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Impact of platelet reactivity on 5-year clinical outcomes following percutaneous coronary intervention: a landmark analysis

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Abstract
We investigated the impact of suboptimal platelet reactivity on clinical outcomes after percutaneous coronary intervention (PCI). We enrolled 500 patients with stable coronary artery disease undergoing elective PCI. Platelet reactivity was measured before PCI using the VerifyNow P2Y12 assay. Primary endpoint was the incidence of ischemic or bleeding events at 1 month and 5 years. Patients with high platelet reactivity (HPR) showed significantly higher rates of ischemic events both during the 1st month after PCI (HR 2.06, 95% CI 1.02–4.06), and beyond 1 month compared with patients without HPR (HR 1.73, 95% CI 1.02–2.95). Conversely, compared with patients without low platelet reactivity (LPR), patients with LPR presented significantly higher rates of bleeding only during the 1st month (HR 3.67, 95% CI 1.68–8.02). In conclusion, pre-procedural HPR is associated with ischemic events even beyond the 1st month after PCI. The association of LPR with bleeding events seems to be confined to the periprocedural period.

Keywords Platelet function test · Percutaneous coronary intervention · Coronary artery disease

Introduction

The combination of clopidogrel and aspirin is still the antiplatelet treatment of choice for patients with stable coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [1]. However, due to a large inter-individual variability in the response to antiplatelet agents [2], a significant proportion of these patients present suboptimal platelet reactivity at the time of PCI. We have previously shown that among clopidogrel-treated patients undergoing elective PCI, specific thresholds of platelet reactivity could be identified using the VerifyNow P2Y12 assay to define high platelet reactivity [HPR; P2Y12 reaction units (PRU) ≥ 240], which was associated with increased risk of ischemic events, and low platelet reactivity (LPR; PRU ≤ 178), which was associated with increased risk of bleeding events at 1 month follow-up [3]. These results were confirmed in a pooled analysis of > 20,000 patients, where, although using different thresholds for HPR and LPR definition (PRU > 208 and < 85, respectively), platelet reactivity was able to identify PCI-treated patients at higher risk of death and ST or at higher risk of bleeding [4]. The impact of suboptimal pre-PCI platelet reactivity, either high or low, on very long-term clinical outcomes is however largely unknown.

Methods

Patients population

In this study we prospectively enrolled 500 consecutive patients with stable CAD undergoing elective PCI from 2010 to 2011 at Campus Bio-Medico University, Rome, Italy.

Treatment protocol

All patients received clopidogrel, either a 600-mg loading dose ≥ 6 h before intervention or a maintenance dose

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of 75 mg/day for at least 5 days. Patients on chronic treatment did not receive any further loading dose of clopidogrel. Technicalities of the procedure, including use of the radial approach, drug eluting stents, and glycoprotein IIb/IIIa inhibitors, were left to the operator's discretion. Procedural anticoagulation consisted of unfractionated heparin administrated to achieve an activated clotting time of 250–300 s. Procedural success was defined as a reduction in percent diameter stenosis to below 30% in the presence of thrombolysis in myocardial infarction (TIMI) flow grade 3 in the main vessel and all side branches > 2 mm in diameter. After PCI, patients receiving bare-metal stents (BMS) received clopidogrel 75 mg/day for at least 4 weeks, whereas those receiving drug-eluting stents (DES) were prescribed clopidogrel for 12 months. All patients were on aspirin treatment before intervention and continued aspirin (80–100 mg/day) indefinitely. Patients with upstream use of glycoprotein IIb/IIIa inhibitors, treatment with oral anticoagulant drugs, platelet count $< 70 \times 10^9$/L, high bleeding risk (active internal bleeding, history of hemorrhagic stroke, intracranial neoplasm, arteriovenous malformation or aneurysm, ischemic stroke in the previous 3 months), coronary artery bypass surgery in the previous 3 months, and severe renal failure (serum creatinine > 2 mg/dL) were excluded. This study was approved by the local ethics committee, with all patients giving written informed consent.

Platelet function analysis

Platelet reactivity was measured immediately before PCI using the VerifyNow P2Y12 assay, with results expressed as PRUs. HPR was defined in the presence of PRU values ≥ 240, whereas LPR was defined in the presence of PRU values ≤ 178. Consistently, normal platelet reactivity (NPR) was defined in the presence of PRU values between 179 and 239 [3].

Study endpoints

Clinical follow-up data were obtained up to 5 years by means of office visit, telephone interview, or chart review. All events were classified and adjudicated by a physician not involved in the follow-up process. Endpoint of this study was the incidence of ischemic or bleeding events [3] at 1 month and 5 years. Ischemic events were defined as death, myocardial infarction (MI), or target vessel revascularization (TVR). MI included both periprocedural and spontaneous events and were defined according to the third universal definition [5]. TVR was clinically driven and included bypass surgery or repeat PCI of the target vessel(s). Definite stent thrombosis (ST) was also recored and defined according to the Academic Research Consortium definition [6]. Bleeding events included TIMI major bleeding [7], or large entry-site hematoma (> 10 cm in diameter). Entry-site hematomas were repeatedly monitored throughout the hospitalization, and the largest size detected was used for the analysis.

Statistics

Statistical analysis was performed using STATA/IC software, version 13 (STATA Corp., College Station, Texas). Continuous variables are expressed as mean ± SD or median [interquartile range]. Categorical variables are reported as frequencies and percentages. Student's *t* test or Mann–Whitney test were used to compare continuous variables, as appropriate. Comparisons between categorical variables were evaluated using two-tailed Fisher's exact test or Pearson's χ^2 test, as appropriate. Event rates were evaluated by the Kaplan–Meier method and Cox proportional hazard analysis, adjusting for diabetes mellitus, multivessel disease, chronic kidney disease (defined as glomerular filtration rate < 60 mL/min/1.73 m^2), total stent length, and GP IIb/IIIa antagonists. Landmark analyses (survival method) of the Kaplan–Meier estimates of clinical outcomes during the 1st year and from 1 month to 5 years were performed for different platelet reactivity groups. A p value < 0.05 was considered statistically significant.

Results

Patients population

A total of 170 (32.4%) patients presented with HPR, whereas 160 (30.0%) had LPR and 170 (32.4%) had NPR. Main clinical and procedural feature are reported in Table 1. Patients with HPR had higher body mass index compared with patients without HPR, and presented more frequently diabetes mellitus and multivessel disease. No major differences were observed between patients with and without LPR.

Follow-up data

Clinical follow-up was complete in 471 (94.2%). Patients experiencing ischemic and bleeding events at 5-year follow-up were 86 (17.2%) and 49 (9.8%), respectively. Ischemic events occurred in 41 (25.3%) patients with HPR and in 44 (14.2%) patients without HPR [hazard ratio (HR) 1.89; 95% confidence interval (CI) 1.21–2.90; p = 0.005; Fig. 1]. HPR was associated with significantly higher rates of MI (17.9 versus 7.8%; HR 2.22, 95% CI 1.28–3.85; p = 0.004) and definite ST (3.1 versus 0.3%; HR 9.75, 95% CI 1.21–2.90; p = 0.041), whereas no significant differences were observed in death and TVR rates between patients with and without HPR (Table 2). Bleeding events occurred in 25 (16.6%) patients with LPR and in 24

Table 1 Clinical and procedural characteristics

Characteristic	Overall population (n = 500)	HPR (n = 170)	No HPR (n = 330)	p Value	LPR (n = 160)	No LPR (n = 340)	p Value
Age, years	67.0 ± 9.8	68.8 ± 10.2	66.1 ± 9.5	0.003	66.8 ± 9.5	67.1 ± 9.9	0.670
Male, n (%)	391 (78)	130 (76)	261 (79)	0.501	127 (79)	264 (78)	0.662
Body mass index, kg/m^2	27.8 ± 4.1	28.1 ± 4.0	27.2 ± 4.2	0.039	27.7 ± 4.0	28.0 ± 4.2	0.500
Diabetes mellitus, n (%)	156 (31)	63 (37)	93 (28.2)	0.042	51 (32)	105 (31)	0.823
Hypertension, n (%)	407 (81)	144 (84)	263 (80%)	0.173	130 (81)	277 (81)	0.953
Hyperlipidemia, n (%)	355 (71)	121 (71)	234 (71%)	0.950	119 (74)	236 (69)	0.254
Current smoker, n (%)	100 (20)	26 (15)	74 (22)	0.059	39 (24)	61 (18)	0.093
Previous myocardial infarction, n (%)	188 (38)	59 (35)	129 (39)	0.338	62 (39)	126 (37)	0.716
Previous coronary intervention, n (%)	207 (41)	71 (42)	136 (41)	0.927	64 (40)	339 (42)	0.663
Previous bypass surgery, n (%)	31 (6)	10 (6)	21 (6)	0.820	9 (6)	22 (6)	0.726
Left ventricle ejection fraction (%)	55 ± 8	56 ± 8	55 ± 8	0.644	55 ± 8	55 ± 8	0.988
Left ventricle ejection fraction < 40%, n (%)	41 (8)	12 (7)	29 (9)	0.504	12 (8)	29 (9)	0.696
White blood cells, x1000/mm^3	6.8 ± 1.7	6.9 ± 1.7	6.8 ± 1.7	0.508	6.7 ± 1.7	6.8 ± 1.8	0.402
C reactive protein, mg/L	2 [1–7]	3 [1–7]	2 [1–7]	0.687	3 [1–8]	2 [1–7]	0.192
Creatinine, mg/dL	0.95 [0.80–1.10]	0.93 [0.80–1.13]	0.96 [0.81–1.10]	0.690	0.93 [0.80–1.13]	0.96 [0.81–1.1]	0.466
Chronic renal failure, n (%)	78 (16)	33 (19)	45 (14)	0.092	23 (14)	55 (16)	0.605
Multivessel disease, n (%)	253 (51)	99 (58)	154 (47)	0.014	76 (48)	177 (52)	0.342
Multivessel intervention, n (%)	102 (20)	40 (24)	62 (19)	0.213	31 (19)	71 (21)	0.696
Radial approach, n (%)	19 (4)	8 (5)	11 (3)	0.813	9 (6)	10 (3)	0.143
Use of DES, n (%)	338 (68)	113 (66)	225 (68)	0.699	106 (66)	232 (68)	0.658
No. of stents implanted, n	1.4 ± 0.9	1.5 ± 0.9	1.4 ± 0.9	0.334	1.4 ± 0.9	1.4 ± 0.9	0.358
Total stent length, mm	15.9 ± 6.3	16.4 ± 5.9	15.6 ± 6.5	0.205	15.6 ± 6.9	16.0 ± 6.1	0.572
Glycoprotein IIb/IIIa inhibitors, n (%)	30 (6)	8 (5)	22 (7)	0.382	13 (8)	17 (5)	0.179

HPR high platelet reactivity, *LPR* low platelet reactivity, *DES* drug eluting stent

(7.5%) patients without LPR (HR 2.66; 95% CI 1.49–4.73; p = 0.001; Fig. 1). LPR was associated with significantly higher rates of entry site hematomas (9.9 versus 2.8%; HR 3.22, 95% CI 1.55–6.68; p = 0.002), whereas there were no differences in the rates of major bleeding between patients with and without LPR (Table 2). Table 3 reports the incidence of ischemic and bleeding events in the three groups of patients with LPR, NPR and HPR.

Landmark analysis

A landmark analysis of the Kaplan–Meier estimates of clinical outcomes during the 1st month and from 1 month to 5 years is provided in Fig. 2. Patients with HPR showed significantly higher rates of ischemic events both during the 1st month after PCI (HR 2.06, 95% CI 1.02–4.06; p = 0.045), and from 1 month to 5 years compared with

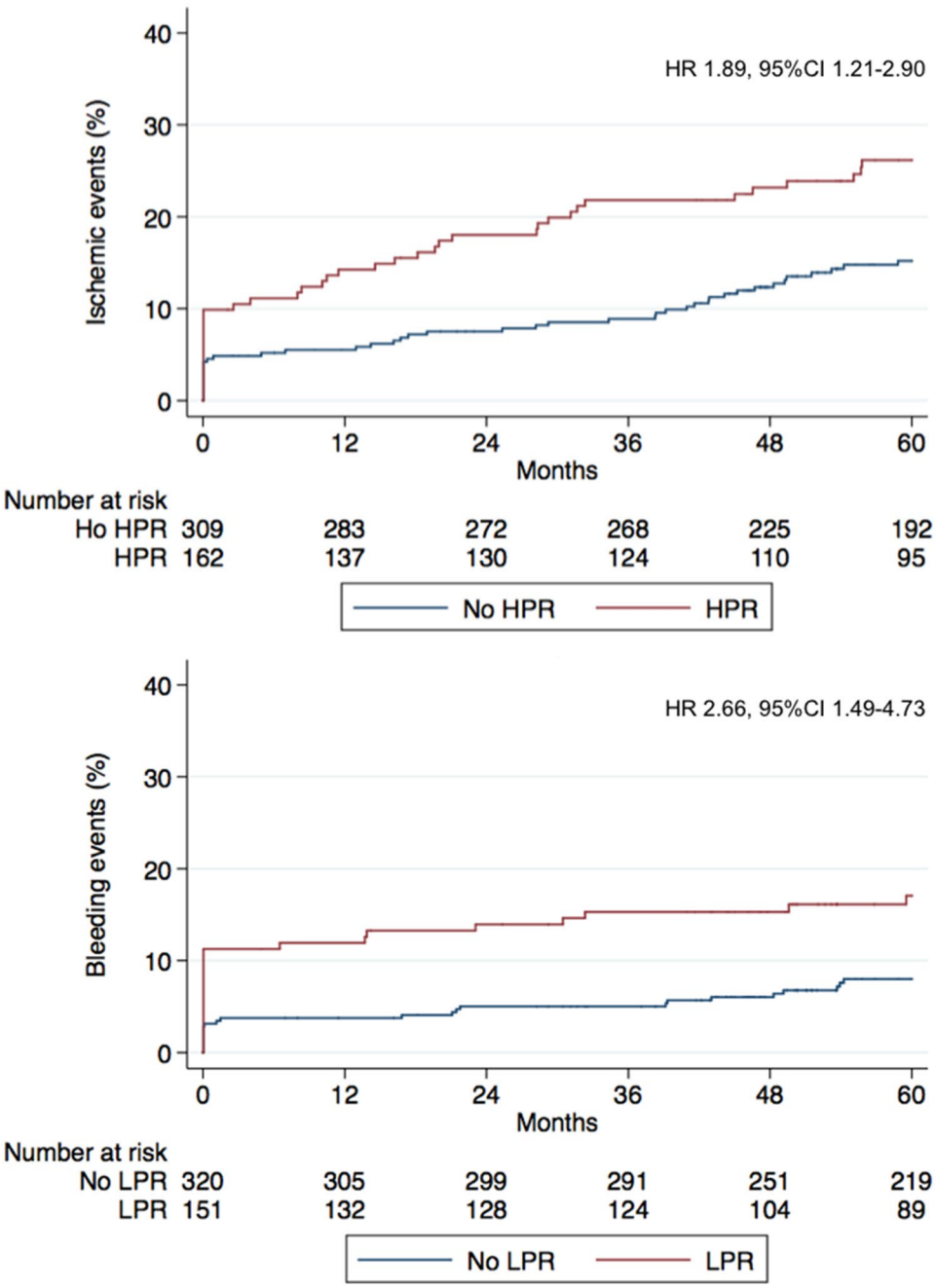

Fig. 1 Kaplan–Meier estimates of clinical outcomes up to 5 years. Upper panel: ischemic events in patients with and without high platelet reactivity (HPR). Lower panel: bleeding events in patients with and without low platelet reactivity (LPR)

patients without HPR (HR 1.73, 95% CI 1.02–2.95; p = 0.038). Conversely, patients with LPR presented significantly higher rates of bleeding during the 1st month (HR 3.67, 95% CI 1.68–8.02; p = 0.001) compared with patients without LPR, whereas similar rates of bleeding were observed from 1 month to 5 years (HR 1.37, 95% CI 0.57–3.26; p = 0.496). These results remained substantially unchanged when the PRU > 208 threshold was used for the definition of HPR and PRU < 85 threshold was used for the definition of LPR.

Discussion

This is the first study assessing the impact of pre-procedural platelet reactivity on long-term outcomes following elective PCI. Main findings of our study are that pre-PCI platelet reactivity is able to predict 5-year clinical outcomes of stable CAD patients treated with clopidogrel; however, while HPR is associated with increased risk of ischemic events even beyond the 1st month from PCI, with

Table 2 Clinical outcomes at 5 years according to HPR and LPR status

	HPR (n = 162)	No HPR (n = 309)	HR (95% CI)	p Value
Death, n (%)	16 (9.9)	19 (6.1)	1.61 (0.80–3.26)	0.185
Myocardial infarction, n (%)	29 (17.9)	24 (7.8)	2.22 (1.28–3.85)	0.004
Target vessel revascularization, n (%)	18 (11.3)	33 (10.7)	1.10 (0.49–1.66)	0.745
Definite stent thrombosis, n (%)	5 (3.1)	1 (0.3)	9.75 (1.10–86.38)	0.041
Ischemic events, n (%)	41 (25.3)	44 (14.2)	1.89 (1.21–2.90)	0.005
	LPR (n = 151)	No LPR (n = 320)	HR (95% CI)	p Value
Entry site hematoma, n (%)	15 (9.9)	9 (2.8)	3.22 (1.55–6.68)	0.002
TIMI major bleeding, n (%)	10 (6.6)	15 (4.7)	1.35 (0.61–3.18)	0.379
Bleeding events, n (%)	25 (16.6)	24 (7.5)	2.66 (1.49–4.73)	0.001

HPR high platelet reactivity, *LPR* low platelet reactivity, *HR* hazard ratio, *CI* confidence interval

Table 3 Clinical outcomes at 5 years in patients with LPR, NPR and HPR

	LPR (n = 151)	NPR (n = 158)	HPR (n = 162)	Log-rank p value
Death, n (%)	10 (6.6)	9 (5.7)	16 (9.9)	0.332
Myocardial infarction, n (%)	10 (6.6)	14 (8.9)	29 (17.9)	0.003
Target vessel revascularization, n (%)	19 (12.6)	14 (8.9)	16 (9.9)	0.520
Definite stent thrombosis, n (%)	1 (0.7)	0 (0)	5 (3.1)	1.000
Ischemic events, n (%)	20 (13.2)	24 (15.2)	41 (25.3)	0.011
Entry site hematoma, n (%)	15 (9.9)	6 (3.8)	3 (1.9)	0.001
TIMI major bleeding, n (%)	10 (6.6)	9 (5.7)	6 (3.7)	0.271
Bleeding events, n (%)	25 (16.6)	15 (9.5)	9 (5.6)	0.005

LPR low platelet reactivity, *NPR* normal platelet reactivity, *HPR* high platelet reactivity

a continuous divergence between the Kaplan–Meier curves of patients with and without HPR, the association of LPR with bleeding events seems to be confined to the periprocedural period.

Our results corroborate the concept that HPR is a marker of risk for post-PCI ischemic events, retaining a negative prognostic value even long after the revascularization and beyond the period of treatment with clopidogrel. In this perspective, the known association of HPR on clopidogrel with increased baseline platelet aggregation, enhanced inflammatory status, and other clinical conditions that are intrinsically related to worse outcomes (e.g. diabetes mellitus, endothelial dysfunction, coronary microvascular impairment) [8–12], could in part explain its negative prognostic value. Moreover, HPR is associated with an increased risk of periprocedural myocardial injury [10, 13–15], which in turn has a detrimental impact on long-term clinical outcomes after PCI [16, 17]. Although previous clinical trials have failed to demonstrate a clinically relevant benefit of adapting antiplatelet therapy based on the presence of HPR [18–20], recent studies have shown the potential of more intensive antiplatelet agents to improve coronary microvascular function [21] and peripheral endothelial function in patients treated with PCI [22]. In this perspective, the selective use of prasugrel or ticagrelor in stable patients with HPR and other high-risk features might prove effective in improving clinical outcomes, and should therefore be the objective of specific investigation.

The persistent association of HPR with ischemic events over time could also provides the rationale for prolonging dual antiplatelet therapy beyond standard duration. Although the optimal duration of dual antiplatelet therapy is still a matter of debate, it is commonly accepted that the decision to withdraw or continue clopidogrel in association with aspirin in stable CAD patients treated with PCI should be based on a thorough evaluation of their risk profile, considering both clinical and procedural variables. At least in patients without an increased risk of bleeding, prolonging dual antiplatelet therapy based on the presence of HPR might confer protection from recurrent ischemic events, as it has already been proven in patients with prior MI [23]. The attempt to find the optimal trade-off between ischemic and bleeding events following PCI, and therefore to guide the duration of dual antiplatelet therapy, has led to the development of several prognostic models and scores, which may help to individualize therapeutic strategies [24, 25]. The addition of platelet reactivity to clinical and procedural variables may confer additional predictive value to these models [26].

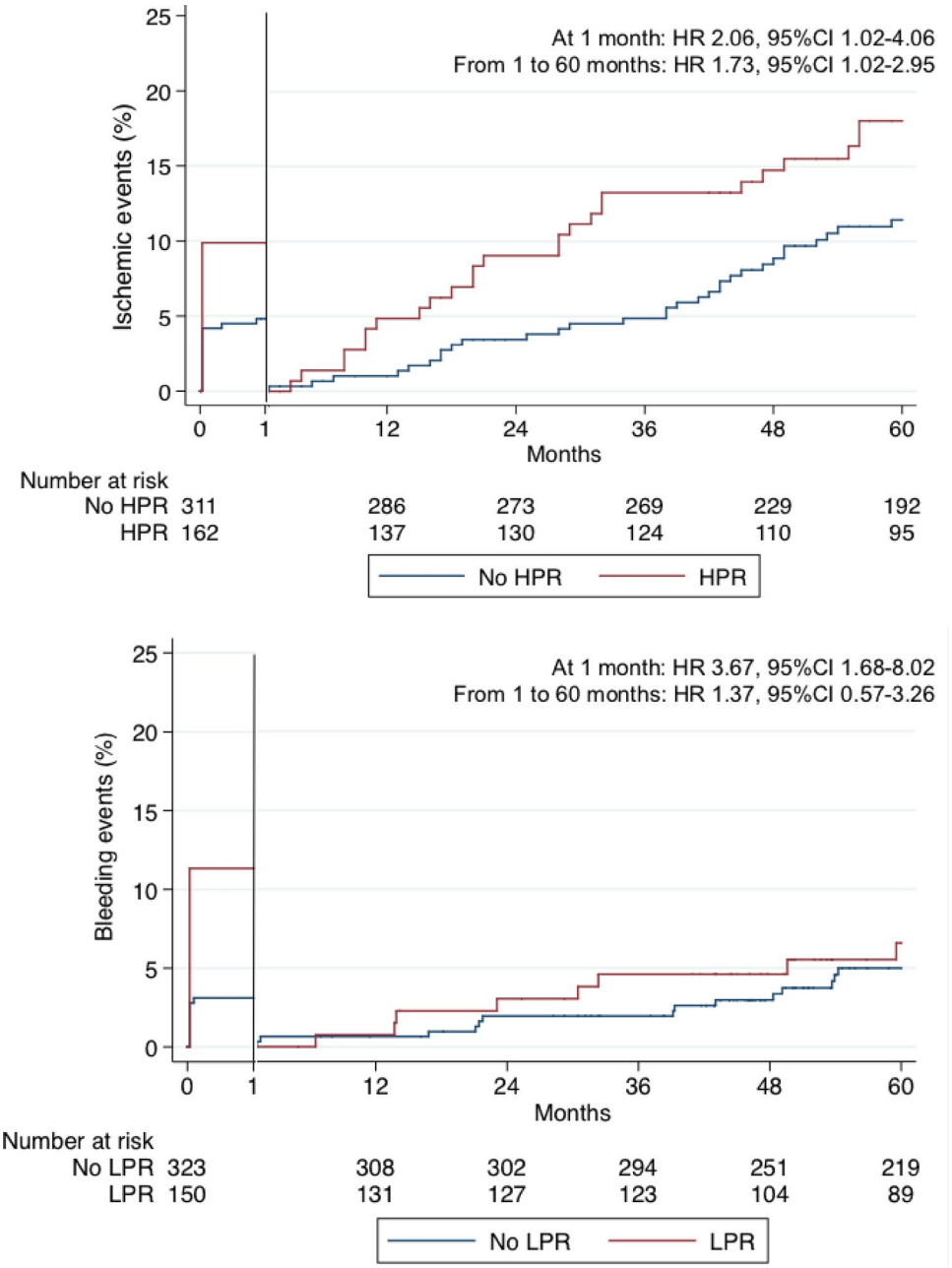

Fig. 2 Landmark analysis of the Kaplan–Meier estimates of clinical outcomes during the 1st month and from 1 month to 5 years. Upper panel: ischemic events in patients with and without high platelet reactivity (HPR). Lower panel: bleeding events in patients with and without low platelet reactivity (LPR)

Our results are reassuring with respect to the bleeding hazard in patients who over-respond to clopidogrel treatment, as LPR does not seem to imply an increased risk of major bleeding on the long run. Moreover, the excess of bleeding observed in our study within the 1st month after PCI was mainly driven by access site complications. It should be noted, however, that the vast majority of our patients underwent PCI via the femoral route; it is presumable that different results would be yielded with the adoption of radial approach as the standard access site strategy.

This study has a number of limitations that need consideration. First, platelet reactivity was only assessed prior to PCI; the prognostic impact of platelet reactivity at different timings remains therefore unknown. Second, nearly one-third of our patients received BMS, which is now an obsolete practice; it cannot be excluded that the use of new-generation DES might alternatively modulate the impact on platelet reactivity on clinical outcomes. Moreover, the presence of both patients treated with BMS and DES implies a different exposure length to dual antiplatelet therapy after PCI. Nevertheless, therapeutic adherence following stent type-based indications was > 80% for both patients receiving BMS and DES. Third, the use of the femoral route as the access site of choice might have led to higher bleeding

rates compared to what would be expected with a routine radial approach.

Overall, our study suggests that, unlike LPR, HPR carries prognostic significance long after coronary revascularization. Whether modulating the type and duration of antiplatelet treatment based on this information could improve patients' outcomes may become a matter of future investigation.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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