totally different from the FRASER study population, and the discrimination ability of haemorrhagic events for all three bleeding risk scores was confirmed to be good.

None of the scores was better compared with others, but we may not exclude that our sample size was too small to highlight a difference. The systematic application of the bleeding risk scores identified most of our population study as "high bleeding risk". According to the selected score, the percentage of HBR ranges from 34 to 73%. In addition, it is plausible that the PARIS score identified a smaller percentage of HBR patients due to the fact that one of its items is the prescription of triple therapy at discharge, but this was an exclusion criterion in our analysis.

The clinical implications are of extreme importance for the choice of the treatment of these patients. In fact, in HBR patients, the current guidelines suggest a shorter DAPT regimen (6 months, class IIb and level of evidence B) [1]. However, it often occurs that in order to avoid a high number of haemorrhagic events, which frequently occur in the first months of DAPT treatment, there is a risk of undertreating a large number of patients with consequent increase of thrombotic events. For this reason, any effort to improve our ability to discriminate HBR patients should be commended.

Previous studies have focused on the association between frailty and bleeding complications, with conflicting results [26–29]. These studies were limited by the short-term occurrence of major bleedings (in-hospital or 30-day), the number of scales of frailty or physical performance were fewer, the adjudication of events was not blinded [27–29]. An additional limitation lies in the fact that the previous studies investigated the incremental value over scores focused on in-hospital bleeding risk (namely, the CRUSADE risk score) [26–28]. A preliminary evidence about PRECISE-DAPT score in older ACS patients has been published by Guerrero et al. [30]. They showed that the vast majority of these patients had PRECISE-DAPT values above the recommended cut-off point for bleeding risk. These data are confirmed by our study. We found that the 73% (95% CI 68–78%) of patients had a PRECISE-DAPT score ≥ 25. In addition, we integrated the information with two other scores (PARIS and BleeMACS) and we investigated if the scales of frailty or physical performance may improve them. We found that, as well as for all-cause mortality and ischemic adverse events [13, 31], the scales of frailty (Columbia, Edmonton, CFS) or physical performance (SPPB) were able to predict the risk of bleeding complications. Interestingly, we found that the discriminative ability was comparable with the one of the bleeding risk scores. Unfortunately, our study was not successful in proving any incremental value in the discrimination of BARC bleedings with the addition of the scales of frailty or physical performance on top of the bleeding risk scores. This is confirmed by the application of different tests.

The comparison of the *C*-statistics with solely the bleeding risk scores and the one including the addition of the frailty and physical performance scales did not show significant differences. The improvement, as assessed by BIC, was inferior to the expected cut-off. IDI and NRI identified, for SPPB and Edmonton scales, an increase in the sensitivity and in the reclassification of patients with or without bleedings, but it was minimal and not clinically meaningful. It should also be taken into account that haemorrhagic complications have a complex pathophysiology.

In fact, bleeding complications are strongly related to: antithrombotic regimen, individual responsiveness to antiplatelet agents, co-treatment (i.e. proton pump inhibitor, steroid, nonsteroidal anti-inflammatory drug), comorbidities (i.e. renal impairment and chronic obstructive pulmonary disease) or unpredictable events as trauma or surgery or other stressors [3]. It is plausible that both bleeding risk scores and scales of frailty capture these determinants and confounding factors in the same manner. This would explain why we did not observe any incremental value after their integration.

Otherwise, we can speculate that these scales of frailty have been generated for the prediction of mortality in geriatric populations and, being bleedings one of the causes of mortality in older people, these scales are able to predict these haemorrhages as "events at risk for life" but without adding specific information for the bleeding risk.

Study Limitations

This study has some limitations that should be pointed out. The major issue is related to the overall number of patients and events. Although the relative occurrence is one of the highest compared with similar studies, the absolute numbers are limited. Consequently, this can contribute to the underestimation of potential differences between bleeding risk scores and scales of frailty or physical performance. Moreover, even though we collected several parameters and information, we may not exclude that emerging predictors for bleeding, including clinical, laboratory, or genetic factors, might be missing in our database. The number of patients in OAT was small, thus considering the strong weight of triple therapy on haemorrhagic events, these patients have been excluded from the main analysis. Therefore, our findings should not be applied to this subgroup. Similarly, most of patients were treated with PCI and we cannot exclude different observations in the case of patients not undergoing coronary revascularization

and/or receiving antiplatelet monotherapy. Finally, the assessment of the scales of frailty and physical performance was performed at hospital discharge. We may not exclude an "overestimation" of the frailty status due to the recent cardiac event and to the effect of longstanding bedridden [32]. However, the estimation of bleeding risk scores should be performed at hospital discharge and previous data showed that a frailty assessment at this time reflects patient's status and predicts future outcomes [8].

Conclusions

The present analysis confirmed the good performance of the bleeding risk scores (PARIS, PRECISE DAPT and BleeMACS) in predicting BARC 3-5 haemorrhages in a study population of ACS patients aged ≥ 70 years. A similar discriminative ability has been observed in the scales of frailty (Columbia, Edmonton and CFS) and in a scale of physical performance (SPPB). However, the addition of these scales to the bleeding risk scores did not result in any clinically meaningful improvement of the prediction of bleedings.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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