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Long-Term Outcomes in Patients With Acute Coronary Syndromes Related to Prolonging Dual Antiplatelet Therapy More Than 12 Months After Coronary Stenting

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Abstract

Objectives—To assess the impact of stent type on the risk of death or myocardial infarction (MI) related to dual antiplatelet therapy (DAPT) more than 12 months (prolonged DAPT) versus 12 or less months after PCI for an acute coronary syndrome (ACS).

Back ground—The recent DAPT study reported lower recurrent ischemic events from prolonged DAPT in patients treated with PCI for an ACS, but was underpowered to determine the impact of stent type.

Methods—We determined clinical outcomes after PCI for an ACS (median follow-up: DES=26 months, BMS=46 months) in 18,484 patients in the Veterans Affairs system treated with first generation drug-eluting stents (DES) or bare-metal stents (BMS). We used landmark analyses starting 1 year after the index PCI to assess the risk of prolonged DAPT on the primary endpoint of death or MI. Multivariable and propensity models adjusted for confounding.

Results—There was a significant interaction between stent type and prolonged DAPT for death and MI ($P = 0.0036$), death ($P = 0.054$), and major bleeding ($P = 0.0013$). Patients treated with prolonged DAPT had lower risks of death or MI (HR=0.71, 95% CI = 0.61, 0.82) and death (HR =

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0.74, 95%CI = 0.62, 0.89) with DES, but not BMS, and higher risks of major bleeding, particularly with BMS (HR = 1.67, $P < 0.001$) than DES (HR = 1.24, $p = 0.01$).

Conclusions—Prolonging DAPT more than 12 months after PCI for ACS only associated with a lower risk of ischemic events in the 1–4 years after PCI in those receiving first generation DES. Stent type may influence the benefit of prolonged DAPT.

Keywords

dual antiplatelet; drug-eluting; bare metal; duration; outcomes

Introduction

The duration of dual antiplatelet therapy (DAPT) after percutaneous coronary interventions (PCI) with stents is vigorously debated. Current PCI guidelines in the United States and Europe support 12 months treatment for an acute coronary syndrome (ACS), but differ according to stent type for stable coronary syndromes [1–5]. In the DAPT study of patients free of ischemic or bleeding events 12 months after PCI, prolonging DAPT for 30 months lowered the risk of subsequent recurrent ischemic events [6]. However, meta-analyses of smaller studies suggest no benefit from prolonging DAPT after PCI [7–12].

Currently, the decision to prolong DAPT is based on stent and patient characteristics associated with a higher risk of ischemic events [13]. Patients treated with PCI for an ACS are thought to be one group who are likely to benefit from prolonged DAPT. In a non-prespecified subgroup analysis of the DAPT study, prolonged DAPT lowered the risk of recurrent ischemic events in patients presenting either with or without myocardial infarction [14]. However, the study could not identify an interaction between stent type and benefit from prolonged DAPT, partly because of the relatively low number of patients receiving bare-metal stents (BMS). In contrast, the smaller ITALIC and PRODIGY studies of patients receiving drug-eluting stent (DES), there was no benefit from prolonged DAPT at 1 and 2 years respectively in the ACS subgroups [15,16]. The latter studies used second generation DES, but were too small to assess ACS subgroups, and it is still uncertain if stent type influences the decision to prolong DAPT more than 12 months after PCI for an ACS.

In prior reports of PCI in all Veterans Affairs (VA) hospitals, we showed that diabetes mellitus and chronic kidney disease were patient factors where prolonging DAPT more than 12 months after PCI related to a lower risk of death or myocardial infarction [17,18]. In this analysis, we assess whether stent type (DES versus BMS) influenced the effect of prolonged DAPT more than 12 months in VA patients having PCI for an ACS.

Methods

Patient Population

We identified all VA patients receiving coronary stents between April 2002 and September 2006 at any VA facility across the United States from the VA National Patient Care Database using the ICD-9 procedure code for a BMS (36.06) or a DES (36.07) [17–19]. This database tracks demographic data, long-term drug use, and healthcare outcomes among veterans.

During this time frame, only first generation DES were available. We considered the first stent placement to be the index procedure. We excluded 2,930 (7%) of patients who died within the first 12 months of the index event and another 10,475 patients as outlined in Fig. 1. For this analysis, we also excluded 10,365 subjects without an ACS during their index admission, leaving 18,484 subjects with an ACS for analysis. Subjects free of the clinical outcomes at 1 year were followed to September 1, 2007 with a maximum follow-up of 4 years after their index PCI. The study was approved by the VA Boston Institutional Review Board.

Demographic Data

Data from the time of the index procedure included the patient age, sex, race, and presentation with an ACS. Comorbid conditions were defined by ICD9 code as those from 5 years prior to 12 months following the index PCI and included prior angioplasty (ICD 9: 36.01-2, 36.05-7,00.66), coronary bypass surgery (ICD9: 36.1), smoking (ICD9: 305.1), hypertension (ICD9: 401), congestive heart failure (ICD9: 428), prior stroke (ICD9: 433.01, 433.11, 434.91, 436, V1254), peripheral arterial disease (ICD9: 443), chronic obstructive lung disease (ICD9: 496), anemia (ICD9: 281-285), and chronic kidney disease (ICD9: 585). An ACS at the time of the index procedure included ST-segment or non-ST segment elevation myocardial infarction or unstable angina (ICD9: 410 & 411).

Medication and DAPT Use

The VA National Pharmacy Database provided medications used at the index PCI, and use of clopidogrel over the follow-up period. Since VA prescriptions are usually written for 90-day time periods, we defined baseline medication as a prescription filled within 90 days before and up to 7 days after the index procedure. Aspirin use is a VA quality control measure and other studies show very high rates of outpatient aspirin use in VA patients with coronary artery disease [20].

Over the follow-up time of the study, we were able to track the date of prescription, the amount, and the delivery of all prescribed drugs. If a clopidogrel prescription lapsed >30 days from the last day of supply, the patient was considered not taking clopidogrel. We divided clopidogrel use into two groups, which were prolonged DAPT use for more than 12 months after the index PCI, versus DAPT 12 months use.

Outcomes

Clinical outcomes after the index PCI were identified using ICD-9 codes until October 2007 from the Veterans' Administration National Patient Care and the Veterans' Administration Death Database. Compared to our earlier report of all patients in this cohort, we have added outcomes occurring in non-VA hospitals by linking our data set to outcomes in the Centers for Medicaid and Medicare database.

These included all-cause death, the combined outcome of death or MI (ICD-9: 410), admissions with a new discharge diagnosis of revascularization by PCI (ICD-9: 36.01, 36.02, 36.05, 00.66) or CABG (ICD-9:36.1), ischemic stroke (ICD-9: 436, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01,434.11, 434.91), and hospitalization for major

bleeding. Our definition of major bleeding was expanded to include more bleeding diagnoses than our prior definition [17–19], and was developed by Jasuja et al. [21] and tested in a VA population. Our definition included bleeding into critical and non-critical anatomical sites as defined by Jasuja et al. [21], for example from intracranial, peritoneal, and gastrointestinal bleeding.

Statistics

The primary objective of this study determined whether stent type (DES versus BMS) influenced the relationship of prolonged DAPT use to the risk of death and death or MI 1–4 years after the index PCI in patients presenting with ACS. The analysis was prospectively stratified by stent type, but models combining both stent types were used to test the interaction of stent type-by-prolonged DAPT. The secondary objective determined whether prolonged use was associated with repeat revascularization, stroke, or severe bleeding that required hospitalization.

We used event curves and a landmark analysis assessing outcomes from 12 months after the index procedure among patients who were initially event-free from the outcome under analysis 12 months after their index stenting. Follow-up was censored after September 2007, 12 months after the last recorded VA visit, or 4 years after the index procedure. The hazard ratio (HR) and 95% confidence intervals (95% CI) for pro-longed DAPT use (>12 months) versus DAPT 12 months were assessed for each outcome within each stent type, using Cox proportional hazards regression. To test whether prolonged DAPT had a greater effect in patients receiving DES compared with BMS, we combined data from both stent types and assessed the interaction between prolonged DAPT use and type of stent for each outcome. Multivariable models were developed from more than 50 variables and included if they were related to death or MI. The HRs from final multivariable models for each outcome were adjusted for the baseline characteristics of age, hypertension, smoking, ACS on admission, peripheral vascular disease, chronic kidney disease, congestive heart failure, warfarin use within 7 days of the index procedure, and year of stent placement.

As a second method of adjustment, we used propensity models to adjust for confounding related to the propensity for prolonged DAPT treatment based on baseline variables at the index procedure significantly related to prolonged DAPT using multivariable logistic regression [17–19]. We used inverse probability weighting of the propensity score in the Cox proportional hazards models to assess the HRs associated with prolonged clopidogrel use.

All programming used SAS statistical software. Due to the multiple comparisons in this study, statistical significance was defined as a probability values of < 0.01 for main effects and $P < 0.05$ for interaction effects.

Results

After exclusions (Fig. 1), there were 18,484 patients with ACS who were alive 12 months after their index PCI. Among these patients, 9,442 were treated with DES and 9,042 were treated with BMS. Prolonged DAPT (more than 12 months after the index PCI) was used in 57% of patients with DES and 35% of patients with BMS. The baseline patient populations

are shown in Table I, stratified by whether patients received DES or BMS and whether they were treated with prolonged clopidogrel. Patients treated with BMS had more comorbidities than those treated with DES.

The median (25%, 75%) duration of follow-up in each four group was 25.7 (18.6, 34.0) months for DES and prolonged DAPT, 27.7 (19.7, 36.3) months for DES and DAPT 1 year, 43.9 (31.8, 48.0) months for BMS and prolonged DAPT, and 48.0 (38.8, 48.0) for BMS DAPT 1 year. The median DAPT duration in patients receiving DES was 17.4 months in the prolonged DAPT group versus 6.2 months in the 12 months group, and patients receiving BMS was 21.5 months in the prolonged DAPT group versus 3.0 months in the 12 months group. Non-fatal events between the index PCI and 1 year, which were excluded in the analyses, included MI in 6.5%, repeat revascularization with PCI or CABG in 14.4%, stroke in 0.5%, and major bleeding in 1.3%.

Risk of Events Associated With Prolonged Clopidogrel Use

Between 12 months and 4 years after the index procedure, there were 1,447 deaths, 1,959 death or MIs, and 1,354 episodes of subsequent revascularization with either PCI or CABG. Figure 2 shows the cumulative event curves for death, and death or MI by stent type and DAPT duration from the landmark of 12 months after the index PCI.

Figure 2 and Table II show the risk of events associated with prolonged DAPT. In unadjusted analyses, prolonged DAPT was associated with a lower risk of death or MI (HR = 0.71, 95% CI = 0.61, 0.82) and death alone (HR = 0.74, 95% CI = 0.62, 0.89) among patients treated with DES. In contrast, there was no associated reduction in these events among those treated with BMS (Table II). These relationships were consistent in the multivariable and propensity-adjusted analyses, suggesting these relationships were robust to known confounders.

Prolonged DAPT was associated with increased bleeding with both stent types on univariate analysis (DES, HR= 1.24, BMS, HR= 1.67, Table II). In multi-variable and propensity score adjusted models, pro-longed DAPT was not associated with major bleeding with DES, but remained significant in patients receiving BMS (Table II).

In patients treated with DES or BMS, prolonged DAPT was not associated with the risk of subsequent revascularization or stroke (Table II).

Models With Interaction Effects

Interaction terms for prolonged DAPT and stent type indicated a larger effect of prolonged DAPT with DES compared to BMS on death or MI (interaction $P=0.0036$), death (interaction $P=0.054$), and major bleeding (interaction $P=0.0013$), but not the other endpoints (revascularization $P=0.07$, stroke $P=0.86$).

Discussion

The main finding of this study was that stent type influenced the relationship of prolonged DAPT to the risk of ischemic events and major bleeding in patients presenting with an ACS.

Among ACS patients who were event-free in the first 12 months after PCI with a DES, continuing DAPT more than 12 months associated with less death or MI up to 4 years after their PCI. This finding was not observed in patients treated with BMS for ACS. We found an increased risk of major bleeding with prolonged DAPT, particularly in patients with BMS.

Guidelines for patients with ACS recommend DAPT for 12 months both for patients treated medically and by PCI (Guidelines) [1–5]. The benefit of prolonging DAPT more than 12 months is uncertain given the increased risk of major bleeding with prolonged therapy. Meta-analyses of all subjects treated with DES in randomized PCI trials of short versus longer DAPT indicate a higher risk of bleeding with prolonged DAPT [9,10,12]. This is also the case in patients treated with DES for an ACS. In a meta-analysis of medical and PCI trials in patients with recent MI prolonged DAPT more than 12 months decreased the risk of myocardial ischemic events and increased the risk of major bleeding (relative risk [RR]=1.73, $P=0.004$), but not the risk of fatal bleeds ($RR=0.91$, $P=0.75$), or intracranial bleeding ($RR=1.34$, $P=0.17$) [22]. In our study, we found a smaller risk of major bleeding with DES that was attenuated and non-significant in the multivariable and propensity score analyses. Our new bleeding definition differed from our prior reports by including more ICD9 codes, and was based on a prior publication which was tested in a different VA study [21]. As a result, we identified 5–10 times more bleeding events during follow-up with this definition than our prior reports, and had more power to assess differences in bleeding risk related to DAPT duration. We were unable to use definitions of major bleeding developed in clinical trials such as the BARC, TIMI, GUSTO, and GRACE scores [23] as these require knowledge of a decline in hemoglobin or hematocrit levels, or specific treatment for bleeding which is not easily obtained from medical record data. However, the increased risk of bleeding is consistent with other clinical trials of prolonged DAPT with DES use [9,10,12]

The incidence of major bleeding in patients receiving BMS was nearly twice as high as in patients receiving DES (Table II). This may reflect patient factors related to the choice of stent type, although there were no obvious differences in warfarin use and other comorbidities between patients receiving the two stent types (Table I). Other earlier randomized trials showed no difference in major bleeding events with short (1 month) versus longer treatment (6–12 months) of DAPT in patients treated with BMS for an ACS [24,25]. In all subjects in the DAPT trial, major bleeding was higher with prolonged clopidogrel with both stent types, although with only 23 bleeding events in the BMS group the power to find a significant interaction was low [26]. Our results show that even in patients with ACS there is no support for prolonged clopidogrel in patients treated with BMS.

Our study advances the findings of the ACS subgroup of the DAPT trial [14], where the benefits of prolonged DAPT exceeded the risks for patients receiving first generation DES and BMS, but were underpowered to find a difference between stent type. Our results indicate that this benefit did not occur in patients receiving BMS—a result that is consistent with the overall results of the DAPT study [6,26]. Our study had nine times the number of ACS subjects receiving BMS and four times the number receiving DES than the DAPT study ACS subgroup analysis [14], and therefore had greater power to identify stent type as a modifying factor in the relationship of prolonged DAPT to recurrent ischemic events.

The reasons for the difference in the relationship of prolonged DAPT to outcomes between first generation DES and BMS are not clear. BMS and first generation DES differ in stent thickness, polymer coatings, and drug-delivery which influence time to healing and endothelial strut coverage after implantation [27,28]—factors that may relate to late risks of stent thrombosis. The second generation and first generation DES also differ in some of these design characteristics, which may change the balance of benefit and risks of prolonged DAPT with contemporary second generation DES. Since the second generation DES have a lower risk of ischemic events in long-term follow-up compared to first generation DES [29], the potential benefits of prolonged DAPT may be smaller and not counter the increased risk of bleeding (much as BMS in our study). Multiple smaller randomized studies [15,30–36], largely in patients without ACS, suggest shorter duration of DAPT may be equivalent to longer DAPT with second generation DES. However, current guidelines continue to recommend at least 12 months DAPT after ACS, and prolonged DAPT may offer benefits in the post-MI setting even in second generation DES by preventing MI from new lesions outside of the stented segment as observed in the DAPT study [6].

Limitations

There are several limitations in our study. This is a registry study and could be affected by unmeasured confounders. However, we did use two multivariable adjustments, including a propensity-adjusted method, and our results were robust in that adjusted models did not substantially change the hazard ratios. This study only included first generation DES and only considered DAPT with aspirin and clopidogrel, as compared to newer generation DES or more potent antiplatelet agents that are more commonly used in treating ACS in the current era.

Conclusions

In conclusion, we found that in patients who are event-free 12 months after coronary stenting for ACS, stent type was an important factor in determining the value of prolonged DAPT greater than 12 months. Prolonged DAPT only reduced the risk of ischemic event over very long follow-up in patients receiving first generation DES, not BMS. Prolonged DAPT was associated with increased major bleeding, particularly in patients receiving BMS.

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Fig. 1.

Flow chart showing patient population and reasons for exclusions. Abbreviations: DES, drug eluting stents; BMS, bare metal stents; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; VA, Veterans Affairs health system; ACS, acute coronary syndrome.

Fig. 2. Incidence of death or MI (A and B) and death (C and D) between 1 and 4 years after the index ACS event by clopidogrel duration and stent type.

Table I
Baseline Characteristics of Patients With ACS by Stent Type and Length of Dual Antiplatelet Treatment (DAPT)

Characteristic	Drug-Eluting Stent DAPT Use		Bare-Metal Stent DAPT Use	
	>12 months, <i>n</i> = 5,356	12 months, <i>n</i> = 4,086	>12 months, <i>n</i> = 3,170	12 months, <i>n</i> = 5,872
Age years, mean (SD)	63 (10)	63 (10)	64 (10)	63 (10)
Men, <i>n</i> (%)	5,270 (98)	4,007 (98)	3,119 (98)	5,776 (98)
Race, <i>n</i> (%)				
White	4,342 (81)	3,156 (77)	2,613 (82)	4,682 (80)
Black	503 (9)	491 (12)	335 (11)	794 (14)
Other	40 (0.8)	31 (0.8)	18 (0.6)	41 (0.7)
Unknown	471 (9)	408 (10)	204 (6)	355 (6)
Comorbidities 5 years prior to 1 year after index PCI, <i>n</i> (%)				
Smoking	2,451 (46)	1,985 (49)	1,361 (43)	2,628 (45)
Prior MI	2,005 (37)	1,340 (33)	1,298 (41)	2,162 (37)
Angina	1,663 (31)	1,252 (31)	1,309 (41)	2,354 (40)
Hypertension	4,937 (92)	3,653 (89)	2,954 (93)	5,294 (90)
Diabetes mellitus	2,255 (42)	1,586 (39)	1,421 (45)	2,326 (40)
COPD	1,533 (29)	1,069 (26)	909 (29)	1,643 (28)
Chronic kidney disease	467 (9)	309 (8)	253 (8)	432 (7)
Peripheral vascular disease	902 (17)	625 (15)	584 (18)	1,040 (18)
Anemia (Hemoglobin <12 mg/dL)	780 (15)	738 (18)	589 (19)	1,147 (20)
Stroke	265 (5)	217 (5)	202 (6)	379 (6)
Heart failure	1,341 (25)	986 (24)	901 (28)	1,592 (27)
Comorbidities 1–5 years prior index PCI, <i>n</i> (%)				
Prior CABG	50 (0.9)	58 (1)	60 (2)	109 (2)
Prior PCI	77 (1)	82 (2)	117 (4)	295 (5)
Baseline medications, <i>n</i> (%)				
Aspirin	4,265 (80)	3,207 (78)	2,748 (87)	5,254 (89)
Statin or lipid lowering	4,864 (91)	3,660 (90)	2,906 (92)	5,383 (92)
Beta Blocker	4,729 (88)	3,500 (86)	2,906 (92)	5,339 (92)
Calcium Channel Blocker	1,339 (25)	873 (21)	886 (28)	1,563 (27)
ACE Inhibitor or ARB	3,970 (74)	2,877 (70)	2,440 (77)	4,549 (77)
Proton Pump Inhibitors	2,776 (52)	1,907 (47)	1,649 (52)	2,780 (47)
Warfarin	395 (7)	335 (8)	220 (7)	533 (9)

COPD = chronic obstructive pulmonary disease, CABG = coronary artery bypass grafts, PCI = percutaneous coronary intervention, MI = myocardial infarction, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker.

Table II
Landmark Analysis of the Risk of Clinical Endpoints With Dual Antiplatelet Therapy (DAPT) Use Beyond Versus 12 Months for Outcomes Up To 4 Years After Index Stenting in Patients with ACS

Outcome	Number of events (%) DAPT use		Crude HR (95% CI)	Multivariable HR (95% CI)	Inverse probability weighting ^d HR (95% CI)
	12 months	>12 months			
Drug-eluting stent					
Death	251 (12)	221 (9)	0.74 (0.62, 0.89) ^{**}	0.69 (0.58, 0.83) ^{**}	0.76 (0.63, 0.91) ^{**}
MI or death	359 (17)	307 (13)	0.71 (0.61, 0.82) ^{**}	0.67 (0.58, 0.79) ^{**}	0.73 (0.62, 0.85) ^{**}
PCI or CABG	236 (13)	246 (10)	0.91 (0.76, 1.08)	0.90 (0.75, 1.08)	0.95 (0.79, 1.14)
Stroke	22 (2)	18 (1)	0.7 (0.38, 1.31)	0.69 (0.37, 1.28)	0.74 (0.4, 1.39)
Major bleed	281 (8)	374 (8)	1.24 (1.06, 1.45) [*]	1.04 (0.89, 1.22)	0.98 (0.84, 1.15)
Bare-metal stent					
Death	672 (13)	303 (12)	0.92 (0.81, 1.06)	0.86 (0.75, 0.99)	0.93 (0.8, 1.07)
MI or death	888 (18)	405 (17)	0.94 (0.84, 1.06)	0.90 (0.79, 1.01)	0.92 (0.81, 1.04)
PCI or CABG	569 (13)	303 (15)	1.12 (0.97, 1.29)	1.17 (1.01, 1.35)	1.04 (0.9, 1.21)
Stroke	90 (2)	28 (1)	0.64 (0.42, 0.98)	0.65 (0.42, 1)	0.69 (0.44, 1.07)
Major bleed	793 (15)	432 (15)	1.67 (1.48, 1.88) ^{**}	1.20 (1.07, 1.36) [*]	1.15 (1.01, 1.30)

^a Adjusted for the propensity to use DAPT > 12 months.

^{*} P -value<0.01,

^{**} P -value< 0.001

HR = hazard ratio; 95% CI= 95% confidence interval; DES= drug-eluting stent; BMS= bare metal stent; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.