



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

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Summary

Background Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y₁₂ inhibitor prevents ischaemic events after coronary stenting, but increases bleeding. Guidelines support weighting bleeding risk before the selection of treatment duration, but no standardised tool exists for this purpose.

Methods A total of 14 963 patients treated with DAPT after coronary stenting—largely consisting of aspirin and clopidogrel and without indication to oral anticoagulation—were pooled at a single-patient level from eight multicentre randomised clinical trials with independent adjudication of events. Using Cox proportional hazards regression, we identified predictors of out-of-hospital Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding stratified by trial, and developed a numerical bleeding risk score. The predictive performance of the novel score was assessed in the derivation cohort and validated in patients treated with percutaneous coronary intervention from the PLATElet inhibition and patient Outcomes (PLATO) trial (n=8595) and BernPCI registry (n=6172). The novel score was assessed within patients randomised to different DAPT durations (n=10 081) to identify the effect on bleeding and ischaemia of a long (12–24 months) or short (3–6 months) treatment in relation to baseline bleeding risk.

Findings The PRECISE-DAPT score (age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding) showed a c-index for out-of-hospital TIMI major or minor bleeding of 0·73 (95% CI 0·61–0·85) in the derivation cohort, and 0·70 (0·65–0·74) in the PLATO trial validation cohort and 0·66 (0·61–0·71) in the BernPCI registry validation cohort. A longer DAPT duration significantly increased bleeding in patients at high risk (score ≥25), but not in those with lower risk profiles ($p_{\text{interaction}}=0\cdot007$), and exerted a significant ischaemic benefit only in this latter group.

Interpretation The PRECISE-DAPT score is a simple five-item risk score, which provides a standardised tool for the prediction of out-of-hospital bleeding during DAPT. In the context of a comprehensive clinical evaluation process, this tool can support clinical decision making for treatment duration.

Funding None.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor reduces ischaemic recurrences in patients with coronary artery disease treated with coronary stents.^{1–3} However, this benefit is counterbalanced by higher bleeding risk, which is linearly related to the treatment duration. Both ischaemic and bleeding risks have potential to negatively impact prognosis.⁴ As a result, although 12 months of DAPT after stenting has been commonly suggested, the optimal duration of treatment is still debated.^{5,6}

Shortening DAPT duration from 12 months to 6 or 3 months significantly reduced bleeding liability.⁴ However, a prolonged treatment beyond 12 months reduced both stent-related and non-stent-related

ischaemic events in selected patients who tolerated the first year of treatment without bleeding.^{4,7}

International guidelines encourage weighting bleeding risk before selection of treatment duration and suggest a shorter than 12 month treatment regimen in patients at high bleeding risk.^{5,6} No standardised tool exists to weigh bleeding risk at the time of DAPT initiation. A prediction rule was recently proposed for patients who tolerated 12 month DAPT to select those eligible for treatment prolongation.⁸ This strategy cannot be applied earlier, at the time of treatment initiation, to select a shorter than 12 month treatment duration in patients at high bleeding risk. Thus, no standardised algorithm is available for defining optimal DAPT duration at the time of coronary stent implantation.

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Research in context

Evidence before this study

Spontaneous bleeding during treatment with dual antiplatelet therapy (DAPT) is the most common complication after coronary stenting, and its incidence increased with the introduction of novel and more potent antithrombotic agents. Despite recommendations from international guidelines, methods to gauge out-of-hospital bleeding risk in patients treated with DAPT are limited. A dedicated risk score specifically designed to predict spontaneous on-DAPT bleeding events might improve risk assessment and support clinicians' decisions with respect to dual antiplatelet therapy.

We searched PubMed without language or date restrictions for publications until Sept 30, 2016, about bleeding risk scores in patients treated with DAPT. We used the search terms "percutaneous coronary intervention", "coronary stent", "acute coronary syndrome", "stable coronary artery disease", "bleeding risk score", "bleeding", "antiplatelet therapy", "dual antiplatelet therapy", "clopidogrel", "prasugrel", and "ticagrelor". We excluded articles regarding antithrombotic treatment in atrial fibrillation, concomitant use of oral anticoagulants, and risk prediction models for in-hospital bleeding. We identified two reports focused on out-of-hospital events in patients treated with DAPT, and one was only applicable after a 12 month course with DAPT was completed without complications.

Added value of this study

We propose a novel risk score for the prediction of out-of-hospital bleeding in patients treated with DAPT using age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding. The PRECISE-DAPT score is a simple bedside risk assessment tool, which can be easily implemented in everyday clinical practice, and that might be particularly useful for its applicability at the time of treatment initiation. The PRECISE-DAPT score showed potential to identify patients at high bleeding risk (score ≥ 25) who might benefit from a shortened (ie, <12 months) DAPT duration. Patients not at high bleeding risk (score <25) might receive a standard (ie, 12 months) or prolonged (ie, >12 months) treatment without being exposed to significant bleeding liability.

Implication of all the available evidence

Our study provides awareness to clinicians regarding out-of-hospital bleeding risk factors in patients treated with DAPT after coronary stent implantation and offers an objective and standardised tool to quantify such risk in clinical practice. Systematic evaluation of these predictors with the novel PRECISE-DAPT bleeding risk score has potential to support clinical decision making with respect to the optimal duration of DAPT, selecting patients at high bleeding risk (score ≥ 25) to a shorter treatment and patients at non-high risk to a standard or long treatment.

We created a bleeding risk score for patients treated with DAPT after coronary stent implantation, in a large pooled dataset of contemporary randomised clinical trials implementing different DAPT duration strategies. We externally validated this novel risk score in two independent cohorts of patients treated with percutaneous coronary intervention (PCI) from a large randomised clinical trial and a contemporary real-world registry. The score was retrospectively applied among patients randomly assigned to a shortened or prolonged DAPT duration to assess ischaemic and bleeding outcomes according to each bleeding risk category with each DAPT regimen.

Methods

Study design and population

The PRECISE-DAPT collaborative study included a total of 14963 patients with coronary artery disease who underwent elective, urgent, or emergent PCI with coronary stent implantation and subsequent DAPT (appendix p 24). DAPT consisted of an association of aspirin plus a P2Y₁₂ inhibitor, most commonly clopidogrel (88%), whereas patients with an indication for long-term oral anticoagulation were excluded. Patients were pooled at an individual level from eight contemporary multicentre randomised clinical trials.⁹⁻¹⁶ The patients were enrolled in 139 different clinical sites from 12 countries worldwide (appendix p 25). Extensive details regarding the pooled

datasets are provided in the appendix (p 4). Inclusion and exclusion criteria are presented in the appendix (p 6). Details regarding population type, randomisation, DAPT duration, and drug adherence are presented in the appendix (p 8). All clinical trials were approved by the ethics committees at each study centre, and all patients provided written informed consent.

Outcomes

All clinical and laboratory variables included in this analysis were prospectively collected. The primary endpoint of this analysis was out-of-hospital bleeding defined according to the Thrombosis in Myocardial Infarction (TIMI) definition, and occurring 7 days or later after the initial invasive procedure, while bleeding occurring earlier was censored. We selected the 7 day timeframe as a conservative estimate based on the upper limit of current hospitalisation trends in patients with acute coronary syndrome, and to exclude events occurring during hospital stay, which are largely related to invasive procedures.¹⁷ Further definitions for bleeding and clinical variables are provided in the appendix (p 4).

Validation cohorts

An external validation of the risk score was done in the context of two independent PCI-treated populations from the PLATElet inhibition and patient Outcomes (PLATO)

See Online for appendix

trial and the BernPCI Registry (appendix p 24).² In brief, the PLATO trial (NCT00391872) included patients with ST elevation or non-ST elevation acute coronary syndrome randomly assigned to receive DAPT with either clopidogrel or ticagrelor in addition to aspirin for up to 12 months. In the current study, we restricted our analysis to patients undergoing PCI during index hospitalisation. The BernPCI registry (NCT02241291) included all patients undergoing PCI at Bern University Hospital, Switzerland, between Feb 23, 2009, and Dec 31, 2014.

The novel score was calculated and assigned to each participant in a similar manner as in the derivation cohort. The information on previous bleeding in PLATO was related to previous gastrointestinal bleeding, as no other previous bleeding types were prospectively collected in the study case report form. We calculated the PARIS bleeding risk score (age, body-mass index, current smoking, anaemia, creatinine clearance, triple therapy on discharge) in the external validation cohorts to provide comparative assessment of two prediction models.¹⁸ Further details for score calculation in the validation cohorts are provided in the appendix (p 4). The primary endpoint for score validation was the occurrence of TIMI major or minor bleeding at 7 days or later after study inclusion and at up to 12 months. Data in both validation cohorts were prospectively collected and a blinded clinical events committee independently adjudicated adverse events. All patients enrolled provided written informed consent.

Statistical analysis

A detailed description of the statistical analysis is provided in the appendix (p 4). We estimated the 1 year cumulative incidence of bleeding by one minus the Kaplan-Meier estimate of bleeding-free survival at 1 year, to take loss to follow-up into account. We studied the associations between possible predictors and TIMI bleeding from day 7 onwards with a Cox regression analysis, stratified by trial. Potential predictors of bleeding were selected at univariable analysis ($p < 0.10$).¹⁹ Independent bleeding predictors were selected with multivariable backward selection ($p < 0.10$). Linear predictor values were scaled and rounded to a score with integer values between 0 and 100. Discrimination of the bleeding risk score was assessed by trial-specific Harrell's c-indices, which were pooled with a random effects meta-analysis.^{20,21} We evaluated the score performance by censoring patients' follow-up time and events occurring after the intended DAPT treatment duration and excluded patients who were not treated with DAPT at discharge (1.7%). The ability to identify patients at high bleeding risk was visualised by Kaplan-Meier cumulative bleeding incidence curves in bleeding risk score quartiles. Calibration was assessed by comparing predicted probabilities with 1 year Kaplan-Meier bleeding incidence estimates. Furthermore, discrimination and calibration of the bleeding risk score were assessed in the two external validation cohorts. c-Indices, integrated discrimination improvement (IDI), and net reclassification

improvement (NRI) were computed to compare the performance of the PRECISE-DAPT score with the PARIS bleeding score in both validation cohorts.^{22,23} Finally, we evaluated the effect of short (ie, 3–6 months) and long (ie, 12–24 months) DAPT duration on bleeding and ischaemic events across bleeding risk score quartiles in patients ($n=10081$) randomly allocated to DAPT duration. Interaction between high (highest quartile) versus non-high (lowest three quartiles) bleeding risk score and DAPT duration was assessed by the heterogeneity in absolute risk differences for bleeding and ischaemic events. The analyses were done in accordance with the TRIPOD statement.²⁴ Data were analysed with R version 3.6 (R Foundation, Vienna, Austria).

Role of the funding source

All trials included in the PRECISE-DAPT collaborative study were investigator initiated and each sponsor had no role in the data analysis, interpretation, or writing of the report. The corresponding and first, second, and fourth authors (MV, FC, DvK, and DH) had full access to the data and had final responsibility for the decision to submit for publication.

Results

The study population included 14963 patients with established coronary artery disease, and treated with coronary stent implantation (appendix p 9). DAPT at discharge was implemented in most patients (14590 of 14848 patients; 98.3%) with a median treatment duration of 360 days (IQR 95–365).

In a total of 21963 person-years of follow-up (median follow-up 552 days, IQR 365–725), out-of-hospital TIMI major or minor bleeding occurred in 218 patients (incidence at 1 year 12.5 per 1000 patients), 124 of whom were major (incidence at 1 year 6.9 per 1000 patients). The median time to first occurrence of TIMI major or minor bleeding was 158 days (IQR 57–333) and 150 days (62–326) for TIMI major bleeding. The rate of bleeding stratified by clinical trial

	Hazard ratio (95% CI)	p value
Age (for each increase of 10 years)	1.34 (1.11–1.48)	0.005
Previous bleeding	4.14 (1.22–14.02)	0.023
White-blood-cell count (for each increase of 10^3 cells per μ L)	1.06 (0.99–1.13)	0.078
Haemoglobin at baseline (for each increase of 1 g/dL)	0.67 (0.53–0.84)	0.001
Creatinine clearance (for each increase of 10 mL/min)	0.90 (0.82–0.99)	0.004

Age was truncated above 90 years and below 50 years. Haemoglobin at baseline was truncated above 12 g/dL and below 10 g/dL. Creatinine clearance was truncated above 100 mL/min. White-blood-cell count was truncated above 20×10^3 cells per μ L and below 5×10^3 cells per μ L.

Table 1: Multivariable analysis for out-of-hospital Thrombosis in Myocardial Infarction major or minor bleeding, study stratified with backward selection at an α level of 0.1

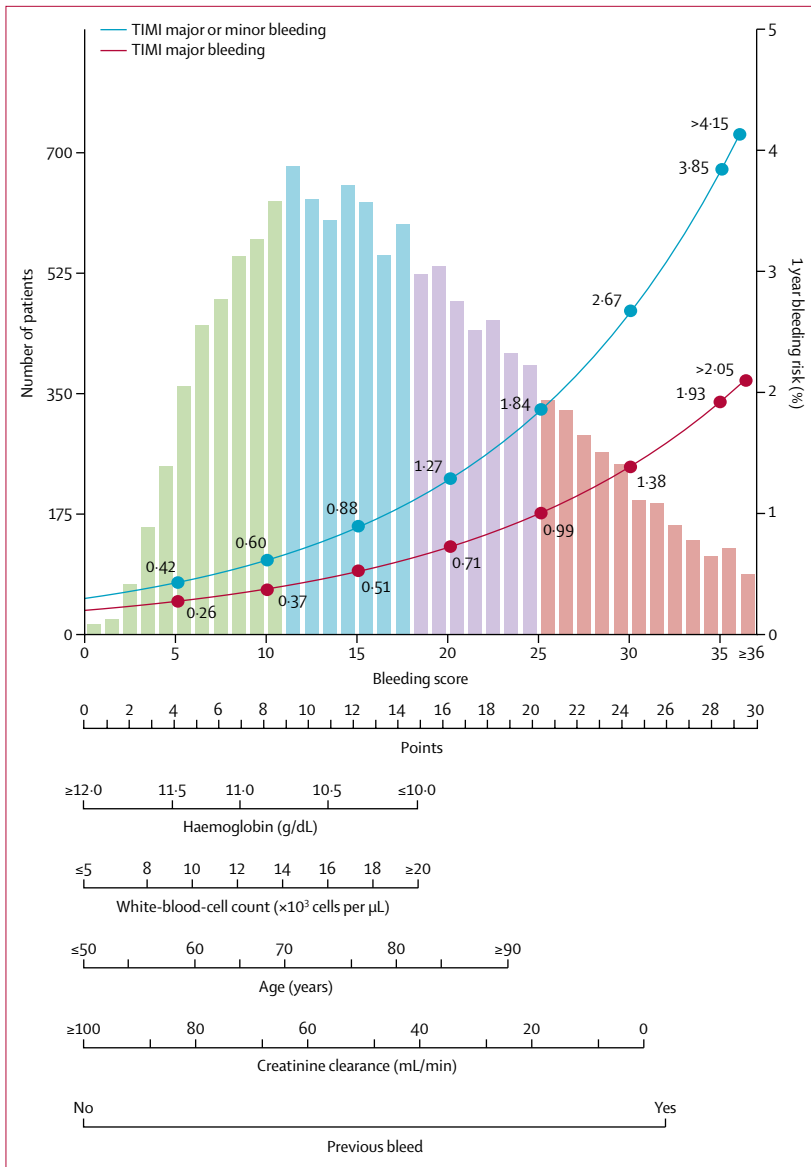


Figure 1: The PRECISE-DAPT score nomogram for bedside application
 Risk curves refer to out-of-hospital Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding and TIMI major bleeding at 12 months while on-treatment with dual antiplatelet therapy (DAPT). Histogram refers to the PRECISE-DAPT score distribution in the derivation cohort: green bars, the first score quartile (very low risk); blue bars, the second score quartile (low risk); purple bars, the third score quartile (moderate risk); and red bars, the fourth score quartile (high risk).

For the **web calculator and mobile app** see www.precisedaptscore.com

and type of P2Y₁₂ inhibitor are presented in the appendix (pp 12, 26).

Predictors with a p value less than 0.10 at univariable analysis (appendix p 9) were included in the multivariable model. Use of proton-pump inhibitors at discharge was excluded because of lack of prediction within studies where DAPT duration was randomised. Five predictors remained in the final model at a p value less than 0.10 (table 1), and showed consistent association with bleeding during the first trimester after treatment initiation as well as beyond (appendix p 13). An alternative

model, which has been generated after excluding white-blood-cell count, is shown in the appendix (p 14).

From the final multivariable model, we developed a five-item bleeding risk score (age, creatinine clearance, haemoglobin, white-blood-cell count at baseline, and previous spontaneous bleeding—the PRECISE-DAPT score) assigning points to each factor based on the magnitude of association of each predictor with bleeding. A nomogram to calculate the score and the risk of bleeding at 12 months is presented in figure 1.

Similar information derived from the model lacking white-blood-cell count is presented in the appendix (p 27). A web calculator and mobile app are available online.

The PRECISE-DAPT score showed a c-index of 0.73 (95% CI 0.61–0.85) for out-of-hospital TIMI major or minor bleeding and 0.71 (0.57–0.85) for TIMI major bleeding within 12 months (table 2). c-Indices for each of the included studies are presented in the appendix (p 15). The score discrimination was consistent regardless of the clinical presentation at the time of PCI or treatment with clopidogrel or ticagrelor, but was apparently lower for patients treated with prasugrel and higher for those treated with proton-pump inhibitors (appendix pp 16–18). The performance of the score lacking white-blood-cell count is presented in table 2 and the appendix (p 29). Kaplan-Meier bleeding rates were consistently separated by score quartiles (very low risk: score ≤10; low risk: score 11–17; moderate risk: score 18–24; and high risk: score ≥25; figure 2).

The PRECISE-DAPT score was validated in 8595 PCI patients from the PLATO trial and 6172 participants from the BernPCI registry (appendix p 19). TIMI major or minor bleeding occurred in 145 patients (1.69%) in the PLATO trial and 94 patients (1.52%) in the BernPCI registry. TIMI major bleeding was noted in 94 patients (1.09%) in the PLATO trial and 62 patients (1.00%) in the BernPCI registry. The c-indices for out-of-hospital TIMI major or minor bleeding were 0.70 (95% CI 0.65–0.74) in the PLATO trial and 0.66 (0.61–0.71) in the BernPCI registry (table 2). Calibration appeared good between the derivation and BernPCI validation cohorts. In the PLATO validation cohort, the score maintained a consistent association between predicted probabilities and observed frequencies, whereas bleeding risk was slightly underestimated (appendix p 28). Score discrimination appeared consistent for Bleeding Academic Research Consortium (BARC) bleeding in the BernPCI cohort (BARC 3 or 5: c-index 0.68 [95% CI 0.63–0.73]; BARC 2, 3, or 4: c-index 0.68 [0.63–0.72]; appendix p 22). Score performance was also consistent, including bleeding occurring earlier than 7 days after PCI (appendix p 23). Discrimination for the score lacking white-blood-cell count was similar to the score including white-blood-cell count in the PLATO trial, whereas it was lower in the BernPCI registry (table 2, appendix p 29).

The PRECISE-DAPT score showed improved integrated discrimination and reclassification performance as

	TIMI major or minor bleeding						TIMI major bleeding					
	c-Index (95% CI)	p value*	NRI		IDI		c-Index (95% CI)	p value*	NRI		IDI	
			Index	p value	Index	p value			Index	p value	Index	p value
Derivation cohort												
PRECISE-DAPT	0.73 (0.61–0.85)	0.71 (0.57–0.85)
PRECISE-DAPT alternative	0.71 (0.57–0.84)	0.69 (0.53–0.85)
Validation cohort 1 (PLATO)												
PRECISE-DAPT	0.70 (0.65–0.74)	0.06	0.16	0.047	0.004	0.007	0.68 (0.63–0.74)	0.01	0.23	0.02	0.004	0.002
PRECISE-DAPT alternative	0.70 (0.66–0.74)	0.02	0.20	0.02	0.005	0.003	0.68 (0.63–0.74)	0.008	0.23	0.02	0.004	0.002
PARIS	0.66 (0.61–0.70)	Ref	Ref	..	Ref	..	0.62 (0.56–0.68)	Ref	Ref	..	Ref	..
Validation cohort 2 (BernPCI)												
PRECISE-DAPT	0.66 (0.61–0.71)	0.09	0.21	0.037	0.004	0.01	0.65 (0.58–0.71)	0.17	0.14	0.23	0.002	0.049
PRECISE-DAPT alternative	0.63 (0.58–0.68)	0.82	0.09	0.37	0.001	0.07	0.62 (0.55–0.68)	0.57	0.03	0.77	0.0001	0.15
PARIS	0.63 (0.58–0.67)	Ref	Ref	..	Ref	..	0.62 (0.56–0.69)	Ref	Ref	..	Ref	..

PRECISE-DAPT score is age, creatinine clearance, haemoglobin, white-blood-cell count at baseline, and previous spontaneous bleeding. PRECISE-DAPT alternative score is age, creatinine clearance, haemoglobin at baseline, and previous spontaneous bleeding. PARIS is age, body-mass index, current smoking status, presence of anaemia (haemoglobin <12 g/dL in men and <11 g/dL in women), creatinine clearance <60 mL/dL, and treatment with triple therapy (ie, aspirin plus P2Y₁₂ inhibitor plus oral anticoagulant) at discharge. TIMI=Thrombosis in Myocardial Infarction. NRI=net reclassification improvement. IDI=integrated discrimination improvement. *The PARIS score has been used as reference to test c-indices, IDI, and NRI as compared with the PRECISE-DAPT scores.

Table 2: Discriminative ability of the PRECISE-DAPT score in the derivation cohort and discriminative-reclassification ability in comparison with the PARIS score in the validation cohorts for out-of-hospital bleeding occurring while on-treatment with dual antiplatelet therapy (DAPT)

compared with the PARIS score in both validation cohorts for TIMI major or minor bleeding (table 2). Discriminative ability according to the c-index was similar between the two scores (table 2). The alternative version of the score lacking white-blood-cell count showed improved discrimination and reclassification in the PLATO validation cohort, and similar performance as compared with the PARIS score in the BernPCI second validation cohort.

DAPT duration was randomly allocated in five of the eight studies included in the generation dataset, with 5050 patients assigned to either 12 months or 24 months of treatment and 5031 to 3 months or 6 months.^{11–15} We observed a significant increase in bleeding with a long (12–24 months) rather than short (3–6 months) duration of treatment exclusively in patients at high bleeding risk (absolute risk difference [ARD] +2.59% [95% CI +0.82 to +4.34]; number needed to treat: 38) but not in those without a high bleeding risk profile (ie, very low risk, low risk, and moderate risk: mean of the first three quartiles ARD +0.14% [–0.22 to +0.49]; $p_{\text{interaction}}=0.007$; figure 3). This remained consistent after censoring events occurring beyond 1 year after PCI ($p_{\text{interaction}}=0.047$; appendix p 30). Concurrently, longer DAPT duration reduced the composite ischaemic endpoint of myocardial infarction, definite stent thrombosis, stroke, or target vessel revascularisation in those at non-high bleeding risk (ARD –1.53% [95% CI –2.64 to –0.41]; number needed to treat: 65), but not in those at high bleeding risk (ARD +1.41% [–1.67 to +4.50]; $p_{\text{interaction}}=0.07$; figure 4). When the composite of myocardial infarction, definite ST, or stroke was assessed, longer DAPT duration was not associated with a clear benefit in patients at non-high bleeding risk (ARD –0.42% [95% CI –1.02 to +0.17])

and to the possibility of harm in those at high bleeding risk (ARD +1.96% [–0.39 to +4.30]; $p_{\text{interaction}}=0.054$; appendix p 31). The resulting net effect on bleeding and ischaemia suggested a favourable outcome with 12–24 month DAPT in patients at non-high bleeding risk, but not in those at high PRECISE-DAPT risk (figure 4).

At sensitivity analysis, we tested the effect of randomised DAPT duration among bleeding risk strata in the subgroup of patients presenting with acute coronary syndrome at the time of PCI, with results remaining largely consistent with those observed in the overall population (appendix pp 32, 33). Patients presenting with acute coronary syndrome and with a PRECISE-DAPT score of at least 25 showed a significant increase in TIMI bleeding after treatment with longer DAPT (ARD +2.61% [95% CI +0.19 to +4.99]; number needed to treat: 38), whereas those with a non-high PRECISE-DAPT risk score did not (ARD +0.14% [–0.22 to +0.49]; $p_{\text{interaction}}=0.034$). At the same time, longer DAPT duration reduced the composite ischaemic endpoint in patients with acute coronary syndrome at a non-high PRECISE-DAPT score (ARD –4.13% [95% CI –6.09 to –2.15]; number needed to treat: 24), but not in those with a PRECISE-DAPT score of at least 25 (ARD +1.54% [–3.27 to +6.32]; $p_{\text{interaction}}=0.032$; appendix p 32).

Discussion

Ischaemic recurrences after stenting have dropped considerably in the last years thanks to the introduction of novel stent technologies and progressive refinement of pharmaco-interventional techniques. However, due to more potent and prolonged platelet inhibition, the incidence of major bleeding has increased.²⁵ DAPT-

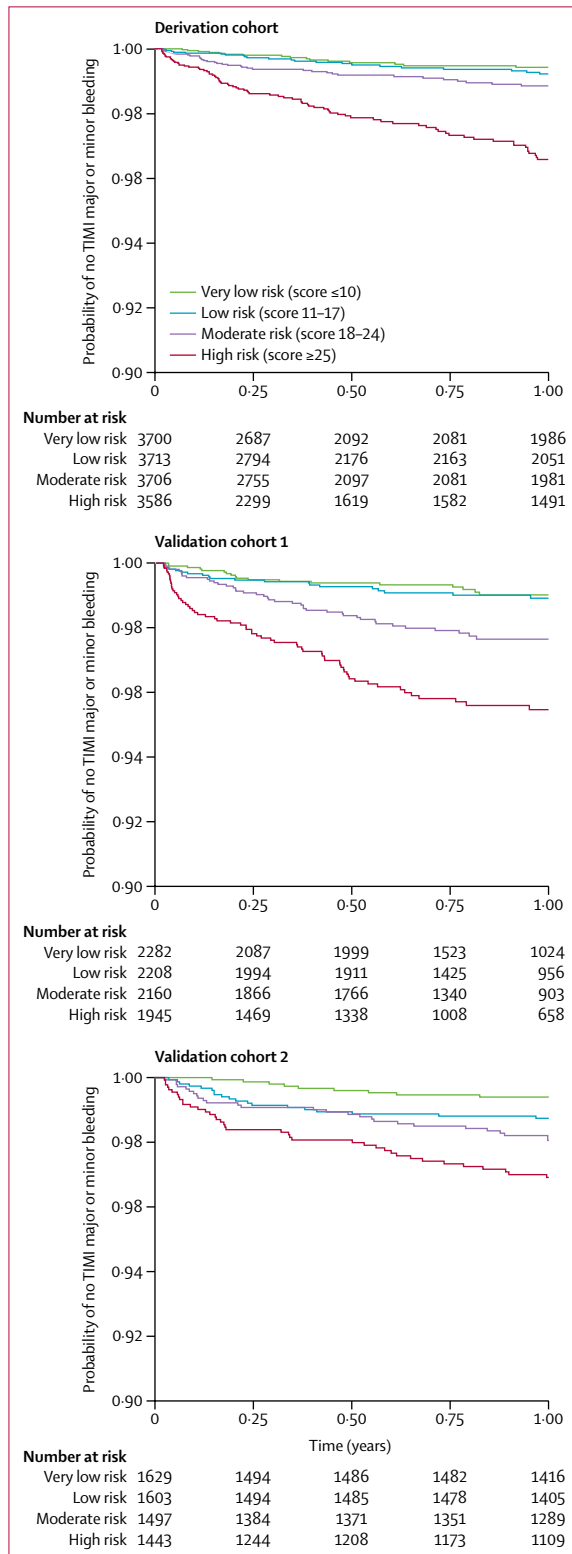


Figure 2: Kaplan-Meier estimates of survival free from bleeding in both derivation and validation cohorts stratified by score quartiles
 Estimates for Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding occurring while on-treatment with dual antiplatelet therapy are presented. Validation cohort 1 from the PLATO trial. Validation cohort 2 from the BernPCI registry.

related bleeding is the most common complication after coronary stent implantation in current practice, and it is associated with lower survival, lower quality of life, and higher health costs.^{26,27}

Numerous bleeding and ischaemic risk scores have been proposed for the prediction of events occurring alternatively in-hospital or out-of-hospital after PCI.^{8,18,28,29} However, most failed to be implemented in everyday clinical practice largely because their use did not affect treatment decisions.^{8,29}

This study developed and validated the PRECISE-DAPT score, a tool for the prediction of out-of-hospital bleeding in patients undergoing coronary stenting. The novel score showed reasonable discrimination and calibration in two independent validation cohorts of patients with contemporary use of all three oral P2Y₁₂ inhibitors and has potential to inform decision making on DAPT duration. We confirmed the role of well-known risk factors associated with out-of-hospital bleeding such as age and haemoglobin at baseline. Similarly, covariates, which have been previously associated with in-hospital bleeding, such as renal function, and white-blood-cell count, remained associated with bleeding occurring at later timepoints.^{27,30} Additionally, we featured the relevance of previous bleeding, which is commonly appraised in practice,³¹ and emerged as the strongest predictor of bleeding in our score.

International guidelines suggest individualisation of the antiplatelet treatment duration,^{5,6} as all randomised studies invariably showed real or potential bleeding liability associated with prolonged versus shortened DAPT duration regimens.^{4,7,13} We observed that among patients deemed at high bleeding risk based on the PRECISE-DAPT score, prolonged DAPT was associated with no ischaemic benefit but a remarkable bleeding burden leading to a number needed to treat for harm of 38. A longer treatment in patients without high bleeding risk was associated with a marginal or even no increase of bleeding and a significant reduction of the composite ischaemic endpoint. Selecting upfront a shorter than 12 month treatment duration in patients deemed at high bleeding risk (PRECISE-DAPT score ≥ 25) might prevent exposing them to an excessive bleeding hazard. In turn, patients at non-high bleeding risk (PRECISE-DAPT score < 25) might receive a standard (ie, 12 months) or a prolonged (ie, > 12 months) course of treatment if tolerated. A separate assessment of this treatment strategy in patients with acute coronary syndrome provided consistent findings. Current recommendations for DAPT duration suggest that patients with acute coronary syndrome should undergo at least 12 month treatment unless the bleeding outweighs ischaemic risks.⁵ The PRECISE-DAPT score was able to select patients with acute coronary syndrome with an excessive bleeding risk, who failed to derive ischaemic benefit from 12 month or 24 month DAPT duration, whereas a more favourable net outcome was observed in these selected patients with a shorter DAPT duration.

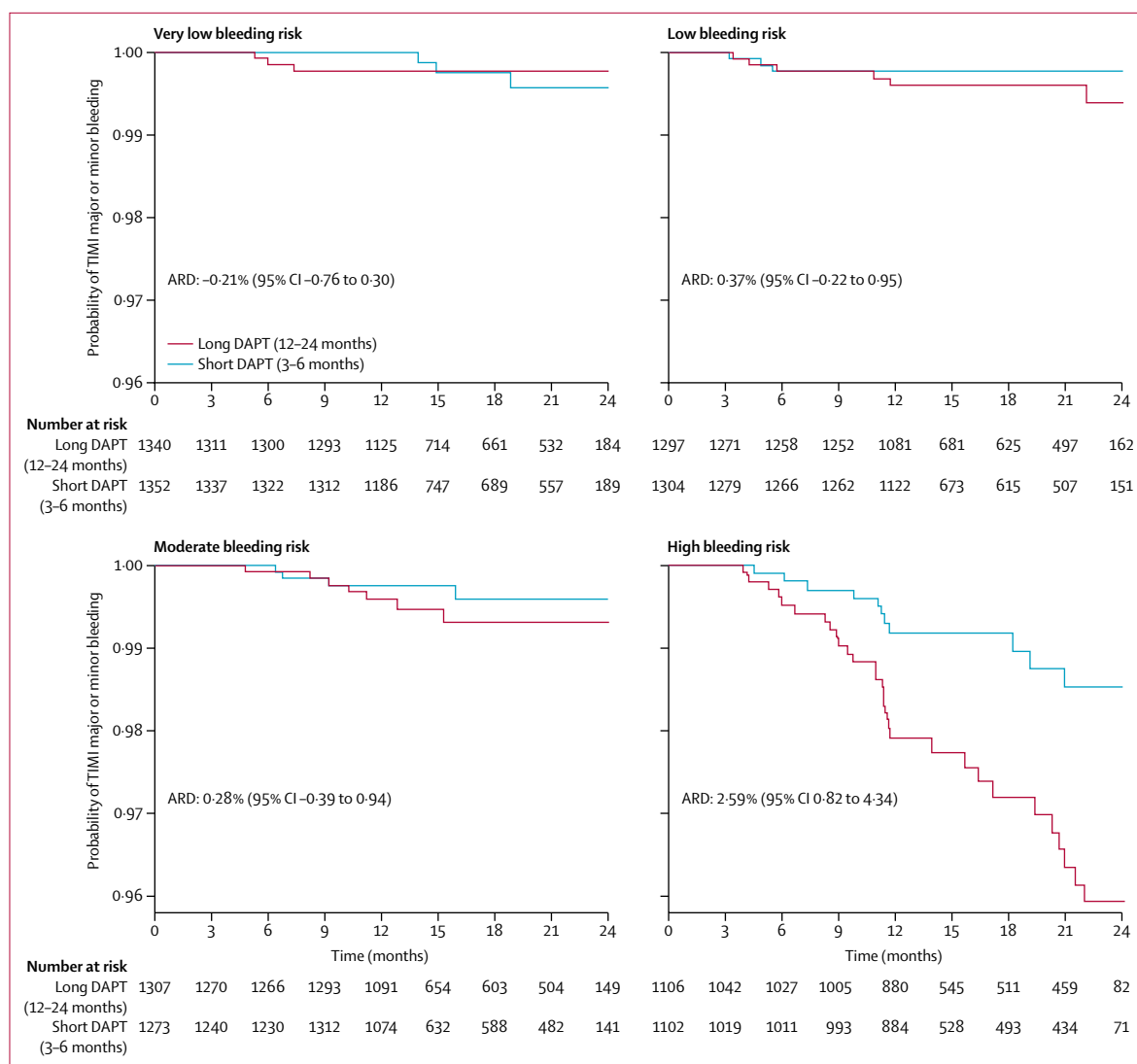


Figure 3: 24 month Kaplan-Meier estimates of survival free from Thrombosis in Myocardial Infarction (TIMI) major or minor bleeding among PRECISE-DAPT bleeding risk quartiles (ie, very low, low, moderate, and high bleeding risk) for patients randomly assigned to long (12–24 months) or short (3–6 months) dual antiplatelet therapy (DAPT)

Absolute risk differences (ARDs) are presented: a positive ARD represents the risk increase for a long, as compared with a short, course of DAPT.

A prediction algorithm was recently proposed for patients who tolerated 12 month DAPT to select those eligible for treatment prolongation.⁸ However, this strategy cannot be applied earlier at the time of treatment initiation, to select a shorter than 12 month treatment duration in patients at high bleeding risk. Earlier decision making is especially desirable for bleeding prevention, considering that, as observed in our analysis, median time to bleeding was 5–6 months.

Two risk scores have been developed to evaluate the absolute ischaemic and bleeding risk after coronary stenting in the context of the PARIS registry.¹⁸ At variance with our analysis, the PARIS study did not provide a decision-making algorithm for deciding upon DAPT duration. With respect to bleeding risk prediction, our

score ultimately proved at least as good as PARIS, showing improved integrated discrimination and net reclassification, whereas c-indices were numerically but not always statistically superior.

Our study had a number of strengths. We derived a simple risk score that was developed and validated from three largely representative, prospectively investigated patient cohorts with rigorous event adjudication, and based on a well standardised and accepted bleeding definition.^{2,5,6} At variance with previous scores designed to predict in-hospital bleeding,²⁸ our model was developed to predict out-of-hospital bleeding events, which are more relevant in the decision making on secondary prevention with antithrombotic medications. This novel score is the first being validated in patients

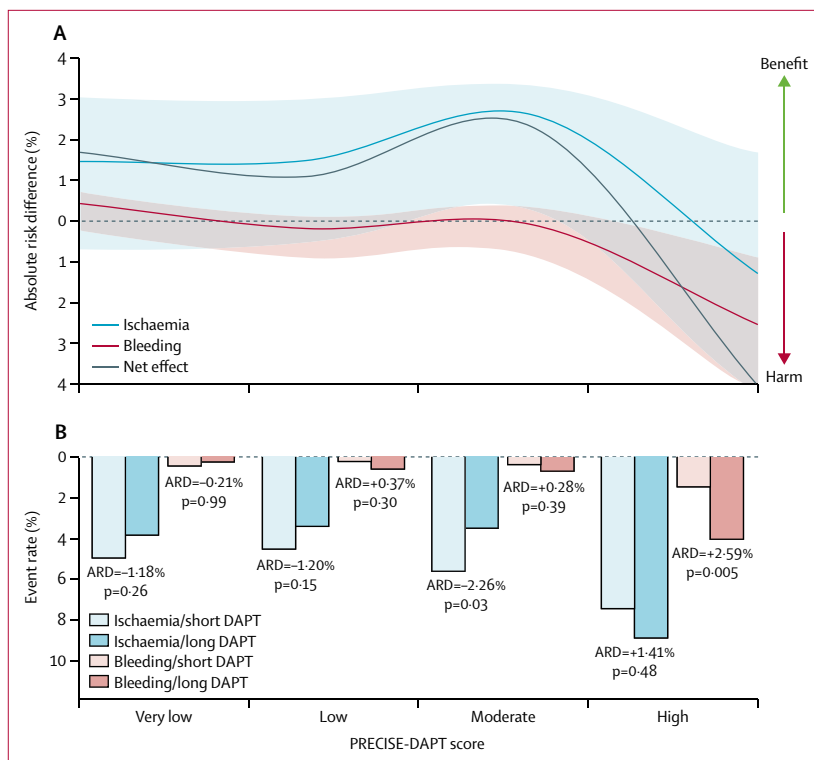


Figure 4: Absolute risk difference (ARD) for a long (12–24 months) as compared with a short (3–6 months) dual antiplatelet therapy (DAPT) duration with respect to ischaemia (myocardial infarction, definite stent thrombosis, stroke, or target vessel revascularisation) and bleeding (Thrombosis in Myocardial Infarction major or minor bleeding) within the four PRECISE-DAPT score quartiles

ARD curves plotted on the upper side of the zero line represent benefit from a long DAPT treatment, whereas curves plotted on the lower side of the zero line represent harm from a long DAPT as compared with a short treatment (A). Event rate for ischaemia and bleeding after a long or short DAPT treatment within the four PRECISE-DAPT quartiles. A positive ARD represents the risk increase for a long as compared with a short course of DAPT (B).

treated with more potent P2Y₁₂ inhibitors, which represent the standard of care for patients with acute coronary syndrome. This score was retrospectively applied among patients randomly assigned to a shortened or prolonged DAPT duration to propose and validate simple DAPT duration treatment strategy according to bleeding risk. A simplified score modelled without white-blood-cell count was also derived and validated, which might prove useful in cases where white-blood-cell count is not available.

Among the limitations, we acknowledge that event discrimination in our score ranged from moderate to good. Emerging predictors for bleeding, including frailty, might be missing in our model,³² and future studies should implement clinical, laboratory, or genetic factors to possibly improve its discriminative capability. Information regarding single patients' drug adherence was lacking in our dataset and each patient was considered on-DAPT treatment according to the prespecified or randomised treatment duration at the time of PCI. A granular collection of patient on-treatment or off-treatment status during follow-up would have been desirable. Information regarding previous bleeding in the

PLATO validation cohort was limited to previous gastrointestinal bleeding. Our score slightly underestimated bleeding risk in the PLATO PCI population possibly because of the higher bleeding risk in the PLATO trial, which included only patients with acute coronary syndrome, or as a reflection of chance. However, given the calibration results observed in the all-comer BernPCI registry, our score appears well suited to predict bleeding risk status in real-world patients. Discrimination in patients treated with prasugrel was poorer. Since prasugrel administration was not randomised in both derivation and BernPCI validation cohorts, and its use in individuals older than 75 years or with increased bleeding liability is discouraged, patients at lower bleeding risk might have been selected for this treatment, potentially hampering the score's ability to correctly discriminate bleeding. Based on similar considerations, the score did slightly better in patients taking proton-pump inhibitors. The PARIS score discrimination might have been underestimated since patients on oral anticoagulants were not included in our study. However, these patients are per se considered at high bleeding risk. Dedicated bleeding risk score for patients on oral anticoagulants should probably be used to better estimate bleeding risk and corresponding treatment strategies. Whether the routine use of the PRECISE-DAPT risk score in an unselected population substantially mitigates bleeding risk by better informing decision making remains to be prospectively ascertained.

In conclusion, we developed and validated the PRECISE-DAPT score, a simple five-item prediction algorithm for the prediction of out-of-hospital bleeding in patients treated with DAPT. The PRECISE-DAPT score identified patients in whom the benefits of prolonged DAPT outweighed the risks and vice versa. In the context of a comprehensive clinical evaluation process, this tool can support clinical decision making for treatment duration. Prospective validation of this score in practice remains desirable.

Contributors

MV and FC conceived, designed and interpreted the study, drafted the manuscript, and revised and approved the final manuscript. DvK designed the study, analysed and interpreted data, and revised and approved the final manuscript. EWS, SJ, FF, LR, TP, DH, TZ, M-KH, H-SK, AC, PGS, TP, LW, DLB, GWS, and SW interpreted data, and revised and approved the final version of the manuscript.

Declaration of interests

MV received research grants from The Medicines Company, Terumo, and AstraZeneca, outside the submitted work. DvK is supported by the National Institutes of Health (grant U01NS086294). EWS is supported by the National Institutes of Health (grant U01NS086294). SJ received institutional research grants from The Medicines Company, AstraZeneca, Abbot Vascular, and Boston Scientific, outside the submitted work. TP received personal fees from Biotronik, Medtronic, and Edwards, outside the submitted work. TZ is supported by the Swiss National Science Foundation. PGS reports grants from Merck, Servier, and Sanofi, personal fees from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, Servier, and The Medicines Company, outside the

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