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FULL RESEARCH PAPER
Pharmacology & pharmacotherapy

Baseline anaemia and short dual antiplatelet therapy in high bleeding risk patients undergoing percutaneous coronary intervention

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Aims In patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI), abbreviated dual antiplatelet therapy (DAPT) has been shown to reduce bleeding without increasing ischaemic risk. However, the optimal duration in specific subgroups, particularly anaemic patients, remains unclear and was the focus of this analysis.

Methods and results This study included 3364 HBR patients from three prospective trials in the XIENCE Short DAPT programme who underwent PCI with cobalt-chromium everolimus-eluting stents. Anaemia was defined as Hb < 11 g/dL. The primary endpoint was all-cause death or myocardial infarction; secondary endpoints included BARC 2–5 and 3–5 bleeding. Outcomes by DAPT duration (1 vs. 3 months), defined according to study protocol, were assessed using propensity score stratification. Anaemia was present in 514 patients (15.3%). At 1 year, anaemic patients experienced higher rates of both ischaemic and bleeding events compared with non-anaemic patients. Among anaemic patients, ischaemic outcomes were similar with 1- and 3-month DAPT [15.7% vs. 16.3%; adjusted hazard ratio (adjHR) 0.94, 95% confidence interval (CI) 0.59–1.52; $P = 0.807$], whereas 1-month DAPT was associated with a lower incidence of major bleeding (6.1% vs. 11.1%; adjHR 0.49, 95% CI 0.24–1.00; $P = 0.050$). In non-anaemic patients, ischaemic and bleeding outcomes were similar irrespective of DAPT duration.

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Conclusion Among HBR patients undergoing PCI, abbreviated DAPT was associated with comparable ischaemic outcomes regardless of anaemia status. In patients with baseline anaemia, 1-month DAPT was associated with lower major bleeding without an apparent ischaemic trade-off.

Lay summary

This study evaluated whether shortening DAPT to 1 month, compared with 3 months, is safe and effective in HBR patients undergoing PCI, with a specific focus on those with baseline anaemia—a subgroup known to be particularly vulnerable to both ischaemic and bleeding complications.

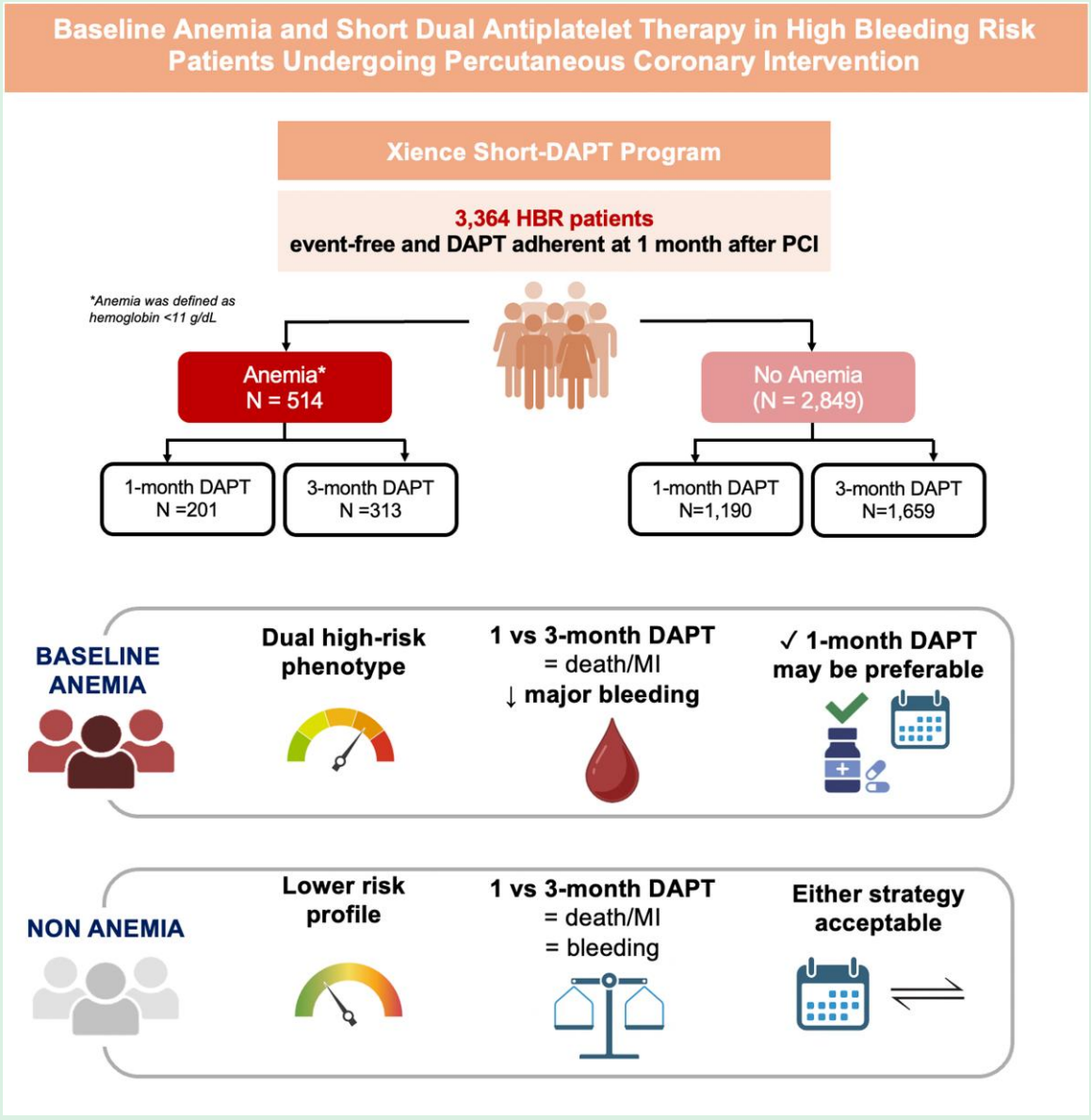
Key findings

- Baseline anaemia identified a high-risk phenotype associated with increased rates of both ischaemic and bleeding events at 1 year.
- Shortening DAPT to 1 month did not increase the risk of ischaemic events compared with 3-month DAPT, regardless of anaemia status.
- In patients with baseline anaemia, 1-month DAPT reduced major bleeding compared with 3-month DAPT, without an apparent ischaemic trade-off.

Clinical implications

These findings support a more individualized approach to antiplatelet therapy after PCI. In patients with baseline anaemia, abbreviated DAPT may represent a reasonable strategy to mitigate bleeding risk without compromising ischaemic protection, although results should be interpreted with caution and confirmed in randomized studies.

Graphical Abstract



Keywords Anaemia • High bleeding risk • Percutaneous coronary intervention • Antithrombotic treatment • Outcomes

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor represents the cornerstone of antithrombotic management following percutaneous coronary intervention (PCI), significantly reducing thrombotic complications, including stent thrombosis and myocardial infarction (MI).[1,2] However, DAPT is associated with an increased risk of bleeding, which adversely affects morbidity and mortality and is strongly influenced by treatment duration and intensity. Optimizing the balance between ischaemic protection and bleeding risk, therefore, remains a major clinical challenge, particularly in patients at high bleeding risk (HBR).[3,4]

Anaemia is a common comorbidity among patients with cardiovascular disease, with a reported prevalence ranging from 10 to 20%.[5,6] It has consistently been associated with frailty, a higher burden of comorbidities, and increased mortality, reflecting worse short- and long-term clinical outcomes.[7–9] Accordingly, several risk stratification tools have been developed to guide DAPT duration, including the PRECISE-DAPT and PARIS scores, which incorporate anaemia as a major determinant of bleeding risk.[10–12] However, despite its well-established prognostic relevance, the optimal antiplatelet strategy in these HBR patients remains insufficiently studied in randomized clinical trials, and current clinical practice guidelines do not provide

specific recommendations regarding DAPT duration in this population.[4,13,14]

The XIENCE Short DAPT clinical programme evaluated abbreviated DAPT strategies in patients at HBR undergoing PCI with contemporary cobalt-chromium everolimus-eluting stents.[13] In this programme, 1- or 3-month DAPT followed by aspirin monotherapy was non-inferior to historical 6- or 12-month DAPT regimens for ischaemic outcomes and was associated with lower bleeding rates, with the 1-month strategy providing further bleeding reduction without increasing ischaemic risk at 1 year. With the present study, we aimed to assess the impact of 1- vs. 3-month DAPT on clinical outcomes in HBR patients undergoing PCI stratified by baseline anaemia status.

Methods

Study design and data source

This analysis used pooled patient-level data from the XIENCE Short DAPT programme, which included three prospective, multicentre studies evaluating abbreviated DAPT strategies in patients at HBR undergoing PCI with implantation of a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE, Abbott). Briefly, it consisted of XIENCE 90 (NCT03218787), conducted at 101 sites in the USA; XIENCE 28 USA (NCT03815175), conducted at 58 sites in the USA and Canada; and XIENCE 28 Global (NCT03355742), conducted at 52 sites in Europe and Asia between July 2017 and February 2020 (all participating sites are listed in Supplementary material online, *Tables S1–S3*). Detailed inclusion and exclusion criteria are provided in Supplementary material online, *Table S4*. The XIENCE 28 and XIENCE 90 studies followed largely similar protocols, with DAPT duration (1 vs. 3 months) defined by study design rather than patient-level randomization. Further details regarding the study design and primary results have been reported elsewhere.[13,15] All participating sites obtained approval from local institutional review boards or ethics committees, and all patients provided written informed consent. Clinical outcomes were independently adjudicated by an external clinical events committee, and safety oversight was provided by an independent data monitoring committee.

Patient population and treatment strategy

Patients undergoing successful PCI with implantation of a cobalt-chromium everolimus-eluting stent were included if they were deemed at HBR according to the original XIENCE Short DAPT trial criteria. Specifically, patients were eligible if, in the opinion of the treating physician, the risk for major bleeding associated with prolonged DAPT outweighed its anticipated ischaemic benefit and at least one HBR criterion was present, including age ≥ 75 years, indication for long-term oral anticoagulation therapy, history of major bleeding requiring medical attention within the previous 12 months, prior ischaemic or haemorrhagic stroke, renal insufficiency (creatinine $\geq$2.0 mg/dL) or dialysis dependence, systemic conditions associated with increased bleeding risk (including thrombocytopaenia or coagulation disorders), and baseline anaemia. For the present analysis, patients were categorized according to baseline anaemia status, defined as haemoglobin < 11 g/dL, and according to DAPT duration (1-month vs. 3-month therapy). Following the index PCI, all patients received DAPT consisting of aspirin in combination with a P2Y12 inhibitor, with selection of the P2Y12 inhibitor left to the treating physician's preference. Both vitamin K antagonists and direct oral anticoagulants were permitted in patients requiring long-term oral anticoagulation therapy according to the original study protocols. Eligibility for discontinuation of the P2Y12 inhibitor was assessed at 1 month in XIENCE 28 studies and at 3 months in XIENCE 90, provided patients remained adherent to therapy and free from ischaemic events. Clinical follow-up was performed at prespecified intervals up to 12 months after the index procedure through in-person visits or structured telephone interviews conducted by trained study personnel.

Clinical endpoints

The primary endpoint was a composite of all-cause death or MI occurring between 1 and 12 months after index PCI. Myocardial infarction was defined according to the modified Academic Research Consortium criteria.[16] Secondary bleeding endpoints included Bleeding Academic Research Consortium (BARC) type 2–5 bleeding and BARC type 3–5 bleeding. Additional clinical outcomes included cardiovascular death, definite or probable stent thrombosis, stroke, ischaemic stroke, target lesion failure, and target vessel revascularization. All endpoint definitions followed standardized Academic Research Consortium criteria, as reported in Supplementary material online, *Tables S5* and *S6*, and were adjudicated by an independent external committee.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate, and were compared using Student's *t*-test or the Mann–Whitney *U* test. Categorical variables are reported as counts and percentages and were compared using the χ^2 test or Fisher's exact test, as appropriate. Time-to-event outcomes were analysed using Kaplan–Meier methods, with between-group comparisons performed using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The association between baseline anaemia and clinical outcomes was assessed using unadjusted and multivariable-adjusted Cox regression models. To account for potential confounding, adjusted estimates were derived using propensity score stratification based on a logistic regression model including baseline demographic, clinical, and procedural characteristics. These included sex, baseline serum creatinine, oral anticoagulation therapy, prior stroke, history of major bleeding, baseline platelet count, baseline haemoglobin, body mass index, hypertension, hypercholesterolaemia, prior PCI, prior coronary artery bypass grafting, prior MI, multivessel disease, acute coronary syndrome presentation, lesion complexity (B2/C), total lesion length, pre-procedural reference vessel diameter and diameter stenosis, bifurcation lesions, number of lesions and vessels treated, number of stents, total stent length, P2Y12 inhibitor at discharge, and PARIS and PRECISE-DAPT bleeding risk scores. Analyses were performed separately in patients with and without baseline anaemia. Because treatment allocation was not randomized, comparisons between 1-month and 3-month DAPT were adjusted using propensity score stratification into quintiles based on the estimated probability of treatment assignment. Interaction testing was performed by including an interaction term between anaemia status and DAPT duration in the Cox models. Missing covariate data used for propensity score estimation were handled using multiple imputation with a Markov chain Monte Carlo method, with parameter estimates combined using Rubin's rules. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6.2 (R Foundation for Statistical Computing). All tests were two-sided, and a $P < 0.05$ was considered statistically significant.

Results

Study population and baseline characteristics

A total of 3652 patients were enrolled in the XIENCE Short DAPT programme between 19 July 2017 and 7 February

2020. Of these, 3364 patients were free from ischaemic events and adherent to treatment at 1 month and were included in the present analysis.

Baseline anaemia was present in 514 patients (15.3%), whereas 2849 patients (84.7%) had no anaemia. Baseline clinical and procedural characteristics according to anaemia status are shown in Supplementary material online, *Table S7*. Compared with patients without anaemia, those with baseline anaemia had a higher prevalence of comorbidities, including chronic kidney disease, diabetes, and prior major bleeding, as well as higher PARIS and PRECISE-DAPT bleeding risk scores. Anaemic patients also had lower body mass index and higher baseline serum creatinine levels.

Baseline characteristics according to anaemia status and DAPT duration are summarized in *Table 1*. Within the anaemia subgroup, clinical and procedural characteristics were generally balanced between patients receiving 1-month and 3-month DAPT, including a similar number of HBR criteria and comparable baseline bleeding risk. Among non-anaemic patients, those treated with 1-month DAPT had a higher prevalence of chronic kidney disease and lower rates of hypertension, dyslipidaemia, and multivessel disease. Procedural characteristics were otherwise comparable across groups.

Clinical outcomes according to anaemia status

One-year clinical outcomes according to baseline anaemia status are reported in Supplementary material online, *Table S8*. Overall, patients with baseline anaemia experienced higher rates of both ischaemic and bleeding events compared with non-anaemic patients, including a higher incidence of the composite endpoint of all-cause death or MI and BARC-defined bleeding.

Clinical outcomes by DAPT duration according to anaemia status

One-year event rates and Kaplan–Meier curves for all-cause death or MI and BARC 3–5 bleeding according to anaemia status and DAPT duration are shown in *Figures 1* and *2*, respectively.

Among patients without baseline anaemia, the 1-year incidence of all-cause death or MI was similar between the 1-month and 3-month DAPT groups (see Supplementary material online, *Table S9*). This finding remained consistent after multivariable adjustment (adjusted HR 1.00, 95% CI 0.73–1.38; $P = 0.988$), with no significant differences in the individual components of the endpoint, as shown in *Table 2* and Supplementary material online, *Figure S1*. Bleeding outcomes were also comparable, with no significant differences in BARC 2–5 or BARC 3–5 bleeding in either the unadjusted or adjusted analyses (see Supplementary material online, *Table S9*, *Table 2*, and Supplementary material online, *Figure S1*).

Among patients with baseline anaemia, the 1-year incidence of all-cause death or MI was likewise similar between the 1-month and 3-month DAPT groups (see Supplementary material online, *Table S9*) and remained so after multivariable adjustment (adjusted HR 0.94, 95% CI 0.59–1.52; $P = 0.807$), with no significant differences in the individual components of the endpoint (*Table 2*; Supplementary material online, *Figure S1*). In this subgroup, 1-month DAPT was associated with a lower incidence of BARC 3–5 bleeding than 3-month DAPT (see Supplementary material online, *Table S9*), a finding that persisted after multivariable adjustment (adjusted HR 0.49, 95% CI 0.24–1.00; $P = 0.050$), with a similar numerical reduction in BARC 2–5 bleeding (*Table 2*; Supplementary material online, *Figure S1*).

Rates of definite or probable stent thrombosis, stroke, ischaemic stroke, target lesion revascularization, and target vessel revascularization were low and did not differ significantly between DAPT strategies in either anaemic or non-anaemic patients.

No significant treatment-by-anaemia interactions were observed for any endpoints.

Discussion

In this pooled analysis of HBR patients undergoing PCI with contemporary DES in the XIENCE Short DAPT programme, the following key findings emerged (*Graphical Abstract*):

(1) Baseline anaemia identified a subgroup at higher risk of both ischaemic and bleeding events at 1 year, supporting its role as a marker of overall cardiovascular vulnerability.
(2) Despite this higher baseline risk, the rates of all-cause death or MI with 1-month vs. 3-month DAPT were similar in both anaemic and non-anaemic patients.
(3) Among patients with baseline anaemia, a 1-month DAPT strategy was associated with a lower incidence of major bleeding (BARC 3–5).
(4) No significant interaction was observed between anaemia status and DAPT duration for either ischaemic or bleeding outcomes.

In the present study, baseline anaemia was observed in approximately 15% of patients undergoing PCI within the XIENCE Short DAPT programme, a prevalence broadly consistent with contemporary PCI registries.[5,6,17] Anaemia was associated with a higher burden of comorbidities, including chronic kidney disease, diabetes, and prior bleeding, as well as higher baseline bleeding risk scores. Importantly, anaemic patients experienced substantially higher rates of both ischaemic and bleeding events at 1 year compared with non-anaemic individuals, identifying a particularly high-risk and clinically frail subgroup. These observations are likely multifactorial. Reduced haemoglobin levels can impair myocardial oxygen delivery and worsen ischaemic vulnerability, while also frequently clustering with inflammation, endothelial dysfunction, and renal impairment, all of which contribute to a more adverse cardiovascular profile.[18] Anaemic patients may also exhibit increased platelet reactivity despite antiplatelet therapy, potentially predisposing to thrombotic complications.[19] At the same time, reduced haematologic reserve and coexisting bleeding diatheses may heighten susceptibility to haemorrhagic events during antithrombotic treatment, making anaemia a marker of both ischaemic and bleeding risk.[20]

Notably, in our analysis, a 1-month DAPT strategy was associated with lower major bleeding rates among patients with baseline anaemia without an apparent increase in ischaemic events. These results align with prior studies supporting abbreviated antiplatelet strategies in HBR populations treated with contemporary DES and further support the feasibility of this

Table 1 Baseline clinical and procedural characteristics by anaemia status and dual antiplatelet therapy regimen

	Anaemia (*n* = 514)			No anaemia (*n* = 2849)		
	1-month DAPT *n* = 201	3-month DAPT *n* = 313	*P*-value	1-month DAPT *n* = 1190	3-month DAPT *n* = 1659	*P*-value
High bleeding risk criteria						
Age ≥ 75 years	109 (54.2%)	163 (52.1%)	0.633	840 (70.6%)	1129 (68.1%)	0.149
Chronic anticoagulant therapy	62 (30.8%)	87 (27.8%)	0.457	555 (46.6%)	718 (43.3%)	0.075
History of stroke	21 (10.4%)	27 (8.6%)	0.489	124 (10.4%)	196 (11.8%)	0.245
Renal insufficiency[a]	51 (25.4%)	79 (25.2%)	0.973	65 (5.5%)	78 (4.7%)	0.359
Thrombocytopaenia[a,b]	8 (4.0%)	9 (2.9%)	0.492	23 (2.0%)	29 (1.8%)	0.667
History of major bleeding	16 (8.0%)	24 (7.7%)	0.904	30 (2.5%)	33 (2.0%)	0.341
Number of HBR criteria	2.3 ± 0.9	2.2 ± 0.8	0.261	1.4 ± 0.6	1.3 ± 0.5	0.007
Clinical characteristics						
Age, years	73.8 ± 10.0	72.9 ± 10.8	0.312	76.3 ± 8.0	75.5 ± 9.0	0.011
BMI	28.1 ± 6.3	30.0 ± 6.7	0.002	28.4 ± 5.9	30.1 ± 6.5	<0.001
Female sex	96 (47.8%)	158 (50.5%)	0.548	357 (30.0%)	543 (32.7%)	0.122
Race						
American Indian or Alaskan Native	1 (0.7%)	3 (1.0%)	0.755	1 (0.1%)	8 (0.5%)	0.160
Asian	35 (23.5%)	10 (3.2%)	<0.001	91 (11.1%)	35 (2.1%)	<0.001
Black or African American	13 (8.7%)	38 (12.1%)	0.273	23 (2.8%)	79 (4.8%)	0.021
Native Hawaiian or Pacific Islander	0 (0.0%)	2 (0.6%)	0.328	0 (0.0%)	3 (0.2%)	0.223
White	100 (67.1%)	249 (79.6%)	0.004	706 (86.0%)	1490 (89.8%)	0.005
Hispanic or Latino ethnicity	24 (12.3%)	12 (3.8%)	<0.001	114 (10.2%)	44 (2.7%)	<0.001
Hypertension	176 (87.6%)	283 (90.4%)	0.307	1003 (84.3%)	1488 (89.7%)	<0.001
Dyslipidaemia	135 (67.2%)	254 (81.2%)	<0.001	804 (67.6%)	1368 (82.5%)	<0.001
Diabetes mellitus	99 (50.0%)	172 (55.0%)	0.275	413 (34.9%)	615 (37.1%)	0.228
Chronic kidney disease[c]	124 (63.3%)	192 (61.5%)	0.696	507 (44.7%)	609 (37.0%)	<0.001
Prior PCI	52 (25.9%)	100 (31.9%)	0.141	338 (28.4%)	507 (30.6%)	0.214
Prior CABG	19 (9.5%)	39 (12.5%)	0.293	93 (7.8%)	207 (12.5%)	<0.001
Prior MI	29 (14.6%)	54 (17.8%)	0.346	198 (16.8%)	263 (16.1%)	0.622
Multivessel disease	89 (44.3%)	159 (50.8%)	0.149	483 (40.6%)	759 (45.8%)	0.006
Chronic coronary syndrome	111 (55.2%)	194 (62.0%)	0.128	805 (67.6%)	1089 (65.6%)	0.264
Acute coronary syndrome	90 (44.8%)	119 (38.0%)	0.128	385 (32.4%)	570 (34.4%)	0.264
NSTEMI	45 (22.4%)	39 (12.5%)	0.003	200 (16.8%)	102 (6.1%)	<0.001
Unstable angina	45 (22.4%)	80 (25.6%)	0.413	185 (15.5%)	468 (28.2%)	<0.001
PARIS bleeding risk score	8.9 ± 2.0	8.8 ± 2.1	0.459	5.6 ± 2.0	5.5 ± 1.9	0.054
PARIS bleeding risk score [IQR]	9.0 (7.0–10.0)	9.0 (7.0–10.0)	0.548	6.0 (4.0–7.0)	5.0 (4.0–7.0)	0.064
PRECISE-DAPT bleeding risk score	41.1 ± 11.5	40.0 ± 11.8	0.335	25.3 ± 9.4	23.6 ± 9.6	<0.001
PRECISE-DAPT bleeding risk score [IQR]	42.0 (34.0–49.0)	40.0 (32.0–46.0)	0.191	25.0 (19.0–31.0)	24.0 (17.0–30.0)	<0.001

Continued

Table 1 *Continued*

	Anaemia (*n* = 514)			No anaemia (*n* = 2849)		
	1-month DAPT *n* = 201	3-month DAPT *n* = 313	*P*-value	1-month DAPT *n* = 1190	3-month DAPT *n* = 1659	*P*-value
Procedural characteristics						
Number of lesions treated [IQR]	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.401	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.752
Number of vessels treated [IQR]	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.672	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.128
B2/C lesion	84 (41.8%)	129 (41.2%)	0.897	413 (34.7%)	558 (33.6%)	0.552
Bifurcation	21 (10.4%)	27 (8.6%)	0.489	139 (11.7%)	126 (7.6%)	<0.001
Radial access	132 (65.7%)	134 (42.8%)	<0.001	854 (71.8%)	894 (53.9%)	<0.001
Number of stents per subject [IQR]	1.0 (1.0–1.0)	1.0 (1.0–2.0)	0.303	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.465
Total stent length, mm	28.8 ± 15.0	27.1 ± 15.5	0.236	26.9 ± 14.3	25.3 ± 13.5	0.002
Pre-procedure RVD, mm	3.1 ± 0.5	3.0 ± 0.5	0.157	3.0 ± 0.5	3.0 ± 0.5	0.654
Pre-procedure % DS	83.2 ± 9.0	83.8 ± 10.0	0.510	82.4 ± 10.5	84.0 ± 9.5	<0.001
Antiplatelet therapy at discharge						
Aspirin	181 (90.0%)	299 (95.5%)	0.015	950 (79.8%)	1502 (90.5%)	<0.001
Clopidogrel	174 (86.6%)	253 (80.8%)	0.091	1029 (86.5%)	1359 (81.9%)	0.001
Prasugrel	2 (1.0%)	7 (2.2%)	0.295	12 (1.0%)	39 (2.4%)	0.008
Ticagrelor	25 (12.4%)	54 (17.3%)	0.140	149 (12.5%)	263 (15.9%)	0.013

Values are *n*/*N* (%) or mean ± SD, unless otherwise specified.
CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; IQR, interquartile range; MI, myocardial infarction; NA, not available; NSTEMI, non–ST-segment elevation myocardial infarction; PARIS, Patterns of Non-adherence to Dual Anti-Platelet Regimen in Stented Patients; PCI, percutaneous coronary intervention; %DS, percentage diameter stenosis; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; RVD, reference vessel diameter.
[a]Renal insufficiency was defined as creatinine ≥ 2.0 mg/dL or dialysis dependence.
[b]Thrombocytopaenia was defined as platelet count < 100 000/mm^3.
[c]Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.
Definitions of high bleeding risk criteria are provided in Supplementary material online, *Table S4*.

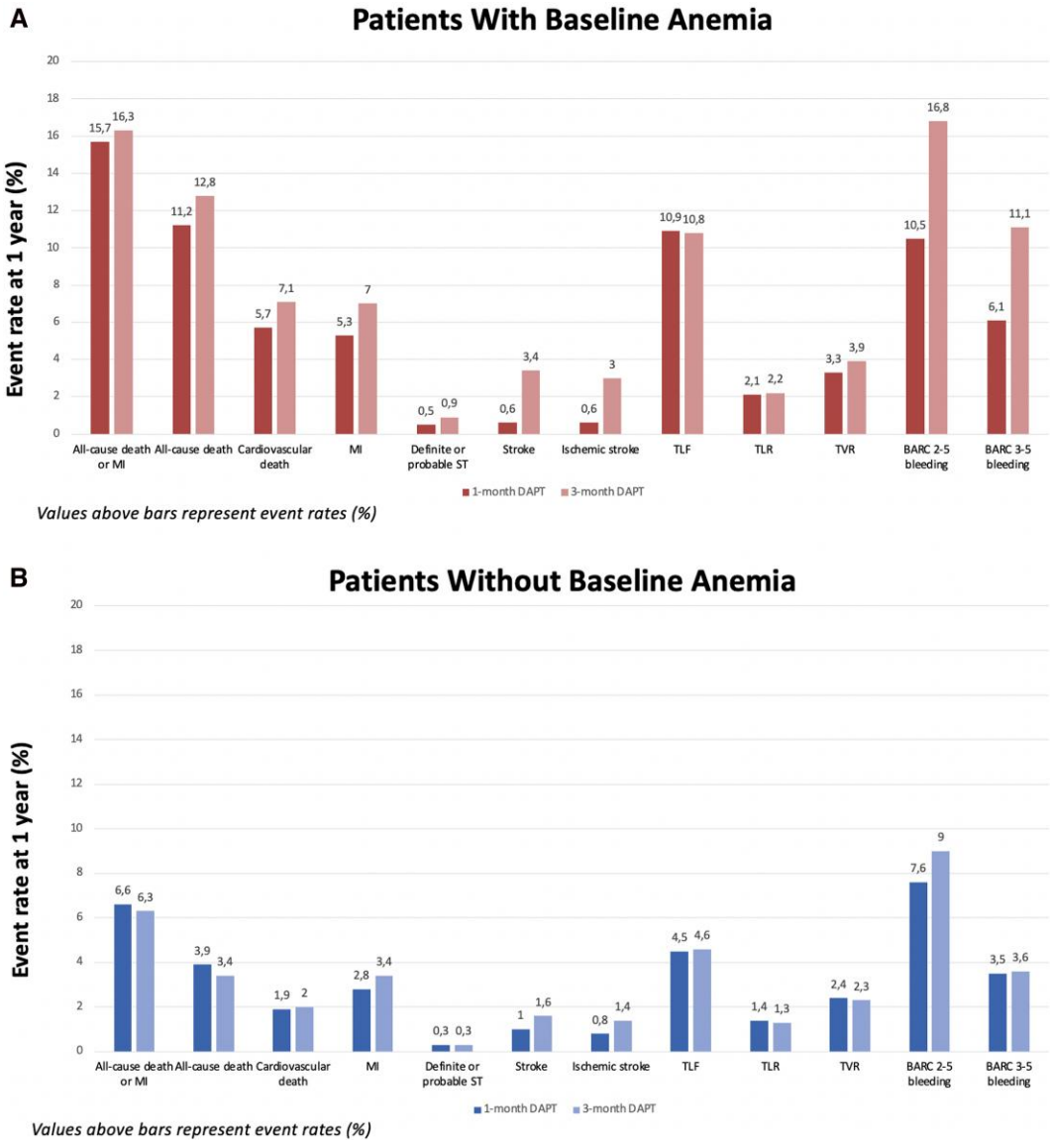


Figure 1 One-year event rates according to dual antiplatelet therapy duration in patients with and without baseline anaemia. Bar graphs display the cumulative incidence of clinical endpoints at 1 year according to dual antiplatelet therapy duration (1-month vs. 3-month) stratified by baseline anaemia status. Panel (*A*) shows patients with baseline anaemia (red bars), while panel (*B*) shows patients without baseline anaemia (blue bars). Values above bars represent event rates (%). BARC, Bleeding Academic Research Consortium; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLF, target lesion failure; TLR, target lesion revascularization.

approach among patients with baseline anaemia.[4,21–23] Similar results were observed in the TWILIGHT anaemia sub-analysis, despite important differences in study design and antiplatelet regimen, including ticagrelor monotherapy after aspirin discontinuation following an initial 3-month course of ticagrelor-based DAPT in TWILIGHT.[17,24] This may reflect the fact that thrombotic risk after PCI is highest during the early post-procedural phase and progressively decreases thereafter, whereas bleeding risk continues to accumulate over time. Accordingly, reducing antithrombotic intensity beyond the early post-PCI phase may mitigate bleeding complications without a clear ischaemic trade-off in carefully selected anaemic patients, with our results further supporting the feasibility of an even shorter DAPT duration, such as 1-month DAPT.

From a clinical standpoint, these observations highlight the importance of a more individualized approach to antiplatelet therapy after PCI in patients with baseline anaemia. Rather than representing only a bleeding risk marker, anaemia likely identifies a broader phenotype of cardiovascular frailty. Accordingly, treatment decisions should balance competing ischaemic and haemorrhagic risks while also taking into account patient comorbidities, procedural complexity, and overall clinical

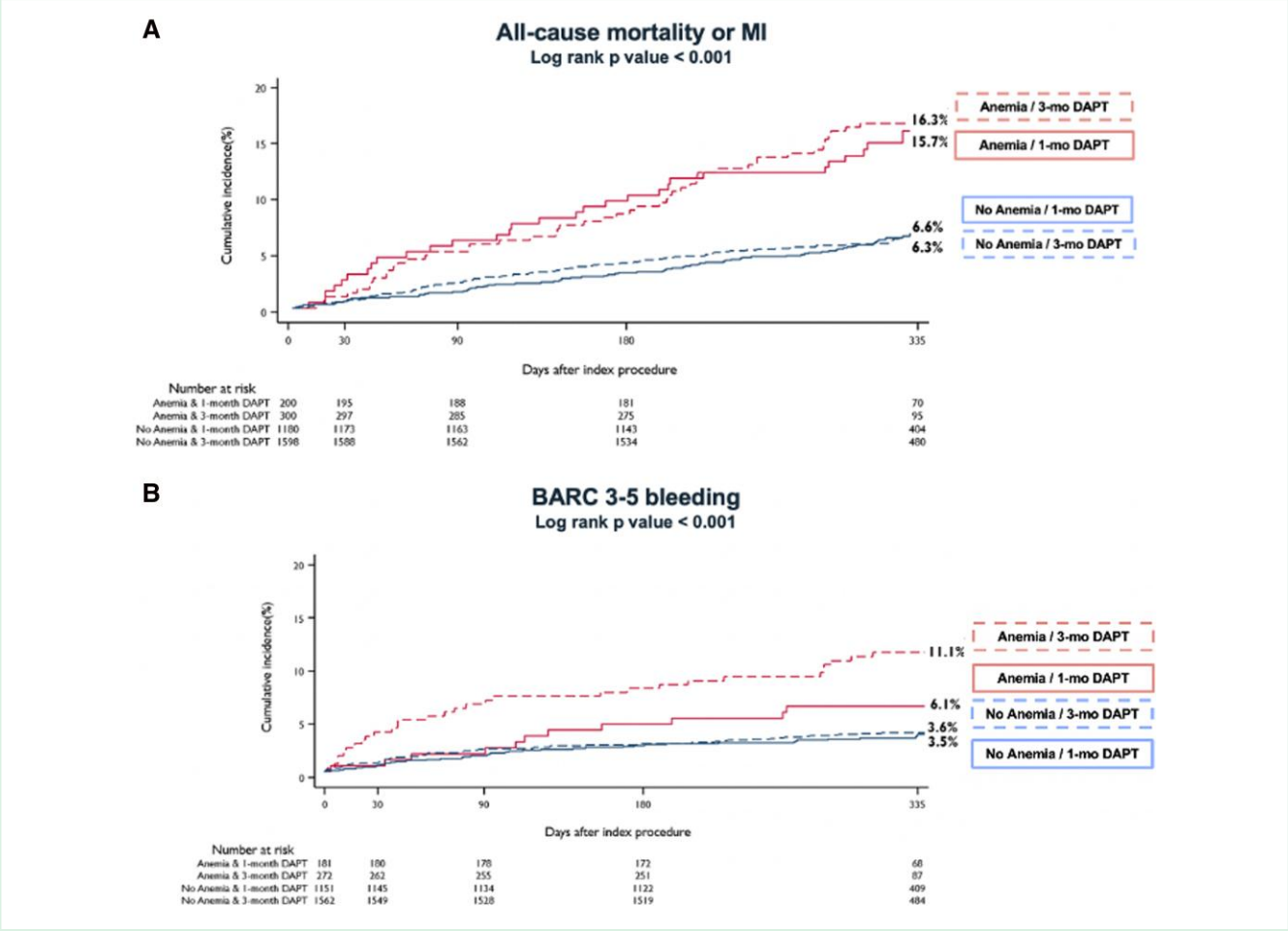


Figure 2 Cumulative incidence curves of all-cause mortality or myocardial infarction (*A*) and BARC 3–5 bleeding (*B*) at 1 year after the index percutaneous coronary intervention, stratified by anaemia status and dual antiplatelet therapy regimen (1-month vs. 3-month dual antiplatelet therapy).

context. Careful clinical assessment and individualized risk stratification, therefore, remain essential when tailoring antiplatelet therapy in this population. Importantly, the identification of anaemia at baseline should also prompt a systematic evaluation of its underlying causes. Potentially reversible conditions—including iron deficiency, chronic inflammatory states, renal dysfunction, or gastrointestinal disorders associated with impaired absorption or occult bleeding—should be actively investigated. In selected patients, targeted interventions such as iron replacement in iron deficiency anaemia or treatment of underlying gastrointestinal pathology may improve haematologic status and potentially overall clinical outcomes.[25,26] Although our study was not designed to assess whether correction of anaemia modifies prognosis, this remains an important area for future investigation. Prospective studies are also needed to define clinically relevant haemoglobin thresholds for intervention and to identify patient subgroups most likely to derive benefit from abbreviated antiplatelet strategies. Finally, future research should also clarify the most appropriate antiplatelet strategy after abbreviated DAPT, including whether aspirin or P2Y12 inhibitor monotherapy should be preferred in vulnerable populations such as patients with anaemia.

Study limitations

When interpreting the results of the present analysis, several limitations should be acknowledged. First, this was a secondary, non-randomized analysis, and the comparison between 1- and 3-month DAPT reflects differences in study protocols rather than patient-level randomization. Accordingly, despite rigorous propensity score adjustment, residual confounding from unmeasured variables cannot be excluded. Second, patients were classified as HBR according to the original XIENCE Short DAPT trial eligibility criteria rather than the subsequently standardized ARC-HBR consensus definition.[27] Although several eligibility criteria overlap with the later ARC-HBR framework, differences in HBR definitions should be considered when comparing the present findings with more contemporary HBR studies. Third, pooling data from three XIENCE Short DAPT studies may have introduced heterogeneity in patient selection, treatment allocation, and follow-up timing. Fourth, this analysis used a 1-month landmark approach, including only patients who were event-free and adherent to DAPT at 1 month, thereby selecting a clinically stabilized population and potentially limiting generalizability to the early post-PCI phase. Fifth, anaemia was

Table 2 Primary and secondary endpoints by anaemia status and dual antiplatelet therapy regimen after propensity score adjustment

Outcomes	Anaemia (*n* = 514)				No anaemia (*n* = 2849)				Interaction *P*-value[b]
	XIENCE 28 1-month DAPT (*n* = 201)	XIENCE 90 3-month DAPT (*n* = 313)	Adjusted hazard ratio[a] (95% CI)	*P*-value	XIENCE 28 1-month DAPT (*n* = 1190)	XIENCE 90 3-month DAPT (*n* = 1659)	Adjusted hazard ratio[a] (95% CI)	*P*-value	
	No. of events (%)				No. of events (%)				
All-cause death, or MI	30 (15.7%)	49 (16.3%)	0.94 (0.59–1.52)	0.807	73 (6.6%)	96 (6.3%)	1.00 (0.73–1.38)	0.988	0.707
All-cause death	22 (11.2%)	38 (12.8%)	0.86 (0.50–1.50)	0.599	42 (3.9%)	50 (3.4%)	1.02 (0.66–1.57)	0.941	0.435
Cardiovascular death	11 (5.7%)	20 (7.1%)	0.88 (0.41–1.90)	0.753	21 (1.9%)	29 (2.0%)	0.88 (0.49–1.59)	0.676	0.718
MI	9 (5.3%)	20 (7.0%)	0.77 (0.34–1.73)	0.523	31 (2.8%)	53 (3.4%)	0.85 (0.53–1.34)	0.482	0.743
Definite or probable ST	1 (0.5%)	2 (0.9%)	1.30 (0.12–14.7)	0.830	3 (0.3%)	4 (0.3%)	0.99 (0.21–4.76)	0.990	0.830
Stroke	1 (0.6%)	9 (3.4%)	0.17 (0.02–1.37)	0.096	10 (1.0%)	24 (1.6%)	0.51 (0.23–1.10)	0.086	0.270
Ischaemic stroke	1 (0.6%)	8 (3.0%)	0.17 (0.02–1.46)	0.107	8 (0.8%)	22 (1.4%)	0.42 (0.18–0.98)	0.044	0.390
Target lesion failure	20 (10.9%)	31 (10.8%)	1.08 (0.60–1.93)	0.808	49 (4.5%)	70 (4.6%)	0.95 (0.65–1.39)	0.782	0.916
Target lesion revascularization	4 (2.1%)	6 (2.2%)	1.47 (0.41–5.34)	0.554	14 (1.4%)	20 (1.3%)	0.94 (0.46–1.91)	0.854	0.930
Target vessel revascularization	5 (3.3%)	11 (3.9%)	0.82 (0.28–2.45)	0.727	24 (2.4%)	35 (2.3%)	1.01 (0.59–1.74)	0.965	0.612
BARC 2–5 bleeding	19 (10.5%)	44 (16.8%)	0.62 (0.36–1.09)	0.099	84 (7.6%)	140 (9.0%)	0.77 (0.58–1.02)	0.068	0.418
BARC 3–5 bleeding	11 (6.1%)	30 (11.1%)	0.49 (0.24–1.00)	0.050	38 (3.5%)	56 (3.6%)	0.89 (0.58–1.36)	0.581	0.188

The percentages mentioned above represent K-M rates at 12 months after index procedure.
DAPT, dual antiplatelet therapy; MI, myocardial infarction; ST, stent thrombosis.
[a]Propensity stratified outcomes according to gender, diabetes, baseline serum creatinine, anticoagulation therapy, stroke, history of major bleeding, baseline platelet, baseline haemoglobin, BMI, hypertension, hypercholesterolaemia, prior PCI, prior CABG, prior MI, multivessel disease, acute coronary syndrome, B2/C lesion, total lesion length, mean pre-RVD, mean pre-DS, bifurcation lesion, number of lesion treated, number of vessel treated, number of stents, total stent length, P2Y12 on discharged, PARIS risk score for major bleeding, and PRECISE DAPT risk score for bleeding.
[b]*P*-value is obtained from the interaction test between anemia status and DAPT duration after applying multiple imputation and propensity score stratification.

defined using a uniform haemoglobin threshold (<11 g/dL) irrespective of sex, in accordance with the original study protocol. Although sex was included as a covariate in the adjusted analyses, some degree of misclassification related to the use of a non–sex-specific definition cannot be excluded. Sixth, adherence to the assigned DAPT duration could not be systematically verified, which may have influenced treatment exposure and clinical outcomes. In addition, the aetiology and temporal evolution of anaemia were not captured, precluding mechanistic insights into the observed associations. Finally, the present findings are restricted to HBR patients undergoing PCI with cobalt-chromium everolimus-eluting stents and may not be generalizable to other stent platforms, PCI populations, or clinical settings.

Conclusion

Among HBR patients undergoing PCI, baseline anaemia identified individuals at higher risk of both ischaemic and bleeding events. A 1-month DAPT strategy provided ischaemic protection comparable to 3-month DAPT irrespective of anaemia status and reduced major bleeding (BARC 3–5) among patients with baseline anaemia. These findings support abbreviated DAPT as a reasonable individualized strategy for anaemic HBR patients treated with contemporary drug-eluting stents. Prospective randomized studies are warranted to confirm these observations and to further define optimal antiplatelet strategy in this high-risk subgroup, including both DAPT duration and the choice of single antiplatelet therapy following DAPT discontinuation.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

Francesca Maria Di Muro (Conceptualization, Methodology, Writing—original draft [lead]), Samantha Sartori (Data curation, Formal analysis [lead]), Dominick J. Angiolillo (Data curation, Visualization [equal]), Deepak L. Bhatt (Supervision, Visualization [equal]), Davide Cao (Visualization [equal]), Bassem M. Chehab (Supervision, Visualization [equal]), George Dangas (Conceptualization, Visualization [equal], Supervision, Writing—review & editing [lead]), Yihan Feng (Data curation [equal], Formal analysis [lead]), Jose M. De La Torre Hernandez (Visualization [equal]), Mitchell W. Krucoff (Conceptualization, Visualization [equal]), Vijay Kunadian (Conceptualization, Visualization, Writing—review & editing [equal]), Aziz Maksoud (Supervision [equal]), Nader Mankerious (Conceptualization, Visualization [equal]), Angelo Oliva (Conceptualization, Visualization [equal]), Hector Picon (Conceptualization, Supervision [equal]), Gert Richardt (Conceptualization, Visualization [equal]), Gennaro Sardella (Conceptualization, Supervision [equal]), Holger Thiele (Conceptualization, Visualization, Writing—review & editing [equal]), Ralph Toelg (Supervision, Visualization [equal]), Olivier Varenne (Supervision, Visualization [equal]), Pascal Vranckx (Visualization, Writing—review & editing [equal]), Stephan Windecker (Conceptualization, Supervision, Visualization [equal]), Marco Valgimigli (Conceptualization, Visualization [equal], Supervision [lead]), and Roxana Mehran (Conceptualization, Supervision, Visualization, Writing—review & editing [lead])

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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