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Mortality Risk Assessment Using PRECISE-DAPT and DAPT Scores in Acute Coronary Syndrome: A Comparative Analysis

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Abstract

Objectives: This study aimed to compare the data on mortality of the clinical scoring system that predicts the risk of ischemia-bleeding under dual therapy.

Materials and Methods: The records of the patients were retrospectively examined through the hospital information system and archival records. The prepared case data registration form and the Morisky Medication Adherence scale drug compliance scale were filled out. With these data, the patients' predicting bleeding complications in Patients Undergoing Stent Implantation and Subsequent dual antiplatelet therapy (PRECISE-DAPT) and DAPT scores were calculated.

Results: A total of 260 patients were included in the study. The PRECISE-DAPT and DAPT scores were calculated for the patients with acute coronary syndrome. A total of 62 patients (23.8%), exhibited a PRECISE-DAPT score of ≥25. The number of patients with a DAPT score ≥2 was found to be 193 (74.2%). In terms of mortality, patients with PRECISE-DAPT ≥25 and those with PRECISE-DAPT <25 were compared with another group (score should be specified here), and mortality was significantly higher in the high-score group [p=0.001 odds ratio: 6.94 confidence interval: (3.53-13.62)]. Patients were divided into 4 groups based on PRECISE-DAPT and DAPT scores and compared with each other (PRECISE-

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DAPT <25 and DAPT ≥2, PRECISE-DAPT ≥25 and DAPT ≥2, PRECISE-DAPT <25 and DAPT <2, PRECISE-DAPT ≥25 and DAPT <2). Patients with a high PRECISE-DAPT score had a significantly higher mortality rate compared to those with a lower DAPT score (p<0.001).

Conclusion: In our study, we discovered that the bleeding risk score was insufficient for predicting bleeding events, but it could identify high-risk patients in terms of mortality.

Keywords: PRECISE-DAPT, bleeding score, dual antiplatelet therapy, coronary artery disease

Introduction

Percutaneous stent implantation is becoming more common for the treatment of acute coronary syndrome (ACS). The guidelines strongly recommend the initiation of dual antiplatelet therapy (DAPT) following stent implantation[1,2]. The optimal duration for initiating DAPT remains a subject of ongoing debate, as a definitive consensus has yet to be reached.

In DAPT, clopidogrel, ticagrelor, and prasugrel may be included in addition to aspirin[3]. Studies have demonstrated that the use of dual antiplatelet combinations leads to a reduction in major ischemic events among individuals with ACS[3]. The diversification of the agents used in conjunction with aspirin, the advancement of stent technology, and the development of less thrombogenic stents have resulted in divergent outcomes in studies examining the duration of dual therapy. Researchers have developed risk scoring systems to evaluate the dual therapy duration of patients with stents, based on the available data, which has yielded varying results[4]. The ischemia-bleeding balance is the basis of these scoring systems, which analyze the patient's individual and procedural conditions. A risk score for ischemic events was developed in the DAPT study for this purpose by evaluating 9 parameters. Prolonging DAPT in patients with a DAPT score <2 did not result in a reduction in ischemic outcomes, but did result in a significant increase in moderate/severe bleeding events[4]. The predicting bleeding complications in Patients Undergoing Stent Implantation and Subsequent (PRECISE)-DAPT score is another DAPT scoring system. This scoring system is a risk score developed for bleeding events. Extensive DAPT in patients with a high risk of bleeding based on the PRECISE-DAPT score (PRECISE-DAPT ≥25) did not provide a significant benefit in ischemic outcomes, but significantly increased the bleeding burden [number needed to harm (NNH): 38][5]. In contrast, extended DAPT has been shown to reduce the risk of myocardial infarction (MI), stent thrombosis, stroke, and target vessel revascularization in patients without a high risk of bleeding (PRECISE-DAPT score <25). For patients at high risk of bleeding, limiting the duration of DAPT to less than 12 months may reduce the risk of excessive bleeding. In contrast, extended dual therapy may be considered a favorable option for patients who exhibit good tolerance to standard therapy and do not possess a high risk of bleeding[1,5]. This study aimed to evaluate the relationship between PRECISE-DAPT, DAPT scores and bleeding and mortality in patients who were admitted with a diagnosis of ACS and had a stent implanted while on DAPT.

Materials and Methods

Study Sample

Patients with ACS who presented to the Dokuz Eylül University Medical Faculty Hospital Department of Cardiology (cardiology service and coronary intensive care) between January 1, 2013, and July 1, 2014, had their records reviewed retrospectively using the hospital information system and archive records. Of the 948 patients screened, those under the age of 18, those with bleeding-prone disease and laboratory findings, those who decided to have a coronary artery bypass graft (CABG)

operation after ACS, those who had not been implanted with a stent, those who used anticoagulants, and those with a malignancy diagnosis, were excluded, leaving 260 patients eligible for the study. The patients were contacted using the phone numbers they had registered on the system. Patients' duration of dual therapy, histories of recurrent MI and coronary angiography (CAG), bleeding histories during or after dual therapy, and drug compliance were all thoroughly investigated. The case data registration form and the Morisky Medication Adherence scale (MORISKY) drug compliance scale were telephone contact with the patients. Approval was obtained from the Dokuz Eylül University Non-interventional Research Ethics Committee (approval no.: 2019/04-23, date: 20.02.2019).

Obtaining Patient Information

The patients were contacted by phone; a case data record form with questions and answers was completed. Patients' bleeding histories, duration of dual therapy, history of recurrent MI and CAG, bleeding history during or after DAPT, and drug compliance were all thoroughly questioned. The laboratory results, echocardiography and CAG reports, and the patients' disease histories were retrieved from the recorded information in the system. With these data, the patients' PRECISE-DAPT and DAPT scores were calculated.

The DAPT score consists of nine parameters. Age, congestive heart failure/low left ventricular ejection fraction (EF), vein graft stenting, MI at admission, previous MI or percutaneous coronary intervention (PCI), diabetes, a stent diameter of 3 mm, smoking, and paclitaxel-eluting stent. These are all factors included in the DAPT score. A DAPT score of ≥2 is considered elevated, and there is a moderate increase in bleeding events with prolonged dual therapy. Prolonging dual therapy in patients with a low DAPT risk score (score <2) did not result in a reduction in ischemic outcomes, but did result in a significant increase in moderate/severe bleeding events. PRECISE-DAPT is a scoring system consisting of five parameters (age, CrCl, hemoglobin levels, white blood cell count, and history of previous spontaneous bleeding) to predict out-of-hospital bleeding in patients who are undergoing dual therapy. Extensive dual therapy in patients with a high risk of bleeding based on the PRECISE-DAPT score (PRECISE-DAPT 25) did not provide a significant benefit in ischemic outcomes, but significantly increased the bleeding burden (NNH: 38)[5]. In contrast, extended dual therapy has been shown to reduce the risk of MI, precise stent thrombosis, stroke, and target vessel revascularization in patients without a high risk of bleeding (number needed to treat = 65) (PRECISE-DAPT score <25).

In addition, the MORISKY drug compliance scale and a questionnaire form were filled out to evaluate each patient's drug compliance. The case data registration form was filled out based on the patients' responses to the questions.

Bleeding Classifications Based on Standard Bleeding Definitions

The patients were questioned about bleeding that necessitated their applying to a healthcare institution and for treatment, bleeding that resulted in death, bleeding from intracranial or other important anatomical organs, bleeding that resulted in a decrease in hemoglobin of 3-5 mg/dL or higher, and bleeding that necessitated a blood transfusion. In light of this information, bleedings were classified according to the Bleeding Academic Research Consortium (BARC), thrombolysis in MI (TIMI), and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) bleeding classifications[6-8].

Patients who could be contacted via phone were asked if they had experienced bleeding. The bleeding focus in the patients, who answered yes, was questioned. The concerns were whether they contacted the doctor in the event of bleeding, what recommendations were made by the doctors, whether the drug was discontinued, and whether blood transfusions were administered to hospitalized patients.

Determination of Drug Compliance

Patients, who were contacted by phone, were asked about their adherence to medications using the Morisky Clinical Drug Compliance scale, which consisted of 8 questions. According to the responses received, the patients' scores were calculated and the patients' degree of compliance was determined based on their scores. Patients with a score of 8 were considered to have high drug compliance, those with a score of 6 were considered to have moderate compliance, and those with a score of 5 or lower were considered to have low drug compliance.

Statistical Analysis

Statistical analysis was performed using the SPSS 24.0 program. The normal distribution of continuous variables was examined. Those with a normal distribution were evaluated using the t-test, and those without were evaluated using the Mann-Whitney U test. Those with more than two variables and a normal distribution were assessed using the ANOVA test, while those without were evaluated using the Kruskal-Wallis test. For categorical variables, the chi-square test, such as the Pearson's chi-square test and Fisher's exact test, was applied. The Kaplan-Meier survival curves of different groups were evaluated, and these groups were compared with the log-rank test. The significant results from the chi-square tests were subjected to a statistical analysis using binary logistic regression. A p-value of <0.05 was considered significant.

Results

The study included 260 patients with ACS who underwent stent implantation at the Clinic of Cardiology, Dokuz Eylul University Medical Faculty Hospital. Of the patients, 211 (81.2%) were male, and the mean age was 60.06±12.71 years. Based on the patients' medical histories, hypertension was found in 149 (57.3%), diabetes mellitus (DM) in 78 (30%), coronary artery disease (CAD) in 56 (21.5%), cerebrovascular accident (CVA) in 9 (3.5%), peripheral artery disease (PAD) in 5 (1%), and heart failure in 4 (1.5%). When the smoking histories of the patients were evaluated, it was found that 70 patients (26.9%) were non-smokers. Smokers were divided into three subgroups as in the DAPT score. There were 121 (46.5%) active smokers, 21 (8.1%) had quit smoking within two years, and 48 (18.5%) had quit smoking more than two years previously. The mean scores of PRECISE-DAPT and DAPT were calculated as 17.84±11.14 and 2.21±1.31, respectively. Table 1 displays the patients' baseline clinical, demographic, and biochemical parameters.

When the patients' admission clinic, peri-procedural angiographic, and procedural characteristics were evaluated, 153 (58.8%) were hospitalized with ST-elevation MI (STEMI), 93 (35.8%) with non-STEMI, and 14 (5.4%) with unstable angina pectoris. These patients had an average EF value of 50% (40-60 interquartile range), with 35 (13.9%) having an EF of below 40%. The target vessel for 114 (43.9%) patients was the left anterior descending artery, the circumflex for 51 (19.6%), the right coronary artery for 81 (31.2%) , and the saphenous vein graft for 14 (5.4%). The complex PCI rate was determined to be 7.3% (19 patients), and multi-vessel intervention was performed on 16.6% (44 patients) patients. Data from patients' angiographic features are shown in Table 1.

In our study, 259 (99.6%) of the 260 patients received aspirin, 254 (97.7%) received clopidogrel, 5 (1.9%) received ticagrelor, 1 (0.4%) received prasugrel, 236 (90.8%) received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 241 (92.7%) received beta-blockers, 256 (98.5%) received statins, and 240 (92.3%) received proton pump inhibitors (PPIs). The mean duration of DAPT use was 17.61±16.72 months. The drugs prescribed to patients at discharge, as well as the duration of DAPT, are displayed in Table 2.

Bleeding occurred in 35 (13.59%) of the 260 patients enrolled in the study. Of these, 4 (11.4%) were hematuria, 13 (37.1%) were melena, 1 (2.9%) was hemoptysis, and 9 (25.7%) were other types of bleeding. 20 patients (57.1%) sought treatment at the hospital because of these bleedings. The medication for 21 (60%) of the bleeding patients was not changed; the drug was discontinued in 13 (37.1%),

Table 1. Demographic characteristics of patients, comorbid diseases, laboratory-clinical characteristics and applied procedures

Age (years) (mean ± SD)			60.12 (12.71)
Sex		Male-n (%)	211 (81.2)
		Female-n (%)	49 (18.8)
BMI (kg/m^2) (mean ± SD)			27.81 (13.6)
Hypertension			57.3
Diabetes, %			30
Cerebrovascular event, %			3.5
Coronary artery disease, %			21.5
Peripheral arterial disease, %			1.9
Smoking, %	Active smokers		46.5
	Those who had quit within the previous 2 years		8.1
	Those who had quit more than 2 years previously		18.5
	Non-smokers		26.9
History of bleeding %			5
PRECISE-DAPT score (mean ± SD)			17.84 (11.14)
DAPT score (± SD)			2.21 (1.31)
WBC (u/mcL)			11.715 (6.800)
Hb (g/dL)			13.69 (1.83)
Hb <11 g/dL			24 (9.2)
Creatinine (mg/dL)			0.86 (0.75-1.04)
GFR mL/minimum			95.37 (29.13)
GFR<60 mL/minimum			28 (10.8)
Clinic of application		STEMI-n (%)	153 (58.8)
		Non-STEMI-n (%)	93 (35.8)
		UAP-n (%)	14 (5.4)
Ejection fraction % - (IQR)			50 (40-60)
EF <40%, n (%)			35 (13.9)
Target vessel, n (%)		LAD	114 (43.8)
		Cx	51 (19.6)
		RCA	81 (31.2)
		Saphenous vein graft	14 (5.4)
Complex PCI-number (%)			19 (7.3)
Number of stents (mean number per individual)			1.39 (0.66)
Number-type of stent %		MVI	48/260 (18.5)
		First generation stent	12/260 (4.6)
		Second generation stent	176/260 (67.7)
		Dissolvable stent	1/260 (0.4)
		MVI and the first generation	3/260 (1.2)
		MVI and the second generation	17/260 (6.5)
		First and second generation	3/260 (1.2)
Total number of stents implanted			361
Multi-vessel interference			44/264 (16.6)
Total stent length - minimum			27.98 (15.8)

Mean ± standard deviation or median [interquartile range]; categorized variables, n (%), SD: Standard deviation, UAP: Unstable angina pectoris, STEMI: ST-elevated myocardial infarction, NSTEMI: Non-ST elevated myocardial infarction, PCI: Percutaneous intervention, LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, EF: Ejection fraction, BMI: Body mass index, WBC: White blood cells, Hb: Hemoglobin, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy, GFR: Glomerular filtration rate, MVI: Multivessel intervention

Table 2. Drugs prescribed for patients at the time of discharge and the duration of use for dual antiplatelet therapy

Aspirin, n (%)		259/260 (99.6)
Clopidogrel, n (%)		254/260 (97.7)
Ticagrelor, n (%)		5/260 (1.9)
Prasugrel, n (%)		1/260 (0.4)
ACE Inh/ARB, n (%)		236/260 (90.08)
Beta-blocker, n (%)		241/260 (92.7)
Statin, n (%)		256/260 (98.5)
PPI, n (%)		240/260 (92.3)
Duration of use for dual therapy, month		17.61±16.72
Non-receiver, n%		5 (1.9)
Receiver	<1 month, n (%)	6 (2.3)
	1-3 months, n (%)	5 (1.9)
	3-6 months, n (%)	5 (1.9)
	6-12 months, n (%)	177 (68.1)
	12-24 months, n (%)	25 (9.6)
	24-36 months, n (%)	8 (3.1)
	>36 months, n (%)	29 (11.2)

PPI: Proton pump inhibitor, ACE: Angiotensin-converting enzyme inhibitör, ARB: Angiotensin II receptor blocker

and a drug vacation was initiated in 1 (2.9%). According to the TIMI classification, 28 (80%) of these bleeding were minimal, 5 (14.3%) minor, and 2 (5.7%) major. According to the GUSTO classification, 28 (80%) of the patients had minimal bleeding, 5 (14.3%) minor bleeding, and 2 (5.7%) major bleeding. According to the BARC classification, there were 15 (42.9%) type 1, 13 (37.1%) type 2.5 (14.3%) type 3A, and 2 (5.7%) type 3D bleeding events. Furthermore, 15 (42.8%) of 35 bleeding events occurred while patients were receiving dual therapy.

BARC3 bleeding, considered major bleeding, occurred in 7 patients, representing 2.8% of all patients included in the study and 20% of patients with bleeding. When we examined the bleeding events in these patients, we observed that a total of 4 individuals (11.4%) experienced bleeding while receiving DAPT, whereas 3 individuals (8.5%) experienced bleeding while receiving single antiplatelet therapy. One (2.8%) of the patients who had bleeding under dual therapy had a hemorrhagic CVA, which resulted in death. The remaining 3 (8.5%) patients were admitted to the hospital with gastrointestinal (GI) system bleeding and required at least two units of erythrocyte suspension. Two of the three (8.5%) patients, who experienced bleeding while undergoing single antiplatelet therapy, were admitted to the hospital with GI bleeding and required at least two units of erythrocyte replacement, while the remaining patient, accounting for (2.8%) experienced a hemorrhagic CVA. Two (5.6%) of the patients who experienced bleeding while on single antiplatelet therapy received aspirin, and one (2.8%) received clopidogrel. Of the 7 (20%) patients who had BARC 3 major bleeding, 4 (11.4%) died due to various causes. Of the patients who died while receiving dual therapy, 1 (2.8%) died due to hemorrhagic CVA, while the other 2 (5.6%) patients died due to causes unrelated to bleeding. The patient, who died while taking clopidogrel, had GI bleeding and was diagnosed with gastric carcinoma via endoscopic examination; this patient succumbed to sepsis in the subsequent period. Data on bleeding rates in patients are shown in detail in Table 3.

The study recorded a mortality rate of 18.8% (n=49) among 260 patients. Of these deaths, 27 (55.1%) were due to cardiovascular causes. The mean time to death after index ACS was 34±21 months. While 10 deaths (20.4%)

occurred within the first year, 39 (79.6%) occurred after one year (Table 3). When the baseline clinical and demographic characteristics of patients who died and those who did not were compared, it was discovered that the patients who died were older, and had more co-morbid diseases. No statistically significant difference was found among bleeding history, MORISKY drug compliance scale score, and mortality (p=0.68, p=0.11, respectively). The mortality data of the patients are shown in Table 4.

Table 3. Patients' bleeding and mortality data

Bleeding, n (%)		**35/260 (13.5)**
Type of bleeding, n (%)	Hematuria - n (%)	4 (11.4)
	Melena - n (%)	13 (37.1)
	Epistaxis - n (%)	8 (22.9)
	Hemoptysis - n (%)	1 (2.9)
	Other - n (%)	9 (25.7)
Application to the hospital due to bleeding, n (%)		20/35 (57.1)
Bleeding management, n (%)	No drug changes	21 (60.0)
	Drug vacation	1 (2.9)
	Drug discontinuation	13 (37.1)
Bleeding under double antiplatelet, n (%)		15/35 (42.8)
TIMI, n (%)	Minimal	28 (80)
	Minor	5 (14.3)
	Major	2 (5.7)
GUSTO	Mild	28 (80)
	Moderate	5 (14.3)
	Severe	2 (5.7)
BARC	Type 1	15 (42.9)
	Type 2	13 (37.1)
	Type 3A	5 (14.3)
	Type 3B	0 (0)
	Type 3C	2 (5.7)
	Type 4	0 (0)
	Type 5	0 (0)
Mortality, n (%)		49 (18.8)
Death due to cardiovascular causes, n (%)		27 (55.1)
Cardiovascular death due to following causes	ME	7 (25.9)
	CTF	6 (22.2)
	Stroke	2 (7.4)
	Sudden cardiac death	8 (29.6)
	Arrhythmia/other	4 (14.8)
Oncological causes, n (%)		11 (22.4)
Other reasons, n (%)		11 (22.4)
Time passed until mortality, month		34 (21)
Death within a year, n (%)		10 (20.4)
Death after one year, n (%)		39 (79.6)

TIMI: Thrombolysis in myocardial infarction, BARC: Bleeding academic research consortium, GUSTO: Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries, CTF: Common terminology criteria for adverse events

In our investigation, patients were categorized into four groups: the first group with PRECISE-DAPT <25 and DAPT ≥2, the second group with PRECISE-DAPT ≥25 and DAPT ≥2, the third group with PRECISE-DAPT <25 and DAPT <2, and the fourth group with PRECISE-DAPT ≥25 and DAPT <2. These groups were subjected to analysis using the Kaplan-Meier survival analysis method to assess the correlation between mortality and PRECISE-DAPT and DAPT scores (Figure 1).

The analysis performed using the Kaplan-Meier method revealed that the PRECISE-DAPT score significantly increased mortality regardless of the DAPT score (p<0.001). The mean PRECISE-DAPT and DAPT scores of the 260 patients included in the study were calculated as 17.84±11.14 and 2.21±1.31, respectively. There were 62 (23.8%) patients with a PRECISE-DAPT score of 25, indicating a high risk for bleeding. There were

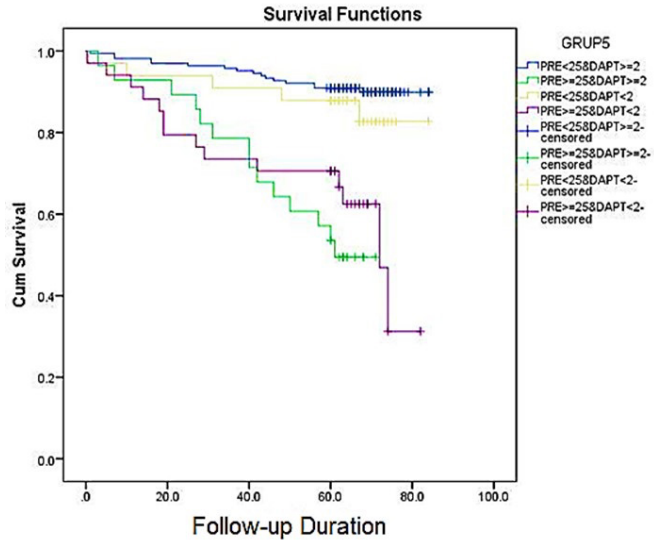

Figure 1. Kaplan-Meier survival analysis (based on PRECISE-DAPT and DAPT scores) log-rank p-value <0.001
BARC: Bleeding academic research consortium, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

Table 4. Comparison of demographic characteristics, examination and score data between patients who died and those who survived

	Survived (n=211)	Died (n=49)	p-value
Age, (mean ± SD)	57.16±11.24	72.86±10.71	<0.001
Female, n (%)	16.6	28.6	0.053
Hypertension, %	55.5	65.3	0.209
Diabetes mellitus, %	25.6	49.0	0.001
Cerebrovascular event, %	1.9	10.2	0.004
Coronary artery disease, %	17.5	38.8	0.001
Peripheral arterial disease, %	0.9	6.1	0.018
Smoker, %	51.2	26.5	0.002
History of bleeding, %	4.7	6.1	0.68
Congestive heart failure, %	0	8.2	0.001
Creatinine, median (IQR)	0.85 (0.74-1.01)	0.94 (0.80-1.33)	0.002
GFR, mean ± SD	99.46±26.78	77.76±32.40	<0.001
WBC, median (IQR)	10800 (8500-13800)	10000 (7900-12300)	0.081
Hb, median (IQR)	14.30 (12.80-15.20)	12.40 (11.20-13.70)	<0.001
EF, median (IQR)	50 (45-60)	50 (35-55)	0.008
BMI, median (IQR)	26.79 (24.67-29.71)	25.39 (22.03-28.57)	0.031
PRECISE-DAPT ≥25	34/62 (54.8%)	28/62 (45.2%)	<0.001
PRECISE-DAPT <25	177/198 (89.4%)	21/198 (10.6%)	
DAPT ≥2	163 (84.5%)	30 (15.5%)	
DAPT <2	48 (71.6%)	19 (28.4%)	0.021

SD: Standard deviation, EF: Ejection fraction, BMI: Body mass index, WBC: White blood cells, Hb: Hemoglobin, IQR: Interquartile range, GFR: Glomerular filtration rate, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

193 (74.2%) patients with a DAPT score of 2 or higher, indicating a high risk of ischemia. The mean age was 71.25±1.30 in the DAPT <2 group, while it was 56±0.79 in the DAPT ≥2 group (p<0.001).

When patients with PRECISE-DAPT scores greater than 25 were compared to patients with PRECISE-DAPT scores of less than 25, it was found that mortality was significantly higher in the group with higher scores [odds ratio (OR): 6.94, 95% confidence interval (CI): 3.53-13.62, p<0.001)] (Table 4). When patients with a DAPT score of 2 were compared to patients with a DAPT score of less than 2, mortality was significantly higher in the group with a low DAPT score [p=0.021 or 0.465 (0.241-0.898)]. When the DAPT score was compared to deaths from cardiovascular causes, no significant effect on cardiovascular mortality was found (p=0.38).

The Morisky clinical drug compliance scale was also used to evaluate patients' drug compliance. The MORISKY drug compliance scale was evaluated in 252 out of the 260 patients, with instances of missing data observed in 8 patients. It was discovered that 101 (38.8%) of these patients were highly drug-compliant.

In our research, we also evaluated the association between sex and mortality, bleeding, and scoring. When females' and males' mortality rates were compared, no significant difference was found (p=0.053); however, females' mortality rate was found to be numerically higher (28.6% vs. 16.6%) (Table 4). While there was no significant difference between the two groups in terms of PRECISE-DAPT and DAPT scores (p=0.21 and p=0.051; respectively), females had higher PRECISE-DAPT scores (30.6% vs. 22.3% PRECISE-DAPT 25) and males had higher DAPT scores (76.8% vs. 63.3%).

The relationship between patients with and without a history of CAD and mortality was compared in our study, and mortality was observed to be significantly higher in the CAD group (OR: 2.97, 95% CI: 1.5-5.8, p=0.001). An examination of the relationship between PAD and mortality revealed that mortality was significantly higher in the group with a PAD history (OR: 6.81, 95% CI: 1.10-41.95, p=0.04). Patients with a history of CVA had significantly higher mortality than patients without a history of CVA (OR: 5.88, 95% CI: 1.51-22.78, p=0.04). When the relationship between diabetes and mortality was evaluated, mortality was discovered to be significantly higher in the DM group compared to that in the non-DM group (OR: 2.79, 95% CI: 1.47-5.29, p=0.001) (Table 5). Considering these findings, individuals aged ≥75 years face a 14.5-fold increase in mortality; a history of PAD corresponds to an 8.5-fold rise; experiencing BARC3 bleeding is associated with an 8.5-fold elevation; glomerular filtration rate <60 mL/min/1.73m^2 leads to a 5-fold surge; a history of CVA results in a 5-fold increase; and having diabetes is linked to a 3.5-fold increase.

In terms of bleeding, no significant difference was found when the group with a high PRECISE-DAPT score was compared to the group with a low score in all bleeding events (p=0.56) (Table 6). Since there was no statistically significant relationship between PRECISE-DAPT scoring and all bleeding events, the relationship between major bleeding (BARC3) and PRECISE-DAPT score was investigated. No statistically significant difference was observed between these two groups (p=0.23) (Table 6). Bleeding history, which is also one of the parameters of the PRECISE-DAPT score, along with all bleeding events that occurred,, were compared in our study. In patients with a previous history of bleeding, no significant difference was observed in all bleeding events (p=0.526) (Table 6). BARC3 bleeding events with a history of bleeding were compared in our study. No significant difference was observed in BARC3 bleeding events occurring in patients with a previous bleeding history (p=0.538). Patients with bleeding were compared to those without bleeding in terms of mortality. When the relationship between the patients with bleeding and mortality was evaluated, no significant difference was found in terms of mortality (p=0.689) (Table 4). Since all bleeding events were found to be unrelated to mortality, the relationship between major and minor bleeding and mortality was evaluated separately.

Since all bleeding events did not have a significant relationship with mortality, BARC1 bleeding (those that did not even necessitate hospitalization) was excluded, and the mortality relationship was evaluated with patients who had BARC2 or BARC3 bleeding. The presence of BARC2 or BARC3 bleeding was found to have no effect on mortality (p=0.18) (Table 5). The correlation between BARC2 bleeding and mortality was evaluated, revealing that it did not significantly affect mortality (p=1). The association with mortality was studied in patients with BARC3 bleeding, later classified as major bleeding. Mortality was found to be significantly increased in patients with BARC3 bleeding (OR: 6.16, 95% CI: 1.33-28.49, p=0.025) (Table 5).

Based on the duration of dual therapy, patients were divided into two groups in our study: those who had

Table 5. Relationship between risk factors and mortality

Subgroup		Survived (number of events/total)	Died (number of events/ total)	p-value
Age	<75	193/224 (88.4%)	26/224 (11.6%)	<0.001
	≥75	13/36 (36.1%)	23/36 (63.9%)	
GFR	<60 mL/min/1.73m^2	12/28 (42.9%)	16/28 (57.1%)	<0.001
	≥60 mL/min/1.73m^2	199/232 (85.8%)	33/232 (14.2%)	
Hb	<11g/dL	10/24 (41.7%)	14/24 (58.3%)	0.003
	≥11g/dL	197/236 (83.5%)	39/236 (16.5%)	
History of bleeding	Yes	10/13 (76.9%)	3/14 (23.7%)	0.52
	No	201/247 (84.4%)	46/247 (16.6%)	
DM	Yes	54/78 (69.2%)	24/78 (30.8%)	0.001
	No	201/247 (84.4%)	25/182 (13.7%)	
History of CAD	Yes	37/56 (66.1%)	19/56 (33.9%)	0.001
	No	174/204 (85.3%)	30/204 (14.7%)	
History of PAD	Yes	2/5 (40%)	3/5 (60%)	0.04
	No	209/255 (82%)	46/255 (18%)	
History of CVE	Yes	4/9 (44.4%)	5/9 (55.6%)	0.04
	No	207/251(82.5%)	44/251 (17.5%)	
Repetitive ME	Yes	48/59 (81.4%)	11/59 (18.6%)	0.96
	No	163/201 (81.1%)	38/201 (18.9%)	
Ejection fraction	<%40	21/35 (60%)	14/35 (40%)	<0.001
	≥40%	187/216 (86.6%)	29/216 (13.4%)	
BARC2	Yes	11/13 (85.6%)	2/13 (15.4%)	1
	No	200/247 (81%)	47/247 (19%)	
BARC2 or BARC3	Yes	14/20 (70%)	6/20 (30%)	0.18
	No	197/240 (82.1%)	43/240 (17.9%)	
BARC3	Yes	3/7 (42.9%)	4/7 (57.1%)	0.025
	No	208/253 (82.2%)	45/253 (17.8%)	
Drug compliance	Yes (8 points)	122/151 (80.8%)	29/151 (19.2%)	0.123
	No (<8 points)	89/101 (63.4%)	12/101 (11.9%)	
DT duration	<12 months	167/198 (84.3%)	44/62 (71%)	0.019
	≥12 months	31/198 (15.7%)	18/62 (29%)	

GFR: Glomerular filtration rate, Hb: Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding Academic Research Consortium, DT: Duration of dual therapy

received dual therapy for 12 months or less and those who had received 12 months or more of therapy. Patients receiving short-term (≤12 months) and long-term (>12 months) dual therapy were compared. When the short-term dual therapy group was compared to the long-term dual therapy group, mortality was found to be significantly higher in the long-term group (OR: 2.20, 95% CI: 1.12-4.30, p=0.019) (Table 7). In our study, a subgroup analysis of increased total mortality was performed after dividing the long-term dual therapy group into two groups based on causes of mortality (cardiac and non-cardiac). When deaths from cardiac and non-cardiac causes were compared between the long-term and short-term dual therapy groups, no significant difference was observed (p=0.51). In order to investigate why long-term dual therapy increased all-cause mortality, the two groups' baseline clinical characteristics and laboratory findings were compared. There were more smokers in the short-term dual therapy group compared to the other group (49.5% vs. 37.1%) (p=0.008). The history of CAD was found to be more common (18.2% vs. 32.3%) in the long-term dual therapy group (p=0.019). However, no significant difference was observed in other basal characteristics (Table 6).

Since the mortality rate in the group receiving long-term dual therapy was significantly higher, the two groups were compared in terms of PRECISE-DAPT score, but there was no significant difference among them (p=0.44)

Table 6. Comparison of patients with low and high PRECISE-DAPT scores

	PRECISE-DAPT <25 (n=198)	PRECISE-DAPT ≥25 (n=62)	p-value
Age (year)	56.52±10.86	71.63±11.31	<0.001
Female, %	17.2	24.2	0.21
HT, %	54.0	67.7	0.57
DM, %	28.3	35.5	0.28
CVE, %	3.0	4.8	0.49
CAD, %	18.2	32.3	0.019
PAD, %	1.5	3.2	0.39
Smoker, %	52.5	27.4	0.001
History of bleeding, %	1.5	16.1	<0.001
CTF	1	3.2	0.21
Creatinine, median (IQR)	0.82 (0.73-0.96)	1.10 (0.89-1.38)	<0.001
GFR, mean ± SD	102.49±24.9	72.62±30.15	<0.001
WBC, median (IQR)	10500 (8300-13350)	11450 (8800-15250)	0.10
Hb, median (IQR)	14.2 (12.9-15.1)	12.5 (10.77-14.40)	<0.001
EF, median (IQR)	50 (45-60)	50 (40-55)	0.008
BMI, median (IQR)	26.80 (24.71-29.75)	25.71 (23.18-28.85)	0.024
Morisky, median (IQR)	8 (5-8)	8 (6.75-8)	0.11
No bleeding	170 (85.9%)	55 (88.7%)	0.56
Bleeding	28 (14.1%)	7 (11.3%)	
No BARC3	194 (98.0%)	59 (95.2%)	0.56
BARC3	4 (2.0%)	3 (4.8%)	
Dual therapy ≤12 months	153 (77.3%)	45 (72.6%)	0.44
Dual therapy >12 months	45 (22.7%)	17 (27.4%)	

SD: Standard deviation, GFR: Glomerular filtration rate, Hb : Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding Academic Research Consortium, DT: Duration of dual therapy, HT: Hypertension, CTF: Common terminology criteria for adverse events, IQR: Interquartile range, BMI: Body mass index, EF: Ejection fraction, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

Table 7. Comparison of patients receiving short and long dual therapy

	DT duration ≤12 months (n=198)	DT duration >12 months (n=62)	p-value
Age (year)	59.44±12.55	62.27±13.06	0.12
Female, n (%)	35/198 (17.7)	14/62 (22.6)	0.38
HT, %	54.5	66.1	0.10
DM, %	29.3	32.3	0.65
CVE, %	3.0	4.8	0.49
CAD, %	18.2	32.3	0.019
PAD, %	1.5	3.2	0.39
Smoker, %	49.5	37.1	0.008
History of bleeding, %	4.5	6.5	0.54
CTF	1	3.2	0.21
Creatinine, median (IQR)	0.86 (0.75-1.03)	0.86 (0.73-1.06)	0.82
GFR, mean ± SD	96.50±29.51	91.76±27.80	0.26
WBC, median (IQR)	10750 (8500-14125)	10300 (7975-12800)	0.072
Hb, median (IQR)	14.1 (12.67-15.1)	13.6 (12.0-14.55)	0.06
EF, median (IQR)	50 (40-50)	50 (45-60)	0.72
BMI, median (IQR)	26.80 (24.71-29.75)	25.71 (23.18-28.85)	0.25
Morisky	8 (5-8)	8 (6-8)	0.44
No bleeding	180 (90.9%)	45 (72.6%)	<0.001
Bleeding	18 (9.1%)	17 (27.4%)	
No BARC3	195 (77.1%)	58 (22.9%)	0.056
BARC3	3 (42.9%)	4 (57.1%)	

GFR : Glomerular filtration rate, Hb: Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding academic research consortium, DT: Duration of dual therapy, HT: Hypertension, CTF: Common terminology criteria for adverse events, IQR: Interquartile range, EF: Ejection fraction, BARC: Bleeding academic research consortium

(Table 6). Following that, the group that received long-term dual therapy was divided into two groups (12-36 months and >36 months). These two groups were compared, and no significant difference was observed between them (p=0.055). In fact, mortality was found to be numerically higher in the 12-36 month group (39.4% vs. 17.2%).

In our study, long-term and short-term dual therapies were compared in terms of bleeding occurrence. Bleeding episodes were found to be significantly higher in the long-term use group (OR: 3.77, 95% CI: 1.80-7.9, p<0.001). After it was discovered that long-term dual therapy increased bleeding significantly, the two groups were compared to investigate the effect of long-term dual therapy on major bleeding. Although the number of BARC3 bleedings was higher in the group receiving long-term dual therapy, it did not reach statistical significance (OR: 4.48; 95% CI: 0.975-20.607, p=0.056) (Table 7).

Discussion

The positive effects of clopidogrel administration in addition to aspirin therapy in patients with stent placement and a diagnosis of ACS in the CURE study have brought DAPT to the literature[9]. Aside from aspirin therapy, different molecules have been developed and tested in the process of DAPT. Ticagrelor was compared to clopidogrel in dual therapy in the Platelet Inhibition and Patient Outcomes study, and it was found that it reduced death, MI, and stroke without increasing major bleeding[10]. It was found in another study that it reduced ischemic events without increasing major bleeding in patients who were started on prasugrel alongside aspirin[11].

Today, clopidogrel, ticagrelor, and prasugrel are initiated in addition to aspirin in DAPT. Although the guidelines strongly recommend starting dual therapy, it is unclear how long it should be used. In studies testing DAPT, different results were observed as a result of developing stent technologies and newly released molecules in terms of the balance between bleeding and ischemia. The researchers developed scoring systems to determine the duration of dual treatment, considering that the patient-based approach will be more effective than general recommendations. The DAPT score evaluates ischemic events that may develop during dual therapy. In this scoring, it is recommended that dual therapy be given for longer than 12 months in patients with a DAPT score of ≥2 to prevent ischemic events[4]. In the study of Costa et al.[5], it was predicted that bleeding events would increase with the lengthening of the dual therapy period, and the PRECISE-DAPT score, which calculates bleeding risk, was developed in this regard. According to this scoring system, which considers factors such as age, creatinine clearance, hemoglobin, white blood cell count, and previous bleeding, patients with a score of 25 or higher have a high risk of bleeding with no significant benefit in terms of ischemia. These scoring systems were subsequently tested in numerous studies. Wester et al.[12] discovered that the PRECISE-DAPT score predicted moderate major bleeding in patients who underwent PCI after MI in their study. The predictive capacity of the score was deemed ineffective, in anticipating major bleeding in individuals with low scores, as this was influenced by factors such as advanced age, low body weight, anemia, and cancer. Similarly, Dannenberg et al.[13] found the PRECISE-DAPT score to be moderately sensitive in predicting bleeding in an analysis of 994 patients who underwent PCI. When all bleeding events were evaluated in our study, no significant difference was observed between patients with high and low PRECISE-DAPT scores (p=0.56). In terms of major bleeding (BARC3), the results were comparable, with no statistically significant difference (p=0.23) observed. The intense use of PPI in our study, the exclusion of patients who underwent CABG and medical treatment, and the fact that there were fewer and more isolated patients all point to the score having an effect on the success of predicting bleeding. When other studies were combined, it was discovered that the score was affected by variable conditions and was not always effective in predicting bleeding risk.

Mortality independent of bleeding was observed to be significantly higher in patients with PRECISE-DAPT ≥25 compared to those with PRECISE-DAPT <25; the group with high scores showed significantly higher mortality (p<0.001). This significant difference indicates that patients who are at high risk of bleeding are also at high risk of mortality. Many studies have shown that mortality increases independently in patients with bleeding events[14,15]. This suggests that the PRECISE-DAPT score is a successful scoring system in selecting high-risk patients. The increase in mortality, independent of bleeding, in our study indicates that patients with high scores are at high risk. Furthermore, in 2019, the Academic Research Consortium published a consensus report on the definition of high bleeding risk in PCI patients[16]. According to this publication, none of the scores, including the PRECISE-DAPT score, are accurate enough to predict bleeding or identify patients at high risk of bleeding. A more reliable scoring system for predicting bleeding in dual therapy should be developed.

The DAPT score is another score that can be used to evaluate mortality during dual therapy. Kwok et al.[17] investigated the relationship between DAPT score and mortality in their study. In this study, which included 243440 patients, who underwent PCI were divided into two groups: those with DAPT scores of 2 and above and those with DAPT scores below 2, and 1- and 3-year mortality rates were compared. It was found that the 1-year and 3-year mortality rates were statistically significantly lower in patients with a DAPT score of ≥2 compared to patients with a DAPT score of <2.17 similarly, in our study, patients with higher DAPT scores had lower mortality (lower DAPT score, higher mortality).

The number of studies in which PRECISE-DAPT and DAPT scores were evaluated concurrently during dual therapy in PCI patients is limited. Boudreau et al.[18] designed a study in which PRECISE-DAPT and DAPT scores were analyzed together. In this study, we aimed to evaluate how well PRECISE-DAPT (predicting bleeding complications in patients receiving stent placement followed by double antiplatelet therapy) and DAPT scores agreed on treatment recommendations and how well they predicted ischemic and bleeding complications. Patients receiving 12 months of dual therapy were divided into two groups based on their PRECISE-DAPT score: extended (>25) and shortened (≤25), and similarly, based on their DAPT score: extended (>2) and shortened (≤2). The PRECISE-DAPT and DAPT score recommendations were found to be compatible in 56.7% of the patients after 1 year. No difference was observed in composite major adverse cardiovascular and cerebrovascular events between patients with high or low PRECISE-DAPT or DAPT scores. Patients with high PRECISE-DAPT scores had a significantly higher 1-year increase in all-cause mortality rate and bleeding events than those with low scores. No difference was found in mortality or bleeding rates between patients with high DAPT scores and those with low DAPT scores. According to the study results, PRECISE-DAPT and DAPT scores frequently result in inconsistent DAPT duration recommendations[18]. Similarly, in our study, patients were divided into four groups based on their scores (PRECISE-DAPT 25 and DAPT 2). Using the Kaplan-Meier survival analysis method, these groups were compared in terms of mortality, and patients with a high PRECISE-DAPT score were found to have a higher mortality independent of other factors ($p<0.001$).

Prolonged use of dual therapy may result in fewer ischemic events but more bleeding events[4,19]. It is recommended to extend and personalize dual therapy based on the individual characteristics of the patient and the stent procedure, due to the risk of bleeding. Prolonging dual therapy reduces ischemic outcomes significantly; however, it increases major bleeding significantly[4,19]. Therefore, when deciding on the duration of dual therapy, evaluating the risk of ischemia and bleeding and tailoring the treatment to the individual are recommended. Many studies and meta-analyses have been conducted to date comparing the short-term dual therapy regimen to the long-term dual therapy regimen[20,21]. According to the results of these studies and meta-analyses, short dual therapy was not inferior to standard or extended dual therapy, and the regimen of short dual therapy resulted in less bleeding[21].

Study Limitations

Taking into account the constraints of these investigations the limitations include an inadequate number of patients, events occurring infrequently compared to the anticipated frequency of events, and the exclusion of many patients (such as those with ACS), leading to the incorporation of low-risk patient populations. In comparison to these investigations, the DAPT study involved 11,648 patients to compare extended dual therapy with standard therapy, and it was discovered that the group that continued thienopyridine treatment for more than 1 year had a 53% reduction in MI and a 71% relative risk reduction in stent thrombosis. However, despite this benefit, it was observed that all-cause mortality increased significantly in the extended dual treatment group ($p=0.05$)[4]. In our study, patients who received short-term (≤12 months) and long-term (>12 months) dual therapy were compared in terms of mortality and bleeding events. In the DAPT study, deaths were found to be significantly higher in the long-term dual therapy group compared to the short-term dual therapy group ($p=0.019$).

In our study, due to the high mortality rates in the long dual therapy group, the groups were evaluated in terms of bleeding risk, using the PRECISE-DAPT score. In terms of PRECISE-DAPT score, there was no significant difference between the two groups (PRECISE-DAPT <25 vs. ≥25) ($p=0.44$). When we compared the baseline demographic characteristics of long-term dual therapy and short-term therapy, we found that a higher history of

CAD was observed in the long-term dual therapy group (p=0.019), with no other significant differences.

The literature contains contradictory results regarding the use of long-term DAPT and mortality. The DAPT study's results revealed that patients receiving long-term dual therapy had high all-cause mortality rates. In a subgroup analysis of deaths in the DAPT study, it was discovered that death from non-cardiovascular causes in the long-term dual group was responsible for this difference[22]. When non-cardiovascular causes were investigated, the results of the subgroup analysis revealed that these deaths were not caused by bleeding. This difference has been explained by cancer-related deaths. It has been stated that this may have happened by chance. More studies are needed to better understand the relationship between extended dual therapy and mortality.

Bleeding rates were found to be significantly higher in the group receiving long dual therapy (OR: 3.77, 95% CI: 1.80-7.90, p<0.001). After it was discovered that long-term dual therapy increased bleeding events significantly, the two groups were compared to investigate the effect on major bleeding. Although the number of BARC3 bleedings was higher in the group receiving long-term dual therapy, it did not reach statistical significance (OR: 4.48, 95% CI: 0.975-20.607, p=0.056). Many studies in the literature support the idea that the prolonged dual therapy regimen is associated with an elevated risk of bleeding[4]. The insignificant relationship between long-term dual therapy and major bleeding in our study could be attributed to the small number of patients who experienced major bleeding.

Conclusion

In our study, we found that the PRECISE-DAPT and DAPT scores, which are scoring systems that calculate the ischemia-bleeding balance to determine the duration of DAPT, did not have a significant relationship with the bleeding events that occurred. Additionally, the mortality of the patient group with a high PRECISE-DAPT score was higher, regardless of the DAPT score. PRECISE-DAPT score was found to be a predictor of mortality independently of DAPT score.

Ethics

Ethics Committee Approval: Approval was obtained from the Dokuz Eylül University Non-interventional Research Ethics Committee (approval no.: 2019/04-23, date: 20.02.2019).

Informed Consent: The records of the patients were retrospectively examined through the hospital information system and archival records.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N, Concept: Alak Ç, Özpelit E, Çırgamış D, Design: Alak Ç, Data Collection and/or Processing: Alak Ç, Analysis and/or Interpretation: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N, Literature Search: Alak Ç, Writing: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N.

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