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ORIGINAL INVESTIGATIONS

External Validation of the DAPT Score in a Nationwide Population

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ABSTRACT

BACKGROUND The dual antiplatelet therapy (DAPT) score guides decisions on DAPT duration after coronary stenting by simultaneously predicting ischemic and bleeding risk.

OBJECTIVES This study sought to assess the performance of the DAPT score in a nationwide real-world population.

METHODS The study used register data in Sweden (2006 to 2014) and followed 41,101 patients who had undergone 12 months of event-free DAPT, from months 12 to 30 after stenting. Risk of myocardial infarction (MI) or stent thrombosis, major adverse cardiovascular and cerebrovascular events (MACCE) (MI, stroke, and all-cause death), and fatal or major bleeding were compared according to DAPT score.

RESULTS The score had a discrimination of 0.58 (95% confidence interval [CI]: 0.56 to 0.60) for MI or stent thrombosis, 0.54 (95% CI: 0.53 to 0.55) for MACCE, and 0.49 (95% CI: 0.45 to 0.53) for fatal or major bleeding. Risk of MI or stent thrombosis was significantly increased at scores of ≥3 while MACCE risk followed a J-shaped pattern and increased at scores of ≥4. Absolute differences in fatal or major bleeding risk were small between scores. Event rates of ischemic and bleeding outcomes in patients with high (≥2) and low (<2) scores differed compared to the DAPT Study from which the score was derived; fatal or major bleeding rates were approximately one-half of those in the placebo arm of the DAPT Study.

CONCLUSIONS In a nationwide population, the DAPT score did not adequately discriminate ischemic and bleeding risk, the relationship between score and ischemic risk did not correspond to the suggested decision rule for extended DAPT, and risk of bleeding was lower compared with the DAPT Study. The score and its decision rule may not be generalizable to real-world populations. (J Am Coll Cardiol 2018;72:1069–78) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DAPT = dual antiplatelet therapy

HR = hazard ratio

MACCE = major adverse cardiovascular and cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

Patients who undergo coronary stenting receive dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor to reduce risk of recurrent ischemic events. For DAPT beyond 1 year after stenting, most of the benefit is in reducing spontaneous myocardial infarctions (MI) (i.e., events that are not related to the stent) (1,2). However, the ischemic protection is partly counterbalanced by an increase in bleeding, and the duration of DAPT therefore needs to be individualized based on the patient's ischemic and bleeding risk (3,4). This is difficult because predictors of the 2 types of events tend to overlap (3,5,6).

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The DAPT score is a clinical prediction tool that simultaneously predicts ischemic and bleeding risk. The score, which was recently included in the focused updates of DAPT guidelines in the United States and Europe (3,4), balances ischemic and bleeding risk to identify patients with larger expected benefit and smaller expected harm from another 18 months of DAPT following 12 months of completed DAPT without a major ischemic or bleeding event (7). Although the effects of 12 versus 30 months of DAPT in groups of patients stratified using the score have only been investigated in the DAPT Study from which the score was derived, studies in external populations have assessed shorter DAPT durations than those used in the DAPT Study (8,9) and evaluated the ability of the DAPT score to stratify patients based on ischemic and bleeding risk (7-10). These analyses, however, have been limited to clinical trial populations, and a clinical registry in Japan (7-10). In addition, a large proportion of the patients in the DAPT Study received first-generation drug-eluting stents (1), which have been replaced by new-generation stents with superior safety profiles (11). The performance of the risk score in an unselected real-world patient population receiving contemporary percutaneous coronary intervention (PCI) treatment is uncertain.

We analyzed data from the nationwide quality registry of coronary care in Sweden, the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry, to assess the ability of the DAPT score to stratify ischemic and bleeding risk after 12 months of DAPT and compare ischemic and bleeding event rates with those observed in the DAPT Study.

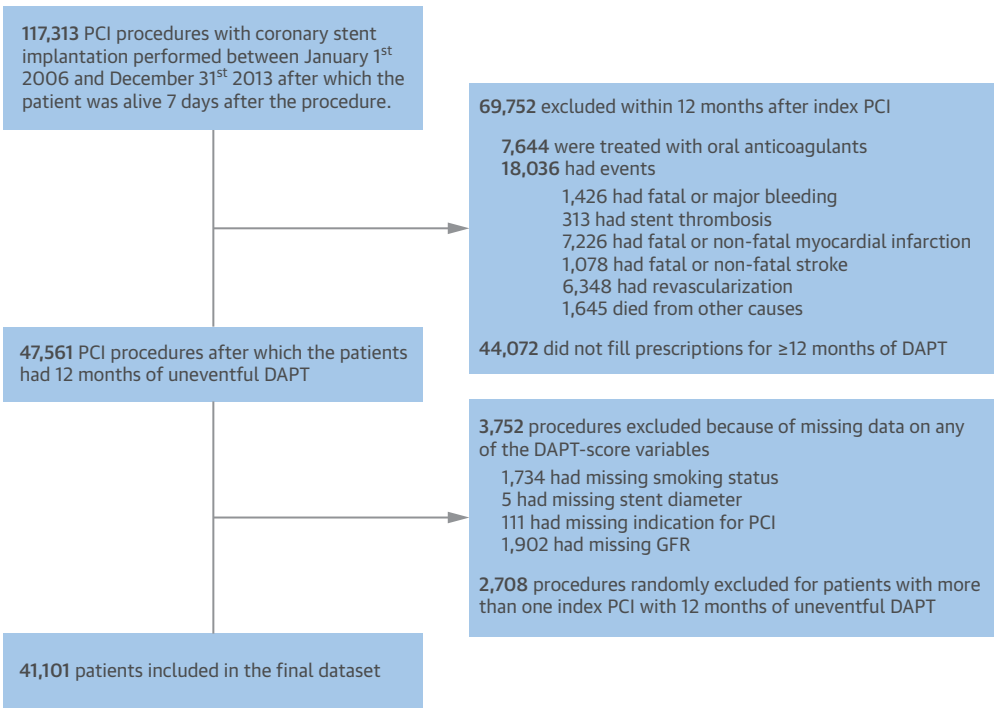
METHODS

DAPT SCORE. The DAPT Study was a clinical trial in which patients who were free of major ischemic and bleeding events during 12 months of DAPT following coronary stenting were randomized to continued DAPT with clopidogrel or prasugrel plus aspirin, or placebo plus aspirin for another 18 months (1). The DAPT score was developed with separate prediction models for bleeding (GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries] major or moderate) and ischemic events (MI or stent thrombosis) (7). The 2 models included a variable for the randomized extension of DAPT and were used to model the risk difference (ischemic risk reduction - bleeding risk increase) from extended DAPT in each patient. In a third prediction model, 9 predictors of the risk difference were identified to constitute the simplified risk score: the DAPT score. The score ranges from -2 to 10 and is calculated by assigning points based on characteristics of the patient and the index procedure. A high score ($\geq$2) is suggested to identify patients for whom reduction of ischemic risk with extended DAPT outweighs bleeding risk and a low score ($<$2) indicates that the patient's bleeding risk outweighs ischemic benefits.

DATA SOURCES. Patients were identified in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) registry, a national registry including patient, procedure and stent characteristics from all coronary angiographies performed in Sweden. The registry is part of the SWEDEHEART registry and has been described in detail elsewhere (12,13). Using the personal identification number, we linked SCAAR registry data with nationwide health registers in Sweden, including the National Patient Register (diagnoses and procedures from hospital admissions), the National Prescribed Drug Register (filled prescriptions), and the Cause of Death Register, as described in the Online Appendix.

STUDY POPULATION. We included all procedures of PCI with coronary stenting in Sweden between January 1, 2006, and December 31, 2013, where the patient was alive 7 days after the procedure. We excluded patients who were treated with anticoagulation therapy at discharge. We then excluded patients who died or experienced stent thrombosis, MI, revascularization, stroke, or a major bleeding event within 12 months after PCI, as described in the Online Appendix. We further excluded patients who did not fill prescriptions corresponding to at least 12 months of continuous DAPT (aspirin and a $P2Y_{12}$ inhibitor

FIGURE 1 Flow Chart for Study Population



The study population included patients in the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry who had completed 12 months of DAPT without ischemic or bleeding events after percutaneous coronary intervention (PCI) with coronary stenting. DAPT = dual antiplatelet therapy; GFR = glomerular filtration rate.

[clopidogrel, once daily; ticagrelor, twice-daily; or prasugrel, once-daily]), including a grace period of 30 days for aspirin and 10 days for $P2Y_{12}$ inhibitors which accounted for nonadherence. The characteristics of the patients excluded due to ischemic or bleeding events or <12 months of DAPT are shown in Online Table 1. Patients with missing data on variables used to calculate the DAPT score were excluded; these included glomerular filtration rate (n = 1,902 [4.0%]), used to diagnose renal insufficiency; smoking (n = 1,734 [3.6%]); indication for PCI (n = 111 [0.2%]); and stent diameter (n = 5 [<0.01%]). For the patients having more than 1 occasion of coronary stenting after which they had completed 12 months of uneventful DAPT, we randomly selected 1 PCI procedure (**Figure 1**). Baseline characteristics of the final study population (n = 41,101) and the clinical trial population of the DAPT Study are shown in Online Table 2.

OUTCOMES. We used International Classification of Diseases-10th revision (ICD-10) codes and procedure codes, selected and validated for identifying bleeding events in Swedish registries (Online Table 3) (14). The primary bleeding outcome was a composite outcome of fatal bleeding and nonfatal major bleeding, which roughly corresponded to the GUSTO moderate or severe bleeding definition (15), and had a sensitivity of 84.5% and specificity of 95.9% when validated against medical records in patients with atrial fibrillation in the Stockholm county (14). Secondary bleeding outcome was a composite outcome of fatal or major bleeding and bleeding requiring hospitalization (sensitivity 99.5% and specificity 94.0% in the same validation study) (14).

For ischemic events we used 2 composite outcomes: 1) MI (ICD-10: I21 to I22 identified in the National Patient Register or the Cause of Death Register) or stent thrombosis (validated through coronary angiograms and recorded in SCAAR); and 2) major adverse cardiovascular and cerebrovascular events (MACCE) including MI, stroke (ICD-10: I60 to I64), and all-cause death.

STATISTICAL METHODS. Patients were followed from 12 months after the index PCI until death, the date corresponding to 30 months after the index PCI, outcome of interest, or end of study period

TABLE 1 Patient Characteristics by DAPT Score Group

	Low DAPT Score (n = 22,615)	High DAPT Score (n = 18,486)
Index year		
2006	571 (2.5)	767 (4.1)
2007	1,264 (5.6)	1,443 (7.8)
2008	1,765 (7.8)	1,987 (10.7)
2009	2,156 (9.5)	2,082 (11.3)
2010	3,006 (13.3)	2,517 (13.6)
2011	4,016 (17.8)	2,980 (16.1)
2012	4,815 (21.3)	3,434 (18.6)
2013	5,022 (22.2)	3,276 (17.7)
Patient characteristics		
Mean age, yrs	69.5 ± 9.8	61.2 ± 9.6
Median age, yrs	70 (65–77)	61 (55–67)
Female	6,328 (28.0)	4,618 (25.0)
Body mass index, kg/m^2	27.0 ± 4.0	28.1 ± 4.6
Diabetes	2,262 (10.0)	5,513 (29.8)
Hypertension	12,735 (56.6)	10,628 (57.9)
Never smoker	11,426 (50.5)	5,414 (29.3)
Previous smoker	9,729 (43.0)	6,146 (33.2)
Current smoker	1,460 (6.5)	6,926 (37.5)
eGFR, ml/min/1.73 m^2	81.0 ± 16.7	87.6 ± 19.0
Comorbidities*		
Renal insufficiency†	2,642 (11.7)	1,629 (8.8)
Previous myocardial infarction	4,310 (19.1)	7,789 (42.1)
Stroke	906 (4.0)	746 (4.0)
Heart failure or LVEF <30%‡	179 (0.8)	2,105 (11.4)
Peripheral artery disease	332 (1.5)	493 (2.7)
Prior PCI	3,894 (17.2)	6,116 (33.1)
Prior CABG	1,246 (5.5)	2,330 (12.6)
Atrial fibrillation	704 (3.1)	645 (3.5)
Cancer	2,082 (9.2)	1,074 (5.8)
Type of $P2Y_{12}$ inhibitor at discharge		
Ticagrelor	4,874 (21.6)	3,825 (20.7)
Clopidogrel	17,218 (76.1)	13,966 (75.5)
Prasugrel	523 (2.3)	695 (3.8)
Other medications at discharge		
Statins	15,771 (96.6)	14,392 (97.3)
ACE inhibitors	10,593 (64.9)	9,951 (67.3)
Angiotensin II receptor blockers	2,461 (15.2)	2,380 (16.3)
Calcium antagonists	2,507 (15.4)	2,287 (15.5)
Beta-blockers	14,519 (88.9)	13,610 (92.0)

Values are n (%), mean ± SD, or median (interquartile range). *Defined as any history of the comorbidity recorded in the National Patient Register (primary or secondary diagnosis) or SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry. †Diagnosed using estimated glomerular filtration rate (eGFR) from the SWEDEHEART registry and was defined as eGFR <60 ml/min/1.73 m^2. ‡Only available for patients with myocardial infarction or unstable angina pectoris as the indication for the index percutaneous coronary intervention (PCI) (n = 290 missing values for these patients). For patients with stable coronary artery disease as the indication for the index PCI, only history of heart failure from the National Patient Register was used. Missing values were: body mass index (n = 1,237); hypertension (n = 260); other medications at discharge: statins (n = 9,976), angiotensin-converting enzyme (ACE) inhibitors (n = 9,991), angiotensin II receptor blockers (n = 10,313), calcium antagonists (n = 9,974), and beta-blockers (n = 9,973).

CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction.

(December 31, 2014). We evaluated: 1) the ischemic and bleeding risk prediction models from which the DAPT score was derived; 2) ischemic and bleeding event rates in the SWEDEHEART registry as compared with those in the DAPT Study; and 3) the DAPT score's ability to stratify patients according to their ischemic and bleeding risk.

In the evaluation of the risk prediction models, we assumed that all patients discontinued DAPT at 12 months by setting the predictor of extended DAPT to "no." This was because patients were not randomized to different treatment durations beyond 12 months after PCI and few patients received long-term DAPT, as this was not recommended in local guidelines during the study period (16). We used Harrell's C-statistics to assess each model's ability to assign a higher risk to a patient who later experienced the event, a property called discrimination. We assessed calibration, a measure of the extent to which estimated risks correspond to observed event rates, by comparing predicted and observed risks by quintile of predicted risk (corrected for censoring with the Kaplan-Meier estimator). We then used Cox proportional hazards regression to calculate coefficients for the associations between predictors and outcomes of the ischemic and bleeding models, respectively.

We assigned points to each patient based on the DAPT score algorithm and assessed the risk score's discrimination for ischemic and bleeding outcomes. The population was then categorized into groups according to the suggested decision rule for extended DAPT (high score [≥2] and low score [<2]) (7). Kaplan-Meier event rates for the ischemic outcomes and the primary bleeding outcome from months 12 to 30 after PCI were compared with those observed in patients receiving placebo in the DAPT Study (7).

We compared ischemic and bleeding event rates in high-score patients versus low-score patients, and by each level of score by calculating hazard ratios (HRs) using Cox regression. Because few patients had scores in the lower or upper extremes of the score range, those with scores of -2 and -1, and ≥5, respectively, were grouped together.

We separately performed the analyses for patients with and without MI as the indication for the index PCI, and in patients receiving new-generation drug-eluting stents as defined in Online Table 4. Finally, we calculated HRs for the DAPT score variables by using Cox regression models with the components of the DAPT score as independent variables and each of the ischemic and bleeding outcomes as the dependent variable.

Analyses were performed in STATA version 15 (StataCorp, College Station, Texas). The study was approved by the regional ethics committees in Stockholm and Uppsala, Sweden. Informed consent was not required.

RESULTS

STUDY POPULATION AND FOLLOW-UP. Of the 41,101 patients completing 12 months of uneventful DAPT after coronary stenting, 22,615 (55%) had a low DAPT score (<2 points) and 18,486 (45%) had a high score (≥2 points). In addition to the expected differences in variables included in the DAPT score, patients with a high versus low score were more likely to have undergone coronary artery bypass grafting and less likely to have a history of cancer (**Tables 1 and 2**). Median and interquartile range of the follow-up time for each outcome are shown in Online Table 5. At 24 months after coronary stenting, 3,797 (Kaplan-Meier-adjusted rate 11.7%) of the patients were still receiving DAPT and at 30 months this number was 2,353 (7.9%). The proportion of patients receiving DAPT at 30 months after stenting was larger for patients with a high score versus low score (10.0% vs. 6.2%; $p < 0.001$).

PERFORMANCE OF THE PREDICTION MODELS USED TO DERIVE THE DAPT SCORE. The ischemic prediction model had a C-statistic of 0.67 (95% confidence interval [CI]: 0.65 to 0.68) (Online Table 6). It overestimated risk of MI or stent thrombosis across quintiles of predicted risk from 0.6 percentage points (observed risk 1.7% vs. predicted risk 2.3%) in the lowest risk quintile to 4.3 percentage points (observed risk 7.9% vs. predicted risk 12.1%) in the highest risk quintile (Online Figure 1). The bleeding model had a C-statistic of 0.67 (95% CI: 0.63 to 0.70) (Online Table 6), and consistently overestimated risk; overestimation ranged from 0.5 percentage points (observed risk 0.3% vs. predicted risk 0.8%) in the lowest risk quintile to 2.4 percentage points (observed risk 1.8% vs. predicted risk 4.2%) in the highest risk quintile (Online Figure 2). Discrimination and calibration were largely similar in patients with and without MI at index PCI, and in those who received new-generation stents (Online Table 6, Online Figures 1 and 2). Cox regression coefficients of the ischemic and bleeding prediction models and the coefficients as estimated in the SWEDEHEART registry are shown in Online Table 7.

COMPARISON OF ISCHEMIC AND BLEEDING EVENT RATES IN THE SWEDEHEART REGISTRY VERSUS THE DAPT STUDY. From months 12 to 30 after PCI, the absolute differences in cumulative incidence of MI and stent thrombosis, and MACCE between patients with high versus low scores were smaller in the SWEDEHEART registry as compared with patients receiving placebo in the DAPT Study (**Central Illustration**). Patients in the SWEDEHEART registry with high scores had lower rates of MI or stent thrombosis than the high-score patients in the DAPT Study (Kaplan-Meier-adjusted cumulative incidence, 4.5% vs. 5.7%), whereas rates were higher in low-score patients in the SWEDEHEART registry versus in the DAPT Study (3.0% vs. 2.3%). Rates of MACCE were 7.1% in the SWEDEHEART registry versus 7.6% in the DAPT Study among patients with high scores and 5.8% versus 3.8% in those with low scores. Rates of fatal or major bleeding in the SWEDEHEART registry were lower than those for GUSTO moderate or severe bleeding in the placebo group of the DAPT Study (high score 0.7% vs. 1.4%; low score 0.8% vs. 1.4%) (**Central Illustration**).

TABLE 2 Procedure and Stent Characteristics by DAPT Score Group

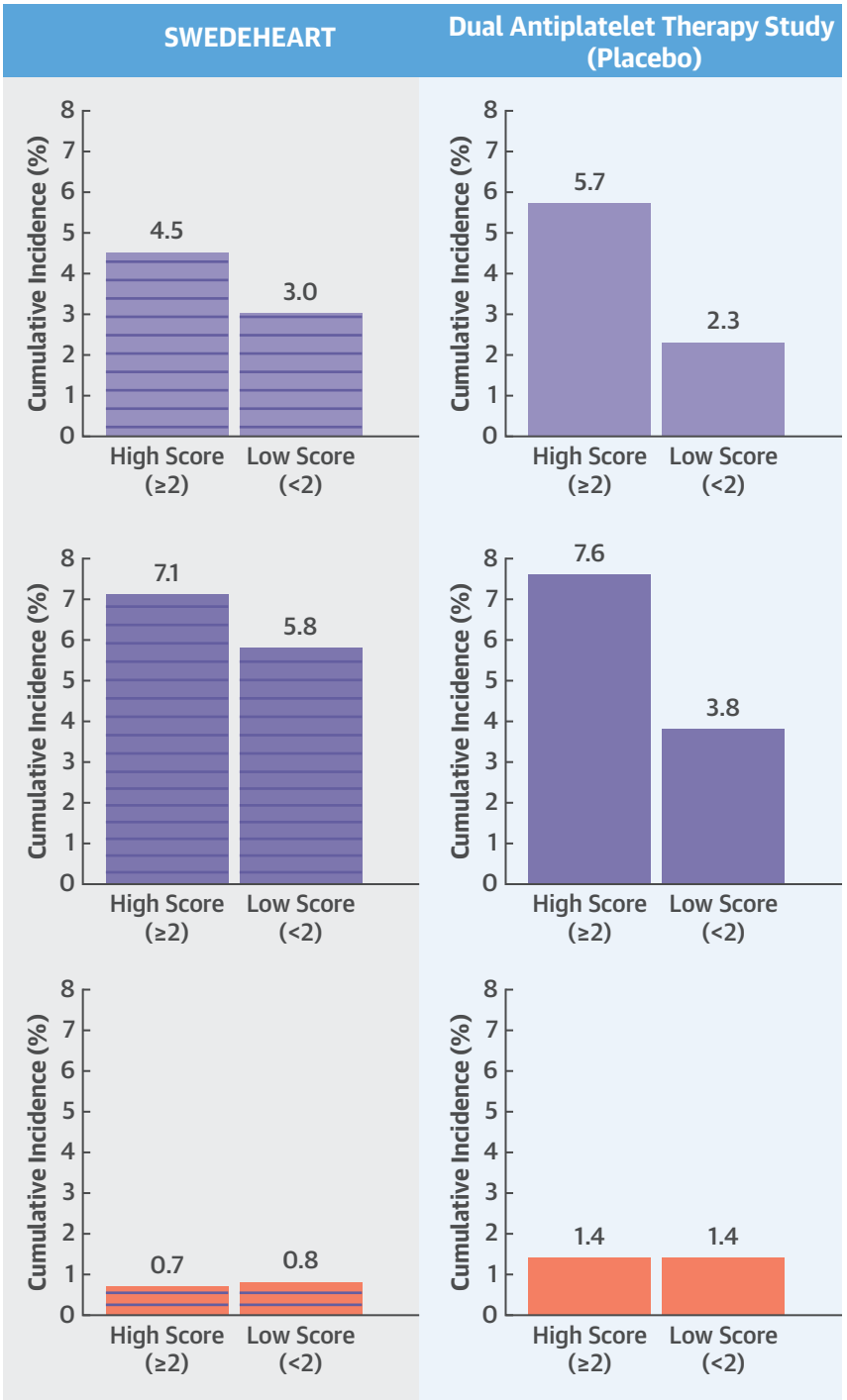
	Low DAPT Score (n = 22,615)	High DAPT Score (n = 18,486)
Indication for PCI		
STEMI	5,047 (22.3)	4,516 (24.4)
NSTEMI	7,974 (35.3)	9,066 (49.0)
Unstable angina pectoris	3,533 (15.6)	1,635 (8.8)
Stable coronary artery disease	6,061 (26.8)	3,269 (17.7)
Procedure characteristics		
Presence of stent thrombosis	112 (0.5)	231 (1.2)
Stents	1.6 ± 0.9	1.7 ± 1.0
Lesions	1.5 ± 0.8	1.6 ± 0.9
Total stent length, mm	29.8 ± 19.3	32.1 ± 21.3
Stent diameter <3 mm	8,873 (39.2)	12,028 (65.1)
PCI on vein graft stent	97 (0.4)	1,109 (6.0)
Stent type		
New-generation DES*	13,904 (61.5)	10,308 (55.8)
Any old-generation DES	2,793 (12.3)	4,236 (22.9)
Any bare-metal stent	6,787 (30.0)	4,887 (26.4)
Type of DES†		
Sirolimus-eluting stent	1,566 (6.9)	1,264 (6.8)
Everolimus-eluting stent	7,490 (33.1)	5,830 (31.5)
Zotarolimus-eluting stent	3,542 (15.7)	2,869 (15.5)
Biolimus-eluting stent	584 (2.6)	392 (2.1)
Paclitaxel-eluting stent	979 (4.3)	2,783 (15.1)
Other	2,986 (13.2)	1,939 (10.5)

Values are n (%) or mean ± SD. All data were collected in the SWEDEHEART registry. *Not including patients also receiving old-generation drug-eluting stent(s) (DES) during the same PCI procedure. †Any use of the DES type (i.e., a patient could receive more than 1 type during the index PCI).

NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in **Table 1**.

ABILITY OF THE DAPT SCORE TO STRATIFY ISCHEMIC AND BLEEDING RISK. The distribution of the DAPT score in the study population is shown in **Figure 2**. The score had a C-statistic of 0.58 (95% CI: 0.56 to 0.60) for MI or stent thrombosis, 0.54 (95% CI: 0.53 to 0.55) for MACCE, 0.49 (95% CI: 0.45 to 0.53) for fatal or major bleeding events, and 0.48 (95% CI: 0.46 to 0.51) for fatal or major bleeding or bleeding requiring hospitalization. Discrimination was similar

CENTRAL ILLUSTRATION **Ischemic and Bleeding Event Rates in the SWEDEHEART Registry and the DAPT Study**



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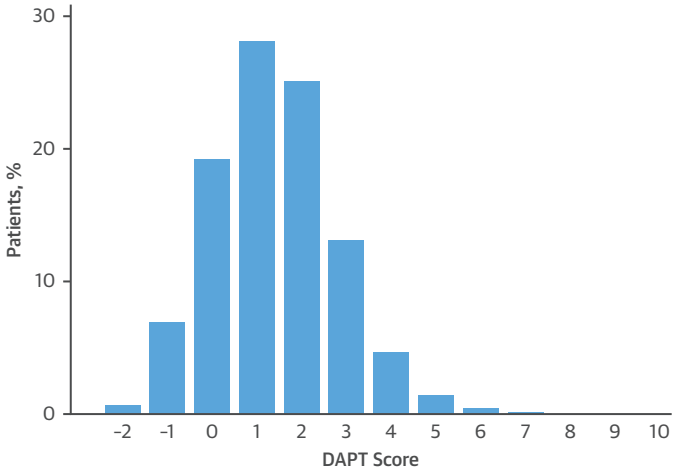
Cumulative incidence of events from months 12 to 30 after coronary stenting in high versus low scores in patients in the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry (n = 41,101) and the placebo arm of the Dual Antiplatelet Therapy (DAPT) Study (n = 5,786). The bleeding outcome was fatal or major bleeding as defined in Online Table 3 in the SWEDEHEART registry and GUSTO moderate or severe bleeding in the DAPT Study. At 30 months after coronary stenting, 7.9% of the SWEDEHEART patients were still receiving DAPT (10.0% in the high-score group and 6.2% in the low-score group).

FIGURE 2 Distribution of the DAPT Score

DAPT Score Variable	Points
Age, y	
≥75	-2
65–<75	-1
<65	0
Cigarette smoking	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
Congestive heart failure or LVEF <30%	2
Vein graft stent	2
Total score range: -2 to 10	



Distribution of DAPT scores in the study population in the SWEDEHEART registry (n = 41,101). LVEF = left ventricular ejection fraction; MI = myocardial infarction; other abbreviations as in Figure 1.

in patients with and without MI at index PCI and in patients receiving new-generation stents (Table 3). HRs for ischemic and bleeding outcomes for each component of the DAPT score are shown in Online Table 8.

Patients with a high score, as compared with those with a low score, had significantly higher rates of MI or stent thrombosis (cumulative incidence 4.5% vs. 3.0%; HR: 1.52; 95% CI: 1.36 to 1.69) and MACCE (7.1% vs. 5.8%; HR: 1.23; 95% CI: 1.14 to 1.34). Differences in rates of MI or stent thrombosis in high-score patients versus low-score patients were largely driven by those with scores of 3 (HR vs. scores of -2 and -1: 1.94; 95% CI: 1.47 to 2.57), 4 (HR: 3.38; 95% CI: 2.51 to 4.56), and ≥5 (HR: 4.99; 95% CI: 3.60 to 6.91) while rates were similar for patients with scores of 0 to 2. Also rates of MACCE did not increase linearly with level of score; compared with scores of -1 and -2, event rates were lower at scores of 1 and 2, and significantly increased only at scores of 4 and ≥5 (Table 4).

Event rates were similar in the high-score group versus low-score group for fatal or major bleeding (cumulative incidence 0.7% vs. 0.8%; HR: 0.88; 95% CI: 0.69 to 1.12), and fatal or major bleeding or bleeding requiring hospitalization (2.1% vs. 2.4%; HR: 0.89; 95% CI: 0.77 to 1.02). Although the absolute differences in risk between score levels were small, the relationship between risk of fatal or major bleeding and score was nonlinear: compared with scores of -2 and -1, risk was significantly lower at score 2 and tended to increase at scores of ≥5 (Table 5). Results were largely similar in patients with and without MI at index PCI, and in those receiving new-generation stents although rates of fatal or major bleeding were significantly higher among patients with scores of ≥5 in this subgroup (Online Tables 9 to 11).

TABLE 3 Discrimination of the DAPT Score for Ischemic and Bleeding Outcomes

	All	New-Generation DES	MI at Index PCI	No MI at Index PCI
MI or stent thrombosis	0.58 (0.56-0.60)	0.57 (0.54-0.59)	0.58 (0.56-0.60)	0.58 (0.55-0.61)
MACCE	0.54 (0.53-0.55)	0.54 (0.52-0.56)	0.54 (0.52-0.55)	0.54 (0.52-0.56)
Fatal or major bleeding*	0.49 (0.45-0.53)	0.51 (0.46-0.57)	0.48 (0.43-0.52)	0.49 (0.42-0.56)
Fatal or major bleeding or bleeding requiring hospitalization*	0.48 (0.46-0.51)	0.48 (0.45-0.51)	0.48 (0.46-0.51)	0.48 (0.45-0.52)

Values are Harrell's C (95% confidence interval). *Discrimination of the DAPT score in analyses where a lower score indicates higher bleeding risk.
MI = myocardial infarction; MACCE = major adverse cardiovascular and cerebrovascular event(s); other abbreviations as in Table 1.

TABLE 4 Event Rates and HRs for Ischemic Outcomes From Months 12 to 30 After Coronary Stenting by Level of DAPT Score

		MI or Stent Thrombosis			MACCE		
Score	n (%)	Events (IR)*	Cumulative Incidence (%)	HR (95% CI)	Events (IR)*	Cumulative Incidence (%)	HR (95% CI)
−2 and −1	3,159 (7.7)	63 (17)	2.4	1.00 (ref)	171 (45)	6.5	1.00 (ref)
0	7,871 (19.2)	202 (21)	3.1	1.28 (0.96-1.70)	416 (44)	6.3	0.97 (0.81-1.16)
1	11,585 (28.2)	294 (21)	3.0	1.24 (0.94-1.63)	515 (36)	5.3	0.80 (0.67-0.95)
2	10,363 (25.2)	274 (21)	3.1	1.27 (0.96-1.67)	482 (37)	5.4	0.82 (0.69-0.97)
3	5,375 (13.1)	218 (32)	4.8	1.94 (1.47-2.57)	347 (52)	7.5	1.14 (0.95-1.36)
4	1,913 (4.7)	136 (56)	8.0	3.38 (2.51-4.56)	193 (80)	11.2	1.76 (1.44-2.17)
≥5	835 (2.0)	85 (83)	11.3	4.99 (3.60-6.91)	126 (124)	16.4	2.73 (2.17-3.44)

*Per 1,000 person-yrs.
CI = confidence interval; HR = hazard ratio; IR = incidence rate; other abbreviations as in Tables 1 and 3.

DISCUSSION

The DAPT score has been incorporated in the U.S. and European guideline updates for DAPT (3,4) and to assess its performance in everyday clinical practice is important (17). Previous analyses of the DAPT score have been limited to clinical trials and a Japanese patient cohort from several years back in time (7-10). Our study expands on the available data on the DAPT score by including an unselected and contemporary real-world population of 41,101 patients from nationwide registers in Sweden.

From months 12 to 30 after PCI, the DAPT score did not discriminate bleeding risk and had poor discrimination for ischemic risk. Although the risk score still identified patients at high ischemic risk, risk did not increase linearly with level of score. Rates of MI or stent thrombosis were significantly elevated only in patients with scores of 3 or higher and the relationship between score and risk of MACCE was J-shaped with lower risks at scores of 1 and 2 and increased risk at levels of 4 or higher. The absolute differences in risk of fatal or major bleeding were small across levels of score. These findings, which remained similar when limiting the analyses to patients receiving new generation drug-eluting stents, indicate that the DAPT score is not useful for discriminating bleeding and ischemic risk. Although the score may help in identifying patients at high ischemic risk, the relationship between score and ischemic risk was nonlinear and did not correspond to the suggested decision rule of extending DAPT in patients with scores of 2 or higher.

The trade-off between ischemic and bleeding risk associated with extended DAPT is influenced by the event rates of ischemic and bleeding outcomes in the patient population. An important assumption for the use of the DAPT score and its decision rule in new populations is that ischemic and bleeding event rates in patients stratified using the score are similar to those in the DAPT Study (i.e., that the risk score is well calibrated) (17,18). In patients with high and low DAPT scores, event rates differed between the SWEDEHEART registry and the DAPT Study. Notably, rates of fatal or major bleeding in the SWEDEHEART registry were roughly one-half of those for GUSTO moderate or severe bleeding in the placebo-arm of the DAPT Study. Although this could partly be explained

TABLE 5 Event Rates and HRs for Bleeding Outcomes From Months 12 to 30 After Coronary Stenting by Level of DAPT Score

		Fatal or Major Bleeding			Fatal or Major Bleeding or Bleeding Requiring Hospitalization		
Score	n (%)	Events (IR)*	Cumulative Incidence (%)	HR (95% CI)	Events (IR)*	Cumulative Incidence (%)	HR (95% CI)
−2 and −1	3,159 (7.7)	27 (7)	1.0	1.00 (ref)	88 (23)	3.3	1.00 (ref)
0	7,871 (19.2)	61 (6)	1.0	0.90 (0.57-1.41)	162 (17)	2.5	0.73 (0.56-0.95)
1	11,585 (28.2)	68 (5)	0.7	0.67 (0.43-1.04)	210 (15)	2.2	0.63 (0.49-0.81)
2	10,363 (25.2)	51 (4)	0.6	0.55 (0.34-0.87)	161 (12)	1.8	0.53 (0.41-0.69)
3	5,375 (13.1)	39 (6)	0.8	0.80 (0.49-1.31)	105 (15)	2.2	0.66 (0.50-0.88)
4	1,913 (4.7)	13 (5)	0.8	0.74 (0.38-1.43)	45 (18)	2.6	0.78 (0.55-1.12)
≥5	835 (2.0)	13 (12)	1.7	1.72 (0.89-3.33)	34 (32)	4.6	1.38 (0.93-2.05)

*Per 1,000 person-yrs.
Abbreviations as in Tables 1, 3, and 4.

by the different bleeding outcome definitions used and the potential risk of incomplete registration of events in health registries (14), the rates of fatal or major bleeding in our study were similar to those in other coronary patient populations from real-world databases (19) and clinical trials (2,7,20). Importantly, in line with current guidelines (3,4), patients in the SWEDEHEART registry could be prescribed <12 months of DAPT after PCI, whereas all patients in the DAPT Study received at least 12 months of DAPT. It is possible that patients perceived to be at high risk of bleeding were prescribed shorter DAPT durations and thereby excluded from our analyses. Moreover, the majority of patients in the SWEDEHEART registry received DAPT with clopidogrel or ticagrelor, whereas clopidogrel or prasugrel was used in the DAPT Study.

Differences in event rates between the DAPT Study and other patient populations have previously been pointed out (7,9,10). For example, in a study using data from 2 clinical trials and 1 clinical registry in Japan, the rate of MI or stent thrombosis in patients with high DAPT scores was less than one-half of that observed in the DAPT Study, whereas bleeding rates were similar (10). Consequently, bleeding prevention could be of greater importance in Japanese patients than in other populations, such as the SWEDEHEART registry, with higher ischemic and lower bleeding risk, indicating that the DAPT score and its decision rule are not generalizable across populations. Other factors that could affect the generalizability of the DAPT score and its decision rule to new settings include how the trade-off between ischemic and bleeding risk is influenced by the type of $P2Y_{12}$ inhibitor used (2,21,22), and weights assigned to bleeding and ischemic events based on the harm (e.g., mortality) associated with each type of event (23,24).

STUDY LIMITATIONS. The absolute risk reduction or increase from a treatment depends not only on a patient's risk of an outcome under no treatment, as was investigated in the present study, but also on the size of the treatment effect (the relative risk). We were not able to investigate the effect of extended DAPT or potential effect modification by DAPT score level because DAPT duration was not randomized in the SWEDEHEART registry and few patients received extended DAPT up to 30 months after stenting (16). No interaction terms between predictors and extended DAPT were retained in the prediction models for ischemic and bleeding events as they did not improve predictive ability in the DAPT Study population (7). However, although not formally tested in the validation of the risk score in the DAPT Study, there were indications that effect modification by high versus low score could partly explain the different absolute treatment effects in the 2 groups. For example, the rates of GUSTO moderate or severe bleeding in patients with a high score in the DAPT Study were 1.8% versus 1.4% for 30 versus 12 months of DAPT (relative risk: 1.3) whereas the corresponding rates for those with a low score were 3.0% versus 1.4% (relative risk: 2.1). The effect of extended DAPT and potential effect modification by level of score in real-world populations remain a topic for further investigation.

Our study has more limitations. We regarded all patients as having discontinued $P2Y_{12}$ inhibitor treatment from 12 months after PCI. Although the proportion of patients receiving DAPT was small at 30 months after PCI (7.9%), it was significantly higher in those with high versus low scores. This may have led to an underestimation of the ability of the DAPT score to stratify patients according to ischemic and bleeding risk. Further, although the algorithm for identifying major bleeding events in the health registers that we used roughly corresponded to the GUSTO moderate or severe bleeding definition used in the DAPT Study, the definitions were not the identical. Finally, we used health registries to obtain information about DAPT status, predictors and outcomes. Swedish registry data have good coverage with respect to cardiovascular outcomes (25), and the algorithm for fatal or major bleeding events had good sensitivity (84.5%) and specificity (95.9%) in a validation study (14).

CONCLUSIONS

In a large, unselected and contemporary population of patients receiving coronary stents in Sweden, the DAPT score did not discriminate bleeding risk and had poor discrimination for ischemic risk. Although the score identified patients at high ischemic risk, the relationship between score and ischemic risk was nonlinear and did not correspond to the suggested decision rule for extended DAPT, and fatal or major bleeding event rates were substantially lower compared with the DAPT Study. The findings indicate that the DAPT score and its decision rule for extended DAPT may not be generalizable to real-world populations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The DAPT score is a clinical decision tool to identify patients likely to benefit from continuing dual antiplatelet therapy for >12 months after coronary stenting. When applied to a nationwide population independent of the one from which it was derived, the score did not adequately discriminate ischemic and bleeding risk, its relationship to ischemic risk did not align with the decision rule for extending treatment, and risk of bleeding was lower than in the DAPT study, from which the score was derived.

TRANSLATIONAL OUTLOOK: Better tools are needed to identify patients most likely to benefit from extending DAPT for >12 months after coronary stenting.

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KEY WORDS bleeding, dual antiplatelet therapy, myocardial infarction, risk prediction, risk score

APPENDIX For expanded Methods and References sections as well as supplemental tables and figures, please see the online version of this paper.