

## **A risk score to predict out-of-hospital bleeding on dual antiplatelet therapy**

**Derivation and validation of the predicting bleeding complications In patients undergoing stent implantation and subsequent dual anti platelet therapy (PRECISE-DAPT) score**

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**Summary:**

**Background:** Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y<sub>12</sub> inhibitor prevents ischemic events after coronary stenting, but increases bleeding. Guidelines support weighting bleeding risk prior to 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 randomized clinical trials with independent adjudication of events. Using Cox proportional hazards regression, we identified predictors of out-of-hospital TIMI major/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 8,595 and 6,172 patients treated with PCI from the PLATelet inhibition and patient Outcomes (PLATO) trial and BernPCI registry, respectively. The novel score was assessed within patients randomized to different DAPT durations (N=10,081) to identify the effect on bleeding and ischemia 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, prior spontaneous bleeding) showed a c-index of 0.73 (95%CI 0.61-0.85) in the derivation cohort, 0.70 (95%CI 0.65-0.74) and 0.66 (95%CI 0.61-0.71) in the two validation cohorts. A longer DAPT duration significantly increased bleeding in high-risk patients (score $\geq$ 25), but not in those at lower risk profiles ( $P_{\text{interaction}}$ : 0.007), and exerted a significant ischemic benefit only in this latter group.

**Interpretation:** The PRECISE-DAPT is a simple five-item risk score, which provides a standardized 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:** No additional external funding was used.

## **Introduction:**

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y<sub>12</sub> inhibitor reduces ischemic recurrences in patients with coronary artery disease treated with coronary stents.<sup>1-3</sup> Yet this benefit is counterbalanced by higher bleeding risk, which is linearly related to the treatment duration. Both ischemic and bleeding risks have potential to negatively impact prognosis.<sup>4</sup> As a result, despite 12 months of DAPT after stenting has been commonly suggested, the optimal duration of treatment is still debated.<sup>5,6</sup>

Shortening DAPT duration to six or three months significantly reduced bleeding liability as compared to longer treatment duration.<sup>4</sup> However, a prolonged treatment beyond 12 months reduced both stent and non-stent related ischemic events in selected patients who tolerated the first year of treatment without bleeding.<sup>4,7</sup>

International guidelines encourage weighting bleeding risk prior to selection of treatment duration and suggest a shorter than 12 month treatment regimen in patients at high bleeding risk.<sup>5,6</sup> No standardized 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.<sup>8</sup> Still, this strategy cannot be applied earlier, at the time of treatment initiation, to select a shorter than 12 month treatment duration in high bleeding risk patients. Thus, no standardised algorithm is available for defining optimal DAPT duration at the time of coronary stent implantation.

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

## **Methods:**

**Study Design and population:** The PRECISE-DAPT (PRODIGY–RESET–EXCELLENT–COMFORTABLE AMI– BIOSCIENCE–SECURITY–ZEUS–OPTIMIZE) collaborative study included a total of 14,963 patients with coronary artery disease who underwent elective, urgent, or emergent percutaneous coronary intervention (PCI) with coronary stent implantation and subsequent DAPT (**eFigure 1**). DAPT consisted of an

association of aspirin plus a P2Y12 inhibitor, most commonly clopidogrel (87.7%), whereas patients with an indication for long-term oral anticoagulation were excluded. Patients were pooled at an individual level from eight contemporary multicentre randomized clinical trials.<sup>9-16</sup> The patients were enrolled in 139 different clinical sites from 12 countries worldwide (**eFigure 2**). Extensive details regarding the pooled datasets are provided in the **appendix**. Inclusion and exclusion criteria are presented in **eTable 1**. Details regarding population type, randomization, DAPT duration and drug adherence are presented in **eTable 2**. All clinical trials were approved by the ethics committees at each study centre, and all patients provided written informed consent.

### **Definitions of Predictors and Outcomes:**

All clinical and laboratory variables included in the current 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 time frame as a conservative estimate based on the upper limit of current hospitalization trends in acute coronary syndrome (ACS) patients, and to exclude events occurring during hospital stay, which are largely related to invasive procedures.<sup>17</sup>

Further details for bleeding and clinical variables definitions are provided in the **appendix**.

### **Validation Cohorts:**

An external validation of the risk score was performed in the context of two independent PCI-treated populations from the PLATelet inhibition and patient Outcomes (PLATO) trial and the BernPCI Registry (**eFigure 1**).<sup>2</sup> In brief, PLATO trial (NCT00391872) included patients with ST- or non-ST elevation ACS randomized 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 hospitalization. The BernPCI registry (NCT02241291) included all patients undergoing PCI at Bern University Hospital, Switzerland, between 2009 and 2014.

The novel score was calculated and assigned to each participant in a similar manner as in the derivation cohort. The information on “prior bleeding” in PLATO was related to prior gastro-intestinal bleeding, as no other prior 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 in order to provide comparative assessment of two

prediction models.<sup>18</sup> Further details for score calculation in the validation cohorts are provided in the **appendix**. The primary endpoint for score validation was the occurrence of TIMI major/minor bleeding 7 days or later after study inclusion and up to twelve 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 including sensitivity analyses:**

A detailed description of the statistical analysis is provided in the **appendix**. We estimated the one-year cumulative incidence of bleeding by one minus the Kaplan Meier estimate of bleeding-free survival at one year, in order 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 ( $p < 0.10$ ).<sup>19</sup> 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 (Figure 1). Discrimination of the bleeding risk score was assessed by trial-specific Harrell's c-indexes, which were pooled with a random effects meta-analysis.<sup>20,21</sup> We evaluated the score performance 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 high bleeding risk patients was visualized by Kaplan Meier cumulative bleeding incidence curves in bleeding risk score quartiles (Figure 2). Calibration was assessed by comparing predicted probabilities with one-year Kaplan Meier bleeding incidence estimates. Furthermore, discrimination and calibration of the bleeding risk score were assessed in the two external validation cohorts. C-indexes, integrated discrimination (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<sup>22,23</sup> Finally, we evaluated the impact of short (i.e. 3-6 months) and long (12-24 months) DAPT duration on bleeding and ischemic events across bleeding risk score quartiles in patients ( $n = 10,081$ ) randomly allocated to DAPT duration as presented in Figure 3 and 4. Interaction between high (highest quartile) vs. non-high (lowest three quartiles) bleeding risk score and DAPT duration was assessed by the heterogeneity in absolute risk differences for bleeding and ischemic events as presented in the text. The analyses were done in accordance with the TRIPOD statement.<sup>24</sup> Data were analysed with R version 3.6 (R Foundation, Austria).

**Role of the funding source:**

No additional funding was used for current analysis. 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, DH) had full access to the data and had final responsibility for the decision to submit for publication.

**Results:**

The study population included 14,963 patients with established coronary artery disease, treated with coronary stent implantation (**eTable 3**). Dual antiplatelet therapy at discharge was implemented virtually in all patients (98.3%) with median treatment duration of 360 days (IQR 95-365).

In a total of 21,963 person-years of follow-up (median follow-up 552 days, IQR 365-725), out-of-hospital TIMI major/minor bleeding occurred in 218 patients (incidence at one-year 12.5 /1000 patients), 124 of whom were major (incidence at one-year 6.9 /1000 patients). The median time to first occurrence of TIMI major/minor was 158 days (IQR 57-333) and 150 days (62-326) for TIMI major. The rate of bleeding stratified by clinical trial and type of P2Y<sub>12</sub> inhibitor are presented in the appendix (**eTable 4** and **eFigure 3**).

**Univariable and Multivariable Analysis:** Predictors with a  $p < 0.10$  at univariable analysis (**eTable 3**) were included into the multivariable model. Use of proton pump inhibitors (PPI) at discharge was excluded because of lack of prediction within studies where DAPT duration was randomised. Five predictors remained in the final model at  $p < 0.10$  (**Table 1**), and showed consistent association with bleeding during the first trimester after treatment initiation as well as beyond (**eTable 5**). An alternative model, which has been generated after excluding white-blood cell count (WBC), is shown in the appendix (**eTable 6**).

**Risk Score:** From the final multivariable model we developed a five-item bleeding risk score (age, creatinine clearance, haemoglobin and WBC at baseline, and prior spontaneous bleeding – 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 WBC is presented in the appendix (**eFigure 4**).

A web-calculator and mobile App are available at [www.precisedaptscore.com](http://www.precisedaptscore.com).

**Score performance in the derivation cohort:** The PRECISE-DAPT score showed a c-index of 0.73

(95%CI 0.61-0.85) for out-of-hospital TIMI major/minor bleeding and 0.71 (95%CI 0.57-0.85) for TIMI major within 12 months (**Table 2**). C-Indexes for each of the included studies are presented in the appendix (**eTable 7**). The score discrimination was consistent irrespective to the clinical presentation at the time of PCI (**eTable 8**) or treatment with clopidogrel or ticagrelor, but was apparently lower for patients treated with prasugrel (**eTable 9**) and higher for those treated with PPI (**eTable 10**). The performance of the score lacking WBC is presented in **Table 2** and **eFigure 6**. Kaplan-Meier bleeding rates were consistently separated by score quartiles (very low: score  $\leq 10$ ; low: score 11-17; moderate: score 18-24; and high risk: score  $\geq 25$ ) (**Figure 2**).

**Score performance in the validation cohort:** The PRECISE-DAPT score was available for 8,595 PCI patients from the PLATO trial and 6,172 participants in the BernPCI registry (**eTable 11**). TIMI major/minor bleeding occurred in 145 patients (1.69%) in PLATO and 94 patients in BernPCI (1.52%). TIMI major bleeding was noted in 94 (1.09%) and 62 (1.00%) respectively. The c-indexes for out-of-hospital TIMI major/minor were 0.70 (95%CI 0.65-0.74) in PLATO and 0.66 (95%CI 0.61-0.71) in the BernPCI cohorts (**Table 2**). Calibration appeared good in derivation and BernPCI validation cohorts. In the PLATO validation cohort the score maintained a consistent association between predicted probabilities and observed frequencies, while bleeding risk was slightly underestimated (**eFigure 5**). 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 5: c-index 0.68, 95%CI 0.63-0.72) (**eTable 12**). Score performance was also consistent including bleeding occurring earlier than 7 days after PCI (**eTable 13**). Discrimination for the score lacking WBC was similar to the score including WBC in PLATO, whereas it was lower in the BernPCI cohort (**Table 2** and **eFigure 6**).

**Comparative bleeding risk prediction assessment:** The PRECISE-DAPT score showed improved integrated discrimination and reclassification performance as compared to the PARIS score in both validation cohorts for TIMI major and 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 WBC showed improved discrimination and reclassification in the PLATO validation cohort, and similar performance as compared to PARIS score in the BernPCI second validation cohort.

**Impact of randomized DAPT duration among bleeding risk strata:** DAPT duration was randomly allocated in 5 of the 8 studies included in the generation dataset, with 5,050 patients assigned to either 12 or 24 months of treatment duration and 5,031 to three or six months.<sup>11-15</sup> 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 (ARD +2.59%, 95%CI +0.82% to +4.34%; NNT: 38) but not in those without a high bleeding risk profile (i.e. very-low/low/moderate risk) (ARD +0.14%, 95%CI -0.22% to +0.49%) ( $P_{int}=0.007$ ) (**Figure 3**). This remained consistent after censoring events occurring beyond 1 year after PCI ( $P_{int}=0.047$ ) (**eFigure 7**). Concurrently, longer DAPT duration reduced the composite ischemic endpoint of MI, definite ST, stroke or TVR in those at non-high bleeding risk (ARD -1.53%, 95%CI -2.64% to -0.41%; NNT: 65), but not in those at high bleeding risk, (ARD +1.41%, 95%CI -1.67% to +4.50%) ( $P_{int}=0.079$ ) (**Figure 4**). When the composite of MI, definite ST or stroke was assessed, longer DAPT duration was not associated to 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%, 95%CI -0.39% to +4.30%) ( $P_{int}=0.054$ ) (**eFigure 8**). The resulting net effect on bleeding and ischemia 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 impact of randomized DAPT duration among bleeding risk strata in the subgroup of patients presenting with ACS at the time of PCI, with results remaining largely consistent to those observed in the overall population (**eFigure 9 and 10**). Patients presenting with ACS and with PRECISE DAPT  $\geq 25$  showed a significant increase in TIMI bleeding after treatment with longer DAPT (ARD +2.61%, 95%CI +0.19% to +4.99%; NNT: 38) whereas those with non-high PRECISE DAPT risk score did not (ARD +0.14%, 95%CI -0.22% to +0.49%) ( $P_{int}=0.034$ ). At the same time, longer DAPT duration reduced the composite ischemic endpoint in ACS patients at non-high PRECISE DAPT score (ARD -4.13%, 95%CI -6.09% to -2.15%; NNT: 24), but not in those with PRECISE DAPT  $\geq 25$  (ARD +1.54%, 95%CI -3.27% to +6.32%) ( $P_{int}=0.032$ ) (**eFigure 9**).

## **Discussion:**

Ischemic 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.<sup>25</sup> DAPT 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.<sup>26,27</sup>

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

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 WBC, remained associated to bleeding occurring at later time points.<sup>27,30</sup> In addition, we featured the relevance of prior bleeding, which is commonly appraised in practice,<sup>31</sup> and emerged as the strongest predictor of bleeding in our score.

International guidelines suggest individualization of the antiplatelet treatment duration,<sup>5,6</sup> as all randomized studies invariably showed real or potential bleeding liability associated with prolonged vs. shortened DAPT duration regimens.<sup>4,7,13</sup> We observed that among patients deemed at high bleeding risk based on PRECISE DAPT, prolonged DAPT was associated with no ischemic 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 to a marginal or even no increase of bleeding and a significant reduction of the composite ischemic endpoint. Selecting upfront a shorter than 12-month treatment duration in patients deemed at high bleeding risk (PRECISE-DAPT score  $\geq 25$ ) may prevent exposing them to an excessive bleeding hazard. In turn, patients at non-high bleeding risk (PRECISE-DAPT score  $< 25$ ) might receive a standard (i.e. 12 months) or a prolonged (i.e.  $> 12$  months) course of treatment if tolerated. A separate assessment of this treatment strategy in ACS patients provided consistent findings. Current recommendations for DAPT duration suggest that ACS patients should undergo at least 12-month treatment unless the bleeding outweighs ischemic risks.<sup>5</sup> PRECISE-DAPT score was able to select ACS patients with an excessive bleeding risk, who failed to derive ischemic benefit from 12 or 24 month DAPT duration, whereas a more favourable net outcome was observed in these selected patients with a shorter DAPT duration.

A prediction algorithm was recently proposed for patients who tolerated 12-month DAPT to select those eligible for treatment prolongation.<sup>8</sup> Still, this strategy cannot be applied earlier, at the time of treatment initiation, to select a shorter than 12 month treatment duration in high bleeding risk patients. Earlier decision-

making is especially desirable for bleeding prevention, considering that, as observed in our analysis, median time to bleeding was 5 to 6 months.

Two risk scores have been developed to evaluate the absolute ischemic and bleeding risk after coronary stenting in the context of the PARIS registry.<sup>18</sup> 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, while c-indexes were numerically but not always statistically superior.

The strengths of our study include: the derivation of a simple risk score, which 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.<sup>2,5,6</sup> At variance with prior scores designed to predict in-hospital bleeding,<sup>28</sup> our model was developed to predict out-of-hospital bleeding events, which are more relevant in the decision making on secondary prevention with anti-thrombotic medications. This novel score is the first being validated in patients treated with more potent P2Y12 inhibitors, which represent the standard of care for patients with ACS. This score was retrospectively applied among patients randomized to a shortened or prolonged DAPT duration so to propose and validate simple DAPT duration treatment strategy according to bleeding risk. A simplified score modelled without WBC was also derived and validated, which may prove useful in case WBC is not available.

Among the limitations we acknowledge that event discrimination in our score ranged from moderate to decent. Emerging predictors for bleeding, including frailty might be missing in our model,<sup>32</sup> 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 pre-specified/randomized treatment duration at the time of PCI. A granular collection of patient on-treatment/off-treatment status during follow-up would have been desirable. Information regarding prior bleeding in the PLATO validation cohort was limited to prior gastrointestinal bleeding. Our score slightly underestimated bleeding risk in the PLATO PCI population possibly because of the higher bleeding risk in the PLATO, which included only ACS patients, 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 randomized 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 ability to correctly discriminate bleeding. Based on similar considerations, the score performed slightly better in patients with PPI. 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 OAC patients should likely 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, significantly 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.

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#### **Research in context:**

**Evidence before this study:** Spontaneous bleeding during treatment with dual antiplatelet therapy is the most common complication after coronary stenting,<sup>27</sup> and its incidence increased with the introduction of novel and more potent antithrombotic agents.<sup>2</sup> Despite recommendations from international guidelines, means to gauge out-of-hospital bleeding risk in patients treated with dual antiplatelet therapy (DAPT) are limited.<sup>5,6</sup> 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 up to September 2016 about bleeding risk scores in patients treated with dual antiplatelet therapy. 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,<sup>8,18</sup> and one was only applicable after a 12-month course with DAPT was completed without complications.<sup>8</sup>

**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. In fact, the PRECISE-DAPT score showed potential to identify patients at high bleeding risk (score $\geq$ 25) who may benefit from a shortened (i.e. less than 12 months) DAPT duration. In turn, patients not at high bleeding risk (score $<$ 25) might receive a standard (i.e. 12 months) or prolonged (i.e. $>$ 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 dual antiplatelet therapy, selecting patients at high bleeding risk (score $\geq$ 25) to a shorter treatment and patients at non-high risk to a standard or long treatment.

**Table 1: Multivariable analysis for out-of-hospital TIMI major/minor bleeding, study stratified with backward selection at a  $\alpha$  level of 0.1**

	<b>Hazard ratio (95% CI)</b>	<b>p</b>
Age (ten years)	1.34 (1.11 - 1.48)	0.005
Prior bleeding	4.14 (1.22 - 14.02)	0.023
White blood cell count ( $10^3$ units/ $\mu$ L)	1.06 (0.99 - 1.13)	0.078
Haemoglobin at baseline (one g/dL)	0.67 (0.53 - 0.84)	0.001
Creatinine clearance (ten ml/min)	0.90 (0.82 - 0.99)	0.004

Age was truncated below 50 years; haemoglobin at baseline was truncated above 12 and below 10 g/dl; creatinine clearance was truncated above 100 ml/min; white blood cell count was truncated above 20 and below  $5 \times 10^3$  units/ $\mu$ L

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

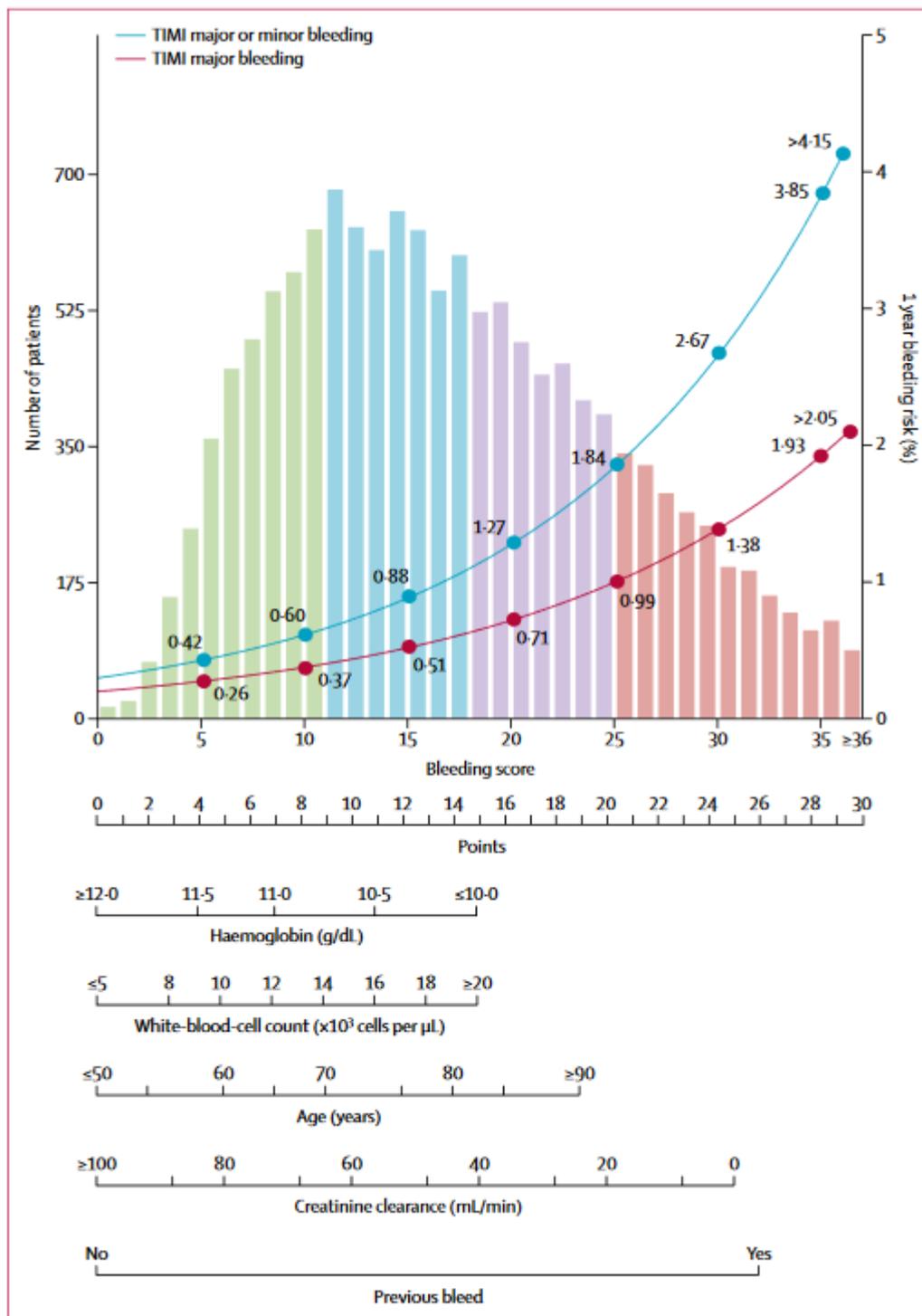
	TIMI major/minor						TIMI major					
	C-Index	p Value*	NRI		IDI		C-Index	p Value*	NRI		IDI	
	(95% CI)		Index	p Value	Index	p Value	(95% CI)		Index	p Value	Index	p Value
<b>Derivation cohort</b>												
PRECISE-DAPT	0.73 (0.61-0.85)	-	-	-	-	-	0.71 (0.57-0.85)	-	-	-	-	-
PRECISE-DAPT alternative*	0.71 (0.57-0.84)	-	-	-	-	-	0.69 (0.53-0.85)	-	-	-	-	-
<b>Validation cohort 1 (PLATO)</b>												
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.	-
<b>Validation cohort 2 (BernPCI)</b>												
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.	-

NRI: Net Reclassification Improvement. IDI: Integrated Discrimination Improvement

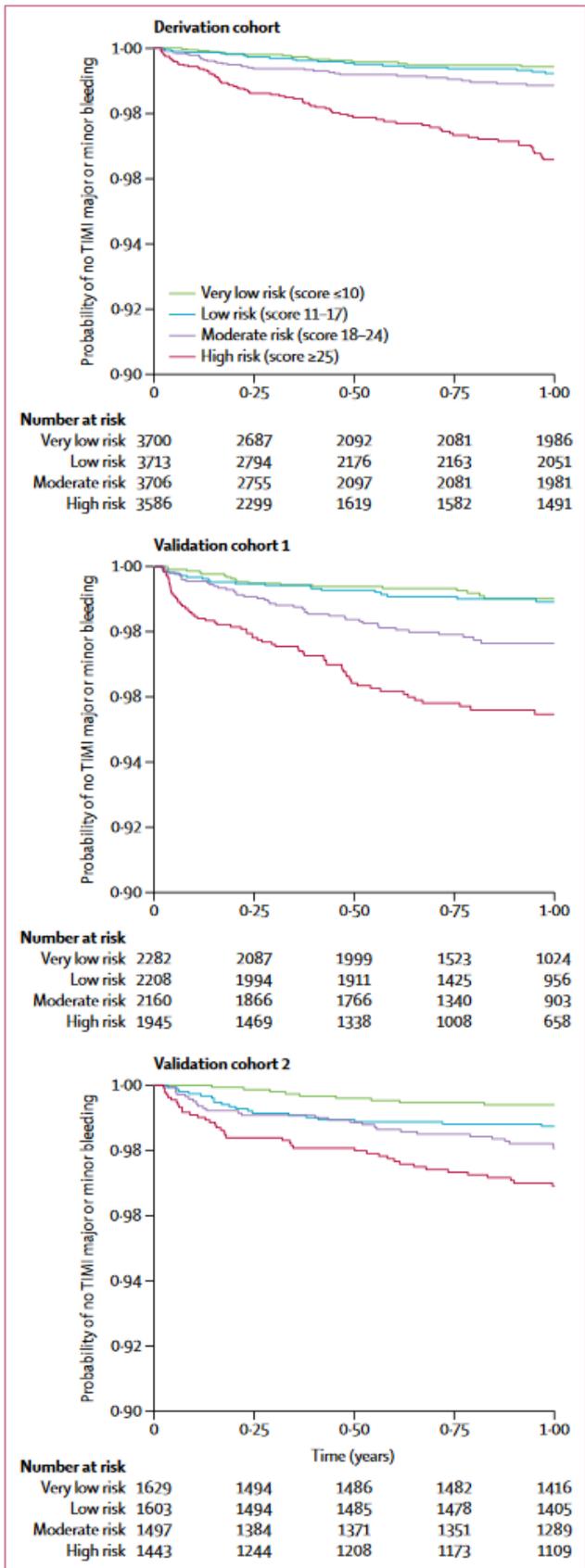
Description of the scores: PRECISE-DAPT score is age, creatinine clearance, haemoglobin and white-blood cell count at baseline, and prior spontaneous bleeding; PRECISE-DAPT Alternative score is age, creatinine clearance, haemoglobin at baseline, and prior spontaneous bleeding; PARIS is Age, body mass index, current smoking status, presence of anemia (haemoglobin < 12g/dl in men and 11g/dl in women), creatinine clearance < 60ml/dl and treatment with triple therapy (i.e. aspirin plus P2Y<sub>12</sub> inhibitor plus oral anticoagulant) at discharge. \*The PARIS score has been used as reference to test C-indexes, integrated discrimination improvement and net reclassification improvement as compared to the PRECISE-DAPT scores.

**Figure Legends:**

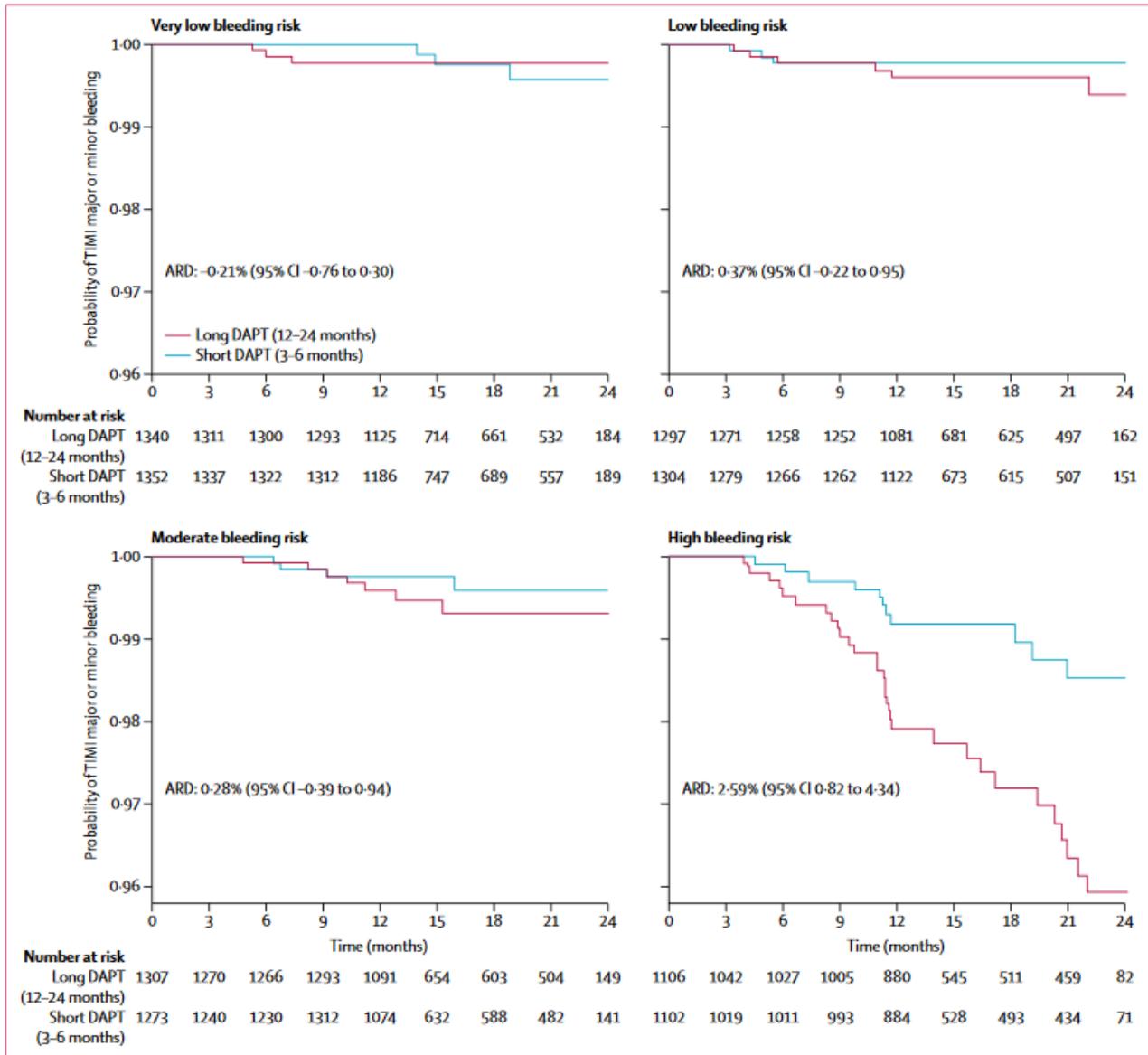
**Figure 1:** The PRECISE-DAPT score nomogram for bedside application. Risk curves refer to out-of-hospital TIMI major/minor and TIMI major bleeding at 12 months, while on-treatment with DAPT.



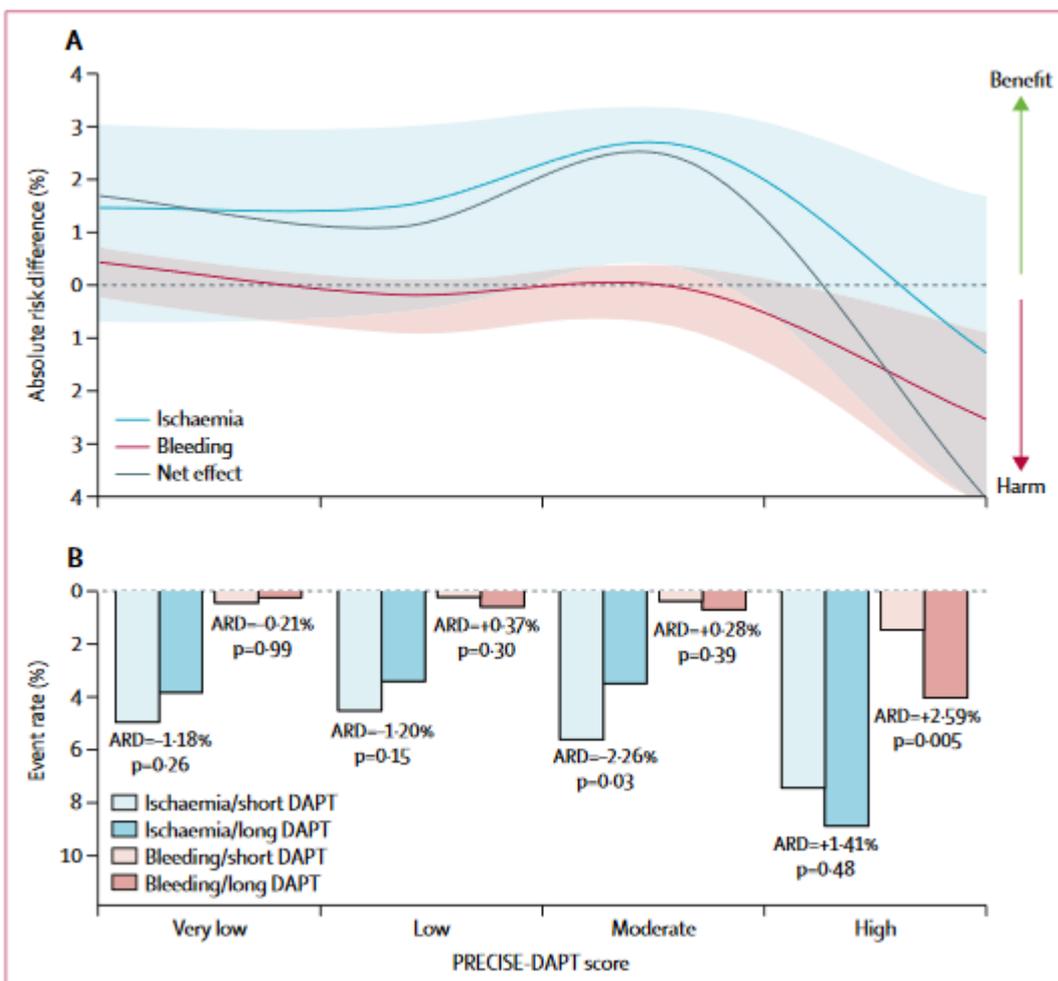
**Figure 2:** Kaplan Meier estimates of survival free from bleeding in both derivation and validation cohorts stratified by score quartiles. Estimates for TIMI major/minor bleeding occurring while on-treatment with DAPT are presented. Validation Cohort 1 from the PLATO trial. Validation Cohort 2 from the BernPCI registry.



**Figure 3:** Twenty-four month Kaplan Meier estimates of survival free from TIMI major/minor bleeding among PRECISE-DAPT bleeding risk quartiles (i.e. very-low, low, moderate and high bleeding risk) for patients randomized to long (12-24 months) or short (3-6 months) dual antiplatelet therapy. Absolute risk differences (ARD) are presented: a positive ARD represent the risk increase for a long as compared to a short course of DAPT.



**Figure 4:** Absolute risk difference (ARD) for a long (12-24 months) as compared to short (3-6 months) DAPT duration with respect to ischemia (myocardial infarction, definite stent thrombosis, stroke or target vessel revascularization) and bleeding (TIMI major/minor) within the four PRECISE-DAPT score quartiles. ARD curves plotted on the upper side of the zero line represents 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 to a short treatment (A). Event rate for ischemia and bleeding after a long or short DAPT treatment within the four PRECISE-DAPT quartiles. A positive ARD represent the risk increase for a long as compared to a short course of DAPT (B).



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## Contributors:

- **Marco Valgimigli:** Conceived, designed and interpreted the study, drafted the manuscript, revised and approved the final manuscript.
- **Francesco Costa:** Conceived, designed and interpreted the study, drafted the manuscript, revised and approved the final manuscript.
- **David Van Klaveren:** Designed the study, analysed and interpreted data, revised and approved the final manuscript.
- **Ewout W. Steyerberg:** Designed the study, interpreted data, revised and approved the final manuscript.
- **Stefan James:** Interpreted data, revised and approved the final version of the manuscript.
- **Fausto Feres:** Interpreted data, revised and approved the final version of the manuscript.
- **Lorenz Räber:** Interpreted data, revised and approved the final version of the manuscript.
- **Thomas Pilgrim:** Interpreted data, revised and approved the final version of the manuscript.
- **Dik Heg:** Interpreted data, revised and approved the final version of the manuscript.
- **Thomas Zanchin:** Interpreted data, revised and approved the final version of the manuscript.
- **Myeong-Ki Hong:** Interpreted data, revised and approved the final version of the manuscript.
- **Hyo-Soo Kim:** Interpreted data, revised and approved the final version of the manuscript.
- **Antonio Colombo:** Interpreted data, revised and approved the final version of the manuscript.
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- **Tullio Palmerini:** Interpreted data, revised and approved the final version of the manuscript.
- **Lars Wallentin:** Interpreted data, revised and approved the final version of the manuscript.
- **Deepak L. Bhatt:** Interpreted data, revised and approved the final version of the manuscript.
- **Gregg W. Stone:** Interpreted data, revised and approved the final version of the manuscript.
- **Stephan Windecker:** Interpreted data, revised and approved the final version of the manuscript.

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- **Deepak L. Bhatt:** Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research

Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda, outside the submitted work.

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